

The advantages and challenges of sorafenib combination therapy: Drug resistance, toxicity and future directions (Review)

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Abstract. Sorafenib, a multi-target tyrosine kinase inhibitor, is widely used for the treatment of advanced hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC). The present review explores the potential of sorafenib combination therapy to overcome drug resistance, mitigate toxicity and enhance efficacy. Sorafenib inhibits tumor growth and angiogenesis but is often limited by rapid resistance development and severe side effects. Combination therapies involving inhibitors of the PI3K/AKT/mTOR pathway, oxidative stress and autophagy inhibitors show promise in improving antitumor efficacy, reducing resistance and lowering toxicity. However, challenges such as complex drug interactions, increased treatment costs and a lack of long-term clinical data remain. Future research should focus on personalized combination strategies, exploring new molecular targets and performing large-scale clinical trials to optimize the safety and efficacy of sorafenib combination therapies, ultimately advancing cancer treatment and improving patient outcomes.

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1. Introduction

In the 1980s, research groups investigated key molecular changes leading to malignant transformation, including the discovery of oncogenes, tumor suppressor genes and epigenetic events such as promoter methylation. These findings advanced the molecular understanding of cancer. Research has revealed that oncogenes encode growth factors, shifting drug discovery from non-specific chemotherapy to targeted pathway inhibition (1). The goal was to develop targeted drugs that inhibit cancer cells while causing minimal harm to normal cells, resulting in fewer side effects compared with traditional chemotherapy. Targeted inhibition improves treatment precision and enhances patients' quality of life, marking the beginning of a new era in cancer therapy (2). In this context, Bayer AG and Onyx Pharmaceuticals, Inc. focused on the RAS-RAF-MEK-ERK pathway, developing a series of drugs (3). Screening for Raf1 kinase inhibitory activity led to a promising compound, optimized to become sorafenib (4).

Double-blind, randomized trials have reported that sorafenib improves prognosis and is well tolerated in patients with advanced hepatocellular carcinoma (HCC) in the Asia-Pacific region (5,6). Based on these results, sorafenib gained U.S. Food and Drug Administration approval, becoming the first targeted drug for unresectable HCC. As the first oral multi-target tyrosine kinase inhibitor (TKI) approved for advanced HCC, sorafenib filled a critical gap in systemic therapy, improving patient survival rates (7). Sorafenib inhibits multiple pathways [including RAF/MEK/ERK and VEGFR/platelet-derived growth factor receptor (PDGFR)] (8), suppressing tumor cell proliferation and angiogenesis. Sorafenib has also shown efficacy in advanced renal cell carcinoma (RCC) and iodine-refractory thyroid cancer, expanding its applications (9). As an oral medication, it improves patient compliance and quality of life. This breakthrough laid the foundation for sorafenib's clinical use and provided an important reference for future targeted therapies for other cancers. The success of sorafenib marks the beginning of a new era

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in the treatment of HCC, offering new hope and treatment options for numerous patients.

Introduction to sorafenib and its clinical applications. Cancer remains a major threat, causing notable burdens for patients. The incidence of malignant tumors such as HCC and RCC continues to rise globally (10), and these cancers are often diagnosed at advanced stages, which complicates treatment. Traditional methods such as surgery, chemotherapy and radiation therapy offer limited improvement for patients with late-stage cancer (11). Previously, targeted therapies have gained attention (12). Since its introduction, sorafenib, a small-molecule TKI (13), has become a standard treatment. Sorafenib directly blocks autophosphorylation of receptor tyrosine kinases (RTKs) such as VEGFR1-3, PDGFR β , KIT proto-oncogene, RTK (c-Kit) and RET proto-oncogene (RET) (14), and inhibits Raf kinase subtypes. It targets RTKs involved in angiogenesis and tumor growth (15).

By inhibiting the VEGFR and PDGFR signaling axes, sorafenib reduces vascular endothelial proliferation, permeability and new vessel formation, thereby disrupting tumor angiogenesis (16). In parallel, it suppresses tumor cell proliferation by downregulating the Ras/Raf/MEK/ERK pathway, a key cascade in oncogenic signaling (17). The dual inhibition of angiogenesis and mitogenic signaling leads to both nutrient deprivation of the tumor microenvironment (TME) and direct cytostatic effects on tumor cells. Moreover, sorafenib can activate intrinsic apoptotic pathways by modulating Bcl-2 family proteins and promoting mitochondrial dysfunction (18). Sorafenib inhibits angiogenesis, tumor growth and induces apoptosis by targeting specific pathways (19). Its anti-proliferative and anti-angiogenic properties make it highly effective (20). Clinical studies have shown sorafenib markedly improves survival in patients with advanced HCC and RCC, extending median overall survival (OS) and delaying disease progression (21).

Limitations and challenges of sorafenib use. However, sorafenib faces challenges in clinical use. While it improves survival, its potent activity can cause side effects such as cardiac dysfunction, myocardial infarction, hypertension, hand-foot syndrome, acute hepatitis, skin reactions and fatigue. These adverse events are dose-dependent and vary widely among individuals, often limiting long-term tolerability and quality of life. Some patients develop severe grade 3 or 4 toxicities even at standard therapeutic doses, necessitating dose reduction or interruption (18).

Additionally, resistance may develop with prolonged use, reducing efficacy. Clinically, both primary resistance (intrinsic insensitivity from the outset) and secondary resistance (acquired after initial response) have been reported, and resistance mechanisms are often multifactorial and patient-specific (22). Optimizing sorafenib, minimizing side effects and improving tolerance remain crucial areas of research. Prolonged use of sorafenib is often associated with reduced efficacy, fluctuating plasma levels and reversible toxic effects on various organs, driven by both acquired resistance and variable metabolism, which may ultimately lead to treatment discontinuation (23).

The drug exhibits variable oral bioavailability and is subject to hepatic metabolism via cytochrome P450 3A4, leading to fluctuations in systemic exposure (24,25).

Furthermore, inter-patient differences in metabolic rates can contribute to unpredictable pharmacokinetics and inconsistent responses (26).

Increasing the dose of sorafenib may enhance antitumor effects but could compromise survival. Reducing toxicity and overcoming resistance are vital to avoid dose reduction or discontinuation, which could undermine treatment outcomes (27). A multidisciplinary approach is needed to improve efficacy and survival while managing adverse events. The present review summarizes drugs that can be combined with sorafenib to reduce efficacy, enhance effects and overcome resistance.

2. Sorafenib resistance and toxicity effects

Common resistance issues in sorafenib treatment. Sorafenib is recommended as a first-line treatment for advanced HCC (7). However, resistance may arise from several factors. While it has achieved encouraging results, resistance to sorafenib remains a major challenge, with most patients developing resistance within 6 months, leading to unsatisfactory survival rates (28).

Common resistance issues in sorafenib treatment for HCC. Sorafenib resistance in HCC arises from a few recurrent pathways that operate upstream of or parallel to RAF/VEGFR signaling (29). Primary epigenetic programs [such as SET domain containing protein 1A (SETD1A)-H3K4me3 with Yes1 associated transcriptional regulator (YAP)-TEA domain transcription factor (TEAD) transcription] set a permissive state, while treatment-induced remodeling of signaling pathways sustains survival via PI3K-AKT and Janus kinase (JAK)-STAT3 signaling and through MAPK reactivation despite RAF inhibition (30). Stress-adaptive pathways, including endoplasmic reticulum (ER) stress/unfolded protein response (UPR)-AMP-activated protein kinase (AMPK)-Unc-51-like kinase 1 (ULK1) autophagy and epithelial-mesenchymal transition (EMT) with AXL receptor tyrosine kinase (AXL)/MET proto-oncogene receptor tyrosine kinase (MET), fibroblast growth factor receptor 1 (FGFR) and integrin-focal adhesion kinase (FAK)-SRC proto-oncogene, non-receptor tyrosine kinase nodes (SRC), further inhibit apoptosis. The TME reinforces resistance through hypoxia/hypoxia-inducible factor 1 α (HIF-1 α) metabolic shifts and increased drug efflux [ATP binding cassette subfamily (ABC) B member 1/ABC G member 2], and this is consolidated by enhancer of zeste homolog 2-associated chromatin repression, microRNA (miR/miRNA) changes (such as miR-181a and loss of miR-122) and cancer stem cell circuits (Notch, Hedgehog and β -catenin). Convergent feedback through Src homology 2 domain-containing phosphatase 2 (SHP2) and bypass via FGF/FGFR, together with vessel co-option, explains incomplete responses to VEGF blockade and motivates use of rational combinations (such as VEGFR plus FGFR, MEK or mTOR add-ons; SHP2 or autophagy inhibition; and IL-6-JAK/STAT3 targeting) guided by biomarker stratification.

i) Primary resistance. Primary resistance can arise from genetic heterogeneity, impaired immune surveillance, rapid drug metabolism or poor absorption. A recurrent epigenetic

determinant is SETD1A, a histone methyltransferase that regulates H3K4me3 and sustains oncogenic transcriptional programs by activating key survival and pro-proliferative genes. This chromatin state attenuates Hippo inhibition and favors Hippo/YAP activation; YAP accumulates in the nucleus, engages TEAD and drives expression of its target genes (such as connective tissue growth factor and cysteine-rich angiogenic inducer 61). In turn, activated YAP upregulates anti-apoptotic factors (including BCL-XL and survivin) and cell-cycle drivers (such as cyclin D1), thereby counteracting sorafenib-induced cytotoxicity (31). Consistent with this mechanism, SETD1A knockdown reduces H3K4me3 at these loci, dampens YAP activity and notably restores sorafenib sensitivity (21,29). These intrinsic features create a permissive state for therapy-induced selection, favoring the survival of cell subpopulations with activated pro-survival programs, such as those with YAP-driven transcriptional activity (32) or overexpression of anti-apoptotic proteins like BCL-xL or MCL-1 (33), after which adaptive bypass signaling becomes the dominant mode of resistance.

ii) Acquired resistance. Acquired resistance often emerges after an initial benefit. The signaling in tumor cells is rewired to bypass the RAF/VEGFR blockade. For example, one route involves the PI3K/AKT axis: Upregulation of RTKs [such as EGFR, insulin-like growth factor 1 receptor (IGF1R) and c-MET/FGFR] activates class I PI3K, leading to phosphatidylinositol (3,4,5)-trisphosphate (PIP3) accumulation and recruitment of AKT to the membrane for phosphorylation by pyruvate dehydrogenase kinase 1 (PDK1; Thr308) and mTORC2 (Ser473) (34). Once active, AKT stabilizes myeloid cell leukemia-1 (MCL-1) via GSK3 β inhibition, suppresses FOXO-dependent Bcl-2-like protein 11 and promotes mTORC1-driven phosphorylation of eukaryotic translation initiation factor 4E binding protein 1 (4E-BP1) to enhance cap-dependent translation, thereby sustaining cell survival despite sorafenib treatment (35,36). A parallel route involves the JAK/STAT3 axis: Autocrine/paracrine IL-6-glycoprotein 130-JAK1/2 signaling yields constitutive STAT3 Tyr705 phosphorylation and nuclear translocation; STAT3 then transactivates anti-apoptotic genes (BCL-XL, MCL1, survivin) and cell-cycle drivers (cyclin D1, c-Myc) while inducing VEGFA. Furthermore, loss or epigenetic silencing of SOCS3 removes the negative feedback, collectively blunting sorafenib cytotoxicity (37-39). In addition, MAPK reactivation can arise through RAF dimerization or auxiliary kinases; for example, p21-activated kinase phosphorylates and activates RAF-1 at Ser338, providing an alternative route to sustain ERK output despite upstream inhibition, which can reinforce acquired resistance (40). In parallel with kinase-pathway rewiring, cells deploy stress-coping programs that buffer cytotoxic signaling.

iii) Autophagy mechanism limitation. Sorafenib has been shown to induce autophagy in tumor cells, functioning as an adaptive, cytoprotective response that allows cancer cells to survive under therapeutic stress (35,41). Mechanistically, sorafenib provokes ER stress and activates the UPR; the inositol-requiring enzyme 1 branch culminates in JNK activation, while the PERK arm phosphorylates eukaryotic translation initiation factor 2A and induces activating transcription factor 4 (ATF4), together increasing transcription of beclin-1 (BECN1), autophagy protein (ATG) 5 and ATG7 and

promoting autophagosome biogenesis; in parallel, activation of AMPK with concomitant inhibition of mTORC1 permits ULK1-dependent initiation of autophagy (42). Consequently, this pro-survival autophagy dampens sorafenib's cytotoxicity and contributes to acquired resistance (43). Consistent with this model, combining sorafenib with autophagy inhibitors [such as hydroxychloroquine (HCQ)] restores sensitivity and enhances its cytotoxic effects, and genetic blockade of autophagy (such as ATG7 knockdown) reduces LC3-II flux and augments apoptosis, thereby resensitizing tumors to sorafenib (44). Thus, targeting autophagy represents a plausible strategy to overcome sorafenib resistance. Sustained survival under stress facilitates phenotypic reprogramming, with EMT emerging as a key route to drug tolerance.

iv) EMT. EMT serves a critical role in promoting resistance to sorafenib by enhancing tumor cell invasiveness and reducing drug sensitivity (45,46). During EMT, the loss of epithelial markers (such as E-cadherin) and the acquisition of mesenchymal traits (such as N-cadherin and vimentin expression) enable tumor cells to evade apoptosis and assume a more aggressive phenotype (45,46). Mechanistically, EMT reroutes signaling toward alternative RTKs (including AXL/MET/FGFR) and integrin-FAK-SRC nodes, reactivating PI3K/AKT and ERK outputs despite RAF/VEGFR blockade. In addition, EMT-related transcription factors (Snail/twist family BHLH transcription factor 1/zinc finger E-box-binding homeobox 1) repress cadherin 1 and engage survival programs-including MCL-1/BCL-XL induction and mTORC1-dependent phosphorylation of 4E-BP1 to enhance eIF4E-mediated cap-dependent translation-thereby limiting drug-induced apoptosis (30). By contrast, sorafenib suppresses MEK/ERK signaling, lowers cyclin D1 expression and reduces phospho-eIF4E with concomitant MCL-1 downregulation-effects that EMT-driven bypass signaling can offset, culminating in a mesenchymal, drug-tolerant state (45). As EMT is reinforced by extrinsic cues, microenvironmental conditions, especially hypoxia, can further enhance resistance.

v) TME. Hypoxia within the TME drives adaptive resistance to sorafenib through HIF-1 α -centered programs: Stabilized HIF-1 α (via prolyl-hydroxylase inhibition and deubiquitylation by ubiquitin specific peptidase 29) transcriptionally upregulates glycolytic and acid-base regulators [glucose transporter 1 (GLUT1), hexokinase 2, PDK1, lactate dehydrogenase A (LDHA), carbonic anhydrase 9 (CAIX)], shifting metabolism toward aerobic glycolysis, lowering mitochondria-dependent apoptosis and sustaining survival under treatment pressure. In addition, HIF-1 α enhances drug efflux by increasing ABC transporters-most notably ABCB1-thereby reducing intracellular sorafenib levels. In parallel, hypoxia activates autophagy and mitophagy (including BCL2 interacting protein 3-PTEN induced kinase 1/Parkin and FOXO3a pathways), providing a cytoprotective buffer against kinase inhibition (30,47).

Beyond tumor cells, stromal and immune crosstalk reinforces resistance: M2 tumor-associated macrophages (TAMs) secrete hepatocyte growth factor (HGF) to drive MET-ERK signaling in a feed-forward loop, while myeloid-derived IL-6 engages JAK/STAT3 to expand stem-like tumor cells and blunt sorafenib cytotoxicity (48). Finally, although intratumoral efflux already limits drug accumulation, acquired-resistance models demonstrate upregulation of efflux transporters (such

as ABCG2) under chronic TKI pressure, thereby compounding TME-mediated resistance (49). Chronic microenvironmental stress is accompanied by durable epigenetic changes that lock in resistant states.

vi) Epigenetic regulation. Epigenetic alterations shape sorafenib response by reprogramming transcription and post-transcriptional control: IL-6/STAT3 signaling can upregulate DNA methyltransferase 3 β , driving promoter hypermethylation and silencing of tumor-suppressive negative regulators such as suppressor of cytokine signaling (SOCS) 1/3, which lifts feedback inhibition of JAK/STAT and supports survival and drug tolerance (47,50,51). In parallel, the H3K27 methyltransferase EZH2 is upregulated in sorafenib-resistant HCC; EZH2-driven repressive chromatin programs modulate NOTCH signaling and miRNAs (such as miR-21-5p/miR-26a-1-5p) to maintain stemness and resistance and genetic or pharmacologic EZH2 inhibition re-sensitizes cells to sorafenib (52). At the miRNA level, miR-181a directly suppresses Ras association domain family member 1, dampening pro-apoptotic signaling and inducing sorafenib resistance (53). Conversely, loss of miR-122, which is frequent in HCC, relieves inhibition of the IGF1R-RAS/RAF/ERK axis, providing a proliferative bypass that sustains survival under treatment (54). Such epigenetic programs help maintain stem-like subpopulations that are intrinsically tolerant to targeted therapy.

vii) Cancer stem cells. Liver cancer stem cells (LCSCs; such as CD133⁺/EpCAM⁺ subsets) sustain sorafenib tolerance by keeping PI3K/AKT and ERK signaling active through upstream RTKs and growth factors. Specifically, tumor-initiating programs activate IGF/FGF signaling to engage the PI3K/AKT pathway despite RAF/VEGFR inhibition, and CD133 stabilizes EGFR-AKT signaling to reinforce this bypass (55-57). Concurrently, LCSCs enhance drug efflux, most notably via ABCG2/BCRP, and the stemness factor SOX9 upregulates ABCG2, lowering intracellular sorafenib and promoting resistance (58). In addition, developmental pathways preserve the LCSC state and blunt therapy-induced apoptosis: Notch3 inhibition re-sensitizes HCC to sorafenib by lowering p21 expression and modulating GSK3 β (Ser9) (59); Hedgehog signaling drives resistance in CD44-high patient-derived organoids (60); and EPH receptor (EPH) B2- β -catenin activation amplifies LCSC traits and drives sorafenib resistance (61). Finally, sorafenib treatment can enrich EpCAM⁺ tumor-initiating cells, further predisposing patients to relapse (62). These LCSC-associated mechanisms align with broader precision-oncology observations that stem-like subpopulations often underlie targeted-therapy failure. At the signaling nexus, adaptor phosphatases integrate multiple RTK inputs that sustain these tolerant states.

viii) SHP2. SHP2 (PTPN11) is a non-receptor phosphatase that integrates RTK into the RAS-RAF-MEK-ERK and PI3K-AKT circuits by dephosphorylating docking proteins [such as GRB2 associated binding protein 1 (GRB2)] and scaffolding GRB2/Son of Sevenless (SOS), thereby promoting RAS-GTP loading. Under sorafenib pressure, compensatory upregulation of multiple RTKs (AXL, EGFR, EPH receptor A2, IGF1R) engages and activates SHP2 (including phosphorylation on Tyr542), restoring downstream ERK/AKT signaling and sustaining survival (63,64). Consistent with this adaptive

role, pharmacologic SHP2 inhibition (SHP099) or genetic silencing disrupts the feedback, triggers senescence/apoptosis and re-sensitizes HCC cell lines, organoids and xenografts to sorafenib (63). Clinically, PTPN11/SHP2 is overexpressed in a majority of HCCs and is associated with aggressive features and poor prognosis; reducing SHP2 diminishes tumor growth, supporting its value as a predictive/therapeutic biomarker for sorafenib combinations (65,66). Among the RTK-driven escapes, FGF/FGFR signaling provides a potent VEGF-independent conduit to reactivate ERK and AKT signaling.

ix) Upregulation of the FGF signaling pathway. Under VEGF inhibition by sorafenib, hypoxia and stromal cues upregulate FGF ligands—most notably FGF2—in tumor and perivascular compartments, thereby enabling evasive angiogenesis (67-69). Upon ligand engagement, FGFR1/2 (and FGFR4 in HCC) recruit fibroblast growth factor receptor substrate 2 (FRS2 α) and reactivate RAS-ERK and PI3K-AKT signaling despite VEGF/RAF blockade. In HCC, FGFR4 signaling drives a particularly strong FRS2-ERK output even in the presence of sorafenib (67,68). At the tumor cell level, FGF19-FGFR4 and FGF2-FGFR1 sustain ERK/AKT activity, proliferation and survival, and genetic or pharmacologic disruption of FGF19/FGFR4 restores sorafenib sensitivity (55,69). Therapeutically, co-targeting FGF/FGFR alongside VEGF/VEGFR can overcome or delay resistance, providing a mechanistic rationale for dual-pathway inhibition in this setting (70,71). Even when angiogenic signaling is restrained, tumors can maintain perfusion by structural adaptation of the vasculature.

x) Vessel co-option. Beyond sprouting angiogenesis, tumors can co-opt pre-existing vessels by collectively migrating along sinusoidal and other endothelial tracks; because this mode of vascularization is largely VEGF-independent, it remains poorly suppressed by VEGF/VEGFR blockade such as sorafenib (72,73). Mechanistically, anti-angiogenic pressure intensifies hypoxia and activates HIF-1 α -dependent programs that upregulate stromal cell-derived factor 1 α /C-X-C chemokine receptor type 4 (CXCR4) signaling and recruit pro-angiogenic bone marrow-derived cells together with TAMs/cancer-associated fibroblasts; acting in concert, these inputs restore perfusion and favor non-sprouting vascularization, including vessel co-option (20,72). These adaptations explain how tumors can maintain blood supply without *de novo* sprouting under VEGF inhibition, and why simultaneous targeting of escape axes [such as angiopoietin 2 (ANGPT2), placental growth factor, CXCR4] alongside VEGF may be required to blunt vessel co-option-driven resistance (72).

Taken together, this supports a systems-level view in which resistance arises from the interplay of intracellular survival programs (autophagy, EMT, epigenetic drift) with extrinsic microenvironmental rewiring (hypoxia-HIF signaling, stromal-immune crosstalk), rather than from any single dominant pathway (20).

Notably, the plasticity of cancer stem cells and their ability to reprogram survival signaling, such as PI3K/AKT or JAK/STAT3, enables both primary and acquired resistance (15). Furthermore, non-genetic adaptive processes such as vessel co-option and HIF-1 α -driven metabolic rewiring, underscore the challenge of targeting a dynamic,

heterogeneous tumor ecosystem (19). Therefore, combination strategies that integrate pathway inhibition (such as MEK, FGFR or autophagy inhibitors), microenvironmental modulation and biomarker-driven patient stratification (including SHP2 or EZH2 levels) may offer the most promising avenue for durable responses. Taken together, this evidence supports a shift from monotherapies to rational polytherapy tailored to tumor-specific resistance signatures.

Common resistance issues in sorafenib treatment for RCC. In RCC, sorafenib resistance centers on bypass signaling and stress adaptation: Under VEGF inhibition, pericyte-derived FGF2 activates FGFR2 and signals via the FRS2 α -GRB2/SOS adaptor complex to re-engage RAS-ERK and PI3K-AKT, while MET/IGF1R together with mTORC2/PDK1 fully activates AKT (67,74-76). Hypoxia/pseudohypoxia [HIF-2 α transactivation of polo-like kinase 1 (PLK1), HIF-1 α metabolic rewiring with MCT4-mediated lactate efflux] and long doublecortin-like kinase 1 (DCLK1) isoforms enforce stem-like, multi-TKI tolerance (77-79). Efflux increases through ABCG2/ABCB1/ABCC2, with NFE2 like BZIP transcription factor 2 (NRF2)-driven ABCG2 expression and lysosomal ABCB1 sequestration, while ncRNAs [miR-30a-BECN1, extracellular vesicle miR-31-5p-MutL homolog 1 (MLH1), sorafenib-resistance-related long nc (lnc)RNA (SRLR)-IL-6-JAK/STAT3, nuclear paraspeckle assembly transcript 1 (NEAT1)-miR-34a-MET] hard-wire resistance (80-89). Therapeutically, these insights lead to development of rational combinations of VEGFR plus FGFR co-targeting (67), MEK add-on and everolimus to suppress ERK reactivation and AKT/mTOR (74,90), efflux modulation (80) and ncRNA-guided autophagy or IL-6-JAK/STAT3 interventions (86).

i) ncRNA. miRNAs can tune the sorafenib response by modulating apoptosis-autophagy and DNA-repair pathways in RCC. For example, miR-30a directly suppresses BECN1 to inhibit autophagy, such that when miR-30a is downregulated, sorafenib-induced autophagy becomes pro-survival, whereas restoring miR-30a or pharmacologic autophagy blockade re-sensitizes RCC cells (86). Beyond cell-intrinsic regulation, resistant cells can export resistance cues: Extracellular-vesicle-shuttled miR-31-5p from resistant RCC cells targets MLH1 in recipient cells, impairing mismatch repair and propagating sorafenib resistance within the tumor (87). At the lncRNA layer, SRLR binds NF- κ B p65 at the IL-6 promoter to increase IL-6 transcription and activate JAK/STAT3 signaling; this STAT3-dependent survival program underlies intrinsic (primary) sorafenib resistance, which is reversed with IL-6/STAT3 inhibition (88). Complementarily, NEAT1 acts as a competing endogenous RNA that sponges miR-34a to de-repress c-MET, promoting EMT and chemoresistance, while NEAT1 knockdown increases sorafenib sensitivity in RCC cells (89). Other RCC-associated lncRNAs include kinesin family member 9-AS1, which sponges miR-497-5p to modulate TGF- β signaling and autophagy which increases the IC₅₀ of sorafenib, and PLK1S1, which sponges miR-653 to upregulate CXCR5, thereby enhancing proliferation and sorafenib resistance (91).

ii) Pro-angiogenic signaling pathway. Host genetics can shape sorafenib response in RCC: In a multi-center cohort, VEGFA rs1570360 and VEGFR2 rs2239702 were

associated with shorter progression-free survival (PFS)/OS with sorafenib treatment, consistent with a higher pro-angiogenic set-point under VEGF blockade (92). A phase-III pharmacogenomic analysis further found that VEGFR2 rs2071559 predicted PFS/OS in sorafenib-treated metastatic RCC (93). Under VEGF/VEGFR inhibition, tumors enlist pericyte-derived FGF2 to activate endothelial FGFR2, which via FRS2 α -GRB2/SOS reactivates RAS-ERK and PI3K-AKT signaling, preserving endothelial proliferation and perfusion independently of VEGF. Dual VEGFR/FGFR blockade (such as with lenvatinib) suppresses this adaptive angiogenesis and restores control in RCC models (67). With chronic VEGF-targeted pressure, alternative ligands (such as FGF, ANGPT, IL-8) are upregulated from tumor and stromal compartments, maintaining neovascularization despite VEGF inhibition (94).

iii) RAF/MEK/ERK and PI3K/AKT/mTOR pathways. As a type-II RAF inhibitor, sorafenib can facilitate RAF dimerization and cross-activation (notably RAF1), allowing MEK/ERK phosphorylation to increase under drug pressure; this, in turn, helps sustain proliferation and survival despite VEGFR inhibition. In RCC models, anti-angiogenic pressure also elevates p-ERK in the tumor endothelium, and adding a MEK inhibitor more completely extinguishes RAS-RAF-MEK-ERK signaling and enhances antitumor activity (74). In parallel, bypass RTKs (such as MET/IGF1R) activate PI3K to generate PIP3, recruiting AKT to the plasma membrane for phosphorylation by PDK1 (Thr308) and mTORC2 (Ser473), achieving full activation (95). Once active, AKT cooperates with ERK/ribosomal S6 kinase to phosphorylate and inhibit tuberous sclerosis complex 2 (such as at AKT Ser939/Thr1462), activating Ras homolog enriched in brain and switching on mTORC1 (75). Activated mTORC1 then hierarchically phosphorylates 4E-BP1, liberating eIF4E to drive cap-dependent translation that preferentially maintains short-lived anti-apoptotic proteins such as MCL-1, thereby counteracting sorafenib-induced apoptosis (76).

Clinically, early experience indicates that sorafenib combined with the mTOR inhibitor everolimus is tolerable at a maximum tolerated dose (everolimus 10 mg qd + sorafenib 400 mg bid) and shows antitumor activity in metastatic RCC, supporting vertical pathway inhibition of the AKT/mTOR axis in combination with sorafenib (90). Taken together with preclinical MEK-inhibitor co-treatment data, these observations demonstrate that dual-pathway inhibition of MAPK and PI3K/AKT/mTOR can suppress both ERK reactivation and pro-survival translation, two escape nodes underlying resistance in RCC.

iv) Intracellular drug disposition and efflux. Sorafenib is an active substrate of ABC transporters, transported efficiently by ABCG2 and more modestly by ABCB1; therefore, overexpression of these pumps lowers intracellular drug levels, whereas genetic or pharmacologic blockade (such as Ko143/elacridar) restores accumulation and sensitivity (80,81). Transcriptionally, oxidative-stress signaling via NRF2 directly drives ABCG2 expression by binding to an antioxidant-response element at -431/-420 bp in the ABCG2 promoter, thereby enhancing efflux capacity; such NRF2-driven ABCG2 upregulation is a recognized chemoresistance pathway (82). Clinically relevant to RCC, high ABCG2 expression is associated with worse

OS, supporting the importance of this efflux mechanism (83). Beyond these pumps, sorafenib is also transported by ABCB2; enforced ABCB2 expression increases the IC₅₀ and reduces intracellular sorafenib (84). Finally, intracellular sequestration contributes to sorafenib resistance: ABCB1-positive lysosomes can trap TKIs and promote exocytosis, reducing cytosolic target engagement; ABCB1 inhibition (such as with verapamil) partially reverses this phenotype and lowers the IC₅₀ of sorafenib in hepatocellular models, a paradigm likely pertinent to RCC as well (85).

v) Hypoxic TME. Hypoxia (or von Hippel-Lindau tumor suppressor loss-driven ‘pseudohypoxia’) stabilizes HIF- α , with HIF-2 α predominating in clear cell RCC; HIF-2 α can directly transactivate PLK1 via a hypoxia-response element, and high PLK1 promotes metastasis and TKI resistance—changes that blunt sorafenib efficacy (77). Concurrently, HIF-1 α reprograms the metabolism, upregulating GLUT1, PDK1, LDHA, CAIX and increasing MCT4-mediated lactate efflux, thereby enhancing glycolysis and inhibiting pyruvate dehydrogenase to lower mitochondrial reactive oxygen species (ROS) and apoptosis under treatment stress, reducing sorafenib's cytotoxicity (78). In addition, hypoxia nurtures stem-like subpopulations: Long DCLK1 isoforms (isoform-2/4) are enriched in RCC and drive aldehyde dehydrogenase 1 family, member A1 and HIF-1 α expression, spheroid self-renewal and resistance to RTKIs/mTOR inhibitors; genetic or antibody targeting of DCLK1 reverses these phenotypes (79). Experimentally, the RCC 786-O cell line under 1% O₂ exhibits HIF-2 α /COX-2-dependent sorafenib resistance that is mitigated by the COX-2 inhibitor NS-398. In addition, hypoxic 3D RCC models also demonstrate sorafenib resistance (96,97). Furthermore, hypoxia-induced stress can activate the NRF2-xCT antioxidant axis, whereby NRF2 upregulates xCT (the cystine/glutamate antiporter light-chain subunit), enhancing cystine uptake and glutathione biosynthesis, which strengthens redox defenses and contributes to sorafenib resistance in RCC (98,99).

Sorafenib resistance in RCC is increasingly recognized as a convergence of intrinsic molecular reprogramming and adaptive microenvironmental responses (100). The interplay between ncRNAs and epigenetic regulation facilitates resistance by reshaping gene expression without altering the DNA sequences, suggesting potential for RNA-targeted therapeutics (101).

Meanwhile, aberrant angiogenic signaling and the compensatory activation of survival pathways such as RAF/MEK/ERK and PI3K/AKT/mTOR illustrate how tumors bypass VEGFR inhibition. Additionally, intracellular drug efflux and metabolic reprogramming reduce sorafenib bioavailability, a challenge that may be mitigated through nanocarrier delivery systems or ABC transporter inhibitors (102). Hypoxia-driven dedifferentiation, particularly the emergence of stem-like RCC cells marked by DCLK1 isoform 2, highlights the need for therapies that target cellular plasticity and metabolic resilience (103). Based on the above, Fig. 1 summarizes and illustrates the mechanisms of sorafenib resistance in HCC and RCC. A deeper understanding of these mechanisms supports a precision medicine approach in which multi-targeted regimens are tailored to the molecular profile of resistance.

Toxicity of sorafenib and its impact on organs. Sorafenib is a multi-kinase inhibitor that, while effective against tumors, causes a spectrum of toxicities affecting multiple organ systems. These toxicities often overlap mechanistically, primarily stemming from sorafenib's inhibition of VEGF receptors, PDGFR, c-Kit, RAF kinases and other targets. In this section, sorafenib's major adverse effects are discussed, including cardiovascular toxicity, bleeding, dermatologic reactions, gastrointestinal and renal toxicities, with an emphasis on their molecular mechanisms.

Cardiovascular toxicity. Sorafenib commonly induces hypertension, often within the first weeks of treatment. Mechanistically, this is an on-target effect of VEGF pathway inhibition. Under normal physiology, VEGF signaling maintains endothelial health and induces nitric oxide (NO) production for vasodilation. Sorafenib's inhibition of VEGFR acutely reduces endothelial NO release, causing unopposed vasoconstriction and removes an endothelial survival signal, leading to capillary rarefaction (104). Sorafenib-induced hypertension can cause cardiac dysfunction, including left ventricular ejection fraction impairment, heart failure and coronary artery disease (105). Patients should undergo cardiac function tests and be monitored carefully (106).

Hypertension. Hypertension is dangerous, as it increases cardiac afterload and impairs the heart's ability to cope with pressure overload, thereby promoting ventricular dysfunction (107). Additionally, VEGF signaling inhibition leads to endothelial dysfunction via oxidative stress and NO reduction, which accelerates atherosclerosis (108). Clinically, sorafenib has been associated with arterial thromboembolic events, such as myocardial infarction and ischemia (109). The mechanism of sorafenib-related arterial thromboembolism (ATE) is associated with endothelial injury and a prothrombotic state: Normally, endothelial cells provide antithrombotic protective surfaces, but sorafenib-induced VEGF inhibition alters these properties (110). Endothelial dysfunction (such as reduced NO and prostacyclin) and damage can expose pro-coagulant surfaces and increase platelet adhesion, heightening the risk of thrombosis (111). Notably, VEGF pathway inhibitors are known to roughly double the incidence of arterial thrombotic events in patients with cancer (112); therefore, anti-thrombotic therapy is recommended (113).

Bleeding tendencies. Paradoxically, while sorafenib can cause thrombosis, it also increases the risk of bleeding in patients (114). Severe hemorrhagic events (such as gastrointestinal bleeding), some of which are life-threatening, have been reported (109), and patients may have an elevated risk of major hemorrhage, especially in tumor sites or organs predisposed to bleed (115). Clinicians should be vigilant for signs of bleeding and correct any coagulopathies. In those with a high bleeding risk, sorafenib should be used cautiously, and if severe hemorrhage occurs, drug discontinuation is usually warranted (54).

Dermatological toxicity. Sorafenib's most characteristic toxicity is a hand-foot skin reaction (HFSR), a dose-limiting dermatologic condition. HFSR typically presents within 2–4 weeks of therapy (116). At the molecular level, recent research has elucidated a crosstalk mechanism between endothelial cells and keratinocytes in sorafenib-induced HFSR (117). Sorafenib's inhibition of VEGFR in skin microvasculature causes damage to dermal endothelial cells, which

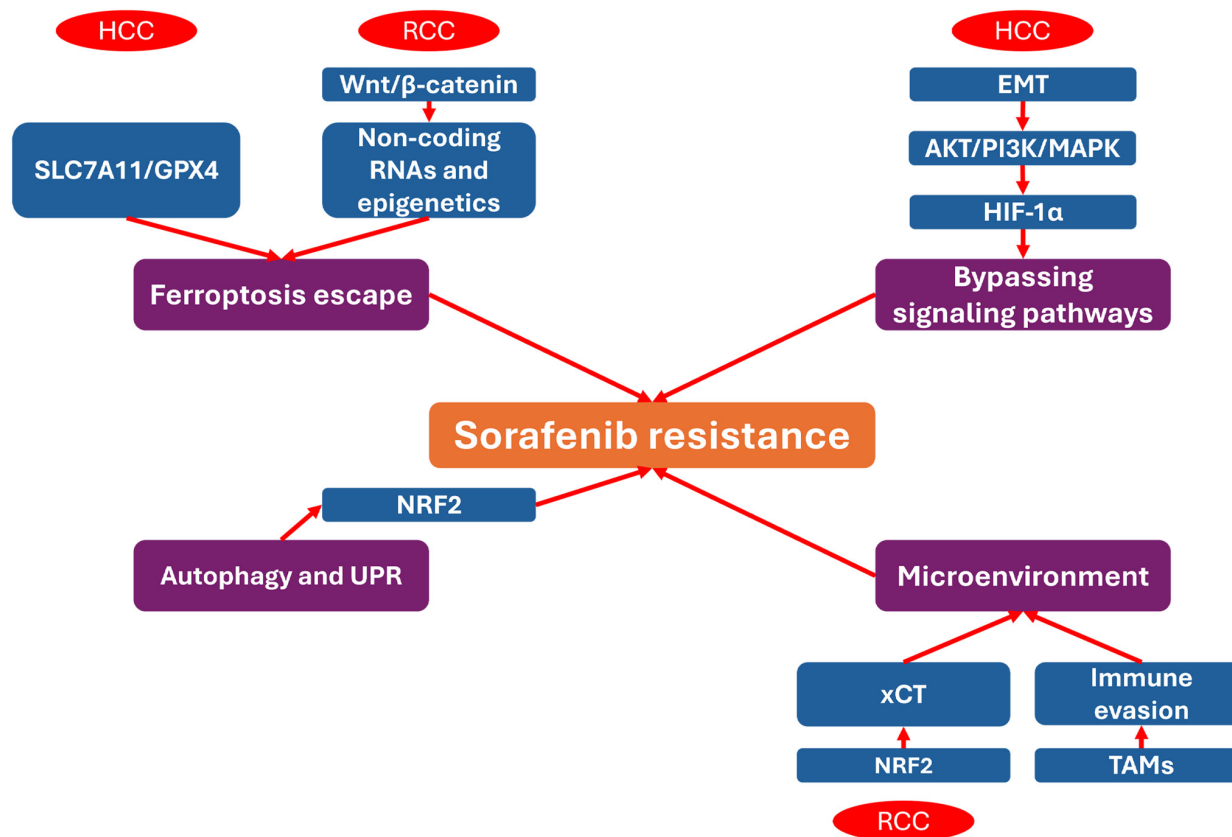


Figure 1. Mechanisms of sorafenib resistance in HCC and RCC. HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; NRF2, NFE2 like BZIP transcription factor 2; TAMs, tumor-associated macrophages; EMT, epithelial-mesenchymal transition; HIF-1 α , hypoxia-inducible factor 1 α ; xCT, cystine/glutamate antiporter light-chain subunit.

then release soluble heparin-binding EGF-like growth factor (HB-EGF) (118). The shed HB-EGF acts on epidermal keratinocytes by activating EGFR signaling, which in turn triggers the JNK2/sirtuin 1 pathway, driving keratinocyte hyperproliferation and abnormal differentiation (hyperkeratosis). This cascade ultimately produces the thickened stratum corneum and lesions characteristic of HFSR (118). Histologically, biopsy of HFSR lesions shows keratinocyte necrosis in the epidermal basal layer and capillary damage (119). Preventive measures (such as keratolytic creams, callus removal and avoiding friction or pressure) are recommended. If HFSR becomes grade 2 or 3 (painful, limiting function), dose reduction or temporary interruption of sorafenib along with topical steroid creams can help manage symptoms (113,120). Notably, the development of HFSR has been associated with improved tumor responses in certain studies (121,122), suggesting it may be a marker of sorafenib's pharmacodynamic effect.

Gastrointestinal toxicity. Sorafenib frequently causes diarrhea, which is usually mild to moderate but can affect quality of life (123). Diarrhea often occurs early in treatment and is considered to be dose-dependent (124). At the molecular level, the precise mechanism of sorafenib-induced diarrhea is not fully understood, but several hypotheses exist. Sorafenib may directly injure the gastrointestinal mucosa or alter intestinal epithelial turnover through off-target effects on kinases in the GI tract. VEGFR and PDGFR are expressed in intestinal vasculature and stromal cells; their inhibition could compromise mucosal blood flow or repair mechanisms,

leading to mucosal inflammation or malabsorption (125,126). Additionally, alteration in the gut microbiota has been implicated: A recent preclinical study in mice found that sorafenib disturbs the gut microbiome, leading to intestinal inflammation, oxidative stress, and tissue damage (127). This dysbiosis-induced mucosal injury could contribute to diarrhea. In practice, sorafenib-related diarrhea is usually manageable with anti-motility agents (such as loperamide) and dose modification. Patients should stay hydrated and report severe or persistent diarrhea (113). Fortunately, diarrhea rarely necessitates permanent drug discontinuation, but supportive care is essential to maintain nutritional status and comfort.

Nephrotoxicity. Renal toxicity from sorafenib manifests primarily as proteinuria and, less commonly, as reduced renal function or acute kidney injury. The incidence of high-grade nephrotoxicity is relatively low, as sorafenib is mainly metabolized by the liver (128). However, even subtle effects on the kidney are of mechanistically importance. VEGF signaling is crucial for glomerular health as VEGF produced by podocytes maintains the fenestrated glomerular endothelium and the integrity of the slit diaphragm (129). Sorafenib's anti-VEGF activity disrupts this homeostasis. Inhibition of the VEGF axis in the kidney leads to the downregulation of nephrin, a key protein of the slit diaphragm that prevents protein leakage (128). Consequently, the glomerular filtration barrier becomes leaky, causing proteinuria. Notably, combining sorafenib with other VEGF inhibitors (such as bevacizumab) may further impair the pathways that maintain glomerular

integrity (130). In summary, sorafenib's nephrotoxicity is chiefly due to its anti-angiogenic impact on the glomerulus, leading to proteinuria and rarely acute renal failure.

Hepatotoxicity. As an oral therapy often used in HCC, sorafenib is administered to patients with preexisting liver dysfunction, making it essential to distinguish drug-induced liver injury from underlying disease progression. Nonetheless, sorafenib itself can cause hepatotoxicity, ranging from asymptomatic liver enzyme elevations to rare cases of severe hepatitis or hepatic necrosis (131). The mechanism of sorafenib-induced hepatotoxicity involves oxidative stress and mitochondrial dysfunction in hepatocytes. Experimental studies in rats have reported that sorafenib treatment induces oxidative stress in the liver, evidenced by increased markers such as NF- κ B and p65 and reduced levels of antioxidant enzymes. This pro-oxidant state leads to damage to cellular components and triggers apoptotic pathways in hepatocytes (132). Specifically, sorafenib has been shown to upregulate pro-apoptotic proteins (Bax, cleaved caspase-3) and downregulate the anti-apoptotic protein Bcl-2 in liver tissue. The result is enhanced hepatocyte apoptosis and occasional hepatocellular necrosis (33,133). In addition, the metabolic activation of sorafenib in the liver may generate reactive intermediates that injure hepatocytes. Long-term sorafenib use has been associated with decreased activity of antioxidant defenses (such as glutathione peroxidase and superoxide dismutase), further exacerbating oxidative injury (134).

Clinically, 8-11% of sorafenib-treated patients experience notable elevations in alanine aminotransferase (ALT) or bilirubin. It is recommended to monitor liver function tests (LFTs) periodically during therapy (135). Patients should be counseled to report symptoms of liver injury (such as jaundice, dark urine and abdominal pain). If drug-induced hepatitis is suspected [for example ALT $>5\times$ upper limit normal (ULN) or bilirubin $>3\times$ ULN causally linked to sorafenib], the drug should be withheld. Supportive care and corticosteroids (in cases of immune-mediated injury) may be employed, although the primary management is cessation until LFTs normalize (114). Notably, in patients with liver cancer, some hepatotoxicity may also result from the cancer itself or underlying cirrhosis; thus, clinical judgment is needed to attribute causality. Overall, sorafenib's hepatotoxicity is considered to result from oxidative stress and apoptosis in hepatocytes, and while uncommon, it can limit therapy if severe.

Fatigue. Fatigue is among the most frequently reported systemic side effects of sorafenib. Patients often experience profound tiredness, weakness and lack of energy during the first weeks to months of treatment (136). This fatigue can be multifactorial. A notable contributor is sorafenib-induced hypothyroidism. Sorafenib and other multi-kinase inhibitors can affect thyroid function, possibly by damaging thyroid follicular cells or reducing thyroid peroxidase activity, although the exact mechanism is unclear (137). Clinical studies have noted that 20-30% of patients on long-term sorafenib develop elevated thyroid stimulating hormone levels or reduced thyroid hormone concentrations (137,138). Even subclinical hypothyroidism can cause symptoms of fatigue, lethargy, cold intolerance and a depressed mood. Indeed, Cancer Research UK notes that sorafenib may lower thyroid hormone levels and patients 'might feel tired, cold, sad or

depressed' as a result (139). Therefore, monitoring thyroid function during therapy is advisable, and thyroid hormone replacement can markedly improve sorafenib-related fatigue in such cases (137).

Aside from thyroid issues, fatigue may also stem from sorafenib's effects on energy metabolism. Sorafenib can induce a catabolic state with loss of appetite and weight, and it may impair mitochondrial function in muscle cells (due to its effect on RAF/ERK and AMPK pathways), leading to reduced endurance (140). Additionally, chronic low-grade toxicities (such as diarrhea and hand-foot pain) and the underlying cancer itself contribute to persistent fatigue. Patients should be encouraged to engage in light physical activity as tolerated, maintain adequate nutrition and rest as needed. Typically, sorafenib-related fatigue is most pronounced in the first 1-2 months and may improve over time. If fatigue is severe (grade 3) and limits self-care, a dose reduction or temporary interruption can be considered until symptoms improve (136). Managing contributing factors (such as hypothyroidism or anemia) is also essential for alleviating fatigue.

Alopecia and hair changes. Some patients on sorafenib experience thinning of the hair or alopecia, which is usually reversible. Hair loss can range from diffuse thinning across the scalp to patchy areas hair loss, and in rare instances, nearly total alopecia, although complete baldness is uncommon (141). Patients might also notice changes in hair texture or color (such as hair becoming dry, brittle or turning white). The underlying mechanism involves sorafenib's impact on hair follicles dynamics and pigmentation pathways (142). Hair follicles are highly proliferative and rely on growth factor signaling to regulate their cycle. Sorafenib's inhibition of the RAF/MEK/ERK pathway likely reduces keratinocyte proliferation in the hair matrix, shortening the anagen (growth) phase of hair (143).

Moreover, sorafenib targets c-Kit, the receptor for stem cell factor (SCF). The SCF/c-Kit signaling axis is crucial for melanocyte function within hair and for the maintenance of hair follicle stem cells. Inhibition of c-Kit can lead to hair depigmentation (loss of hair color) and fragility; indeed, a related TKI (sunitinib) causes a well-known syndrome of intermittent hair depigmentation through this mechanism (144). Similarly, sorafenib's effect on c-Kit and other follicular signaling pathways is considered to contribute to alopecia and pigmentary changes (145,146). Essentially, the drug may injure rapidly dividing cells within the hair bulb and disturb signaling pathways (such as SCF, PDGF, VEGF) that nourish the follicle, causing hairs to shed or grow abnormally (145).

Biopsies in some cases of sorafenib-associated alopecia showed non-scarring hair loss with perifollicular inflammation, suggesting an inflammatory component as well (147). In most patients, hair loss begins after 1-2 months of therapy and is relatively mild; notable alopecia is less common. Management is supportive: Patients should be reassured that hair typically regrows after discontinuing sorafenib (or occasionally even while continuing, as the body adapts) (144). Gentle hair care is advised (avoiding harsh chemicals and tight hairstyles). If cosmetically distressing, options include using wigs or hairpieces during therapy. In some reports, temporary dose reduction helped hair to regrow, but as alopecia is not medically harmful, the priority is cancer control unless the patient's quality of life is seriously impacted. Notably, hair changes

indicate the drug's on-target pharmacological activity; for example, hair depigmentation results directly from c-Kit inhibition in melanocytes, which parallels sorafenib's therapeutic action on c-Kit mutant tumors (148). Thus, while bothersome, such side effects can be viewed as a pharmacodynamic effect of sorafenib.

Overall, sorafenib's toxicity profile is characterized by these on-target effects of kinase inhibition in non-tumor tissues. A number of side effects (hypertension, proteinuria, HFSR) are mechanistically associated with its anti-angiogenic activity, whereas others (fatigue, alopecia) involve off-target effects on hormonal and proliferative pathways. Understanding the molecular basis of these toxicities helps clinicians anticipate and manage them effectively. Dose modification, symptomatic treatments and patient education can mitigate most adverse reactions, allowing patients to continue sorafenib therapy when the therapeutic benefit outweighs toxicity. In severe cases, however, treatment interruption or permanent discontinuation is warranted to ensure patient safety.

3. Combination therapy strategies to enhance the efficacy of sorafenib

Sorafenib as a single agent has shown promising activity in certain cancers, such as RCC, HCC and thyroid cancer. However, numerous clinical studies have demonstrated limitations when sorafenib is used alone in treating other types of cancer (149), including poor pharmacokinetics, low bioavailability, development of resistance and side effects. In combination therapy, the common strategy is to synergistically enhance sorafenib's antitumor effects while reducing its toxicity to protect patients (150).

Enhancing the efficacy of sorafenib with combination therapy. A variety of combination strategies have been developed to enhance the therapeutic efficacy of sorafenib. These strategies mainly fall into three broad categories: i) Targeting key oncogenic signaling pathways, such as the PI3K/AKT/mTOR axis; ii) inducing oxidative stress to sensitize tumor cells; and iii) modulating cellular survival mechanisms, including autophagy and apoptosis. In the following sections, representative combination therapies under each of these mechanistic categories are systematically reviewed, highlighting the underlying molecular rationale and potential therapeutic advantages. Table I summarizes the investigated sorafenib-based drug combinations alongside their respective mechanisms and research stages (preclinical or clinical), providing a comprehensive reference for translational relevance.

Inhibition of the PI3K/AKT/mTOR signaling pathway.

i) PI3K/AKT/mTOR. The PI3K/AKT/mTOR pathway serves a pivotal role in cell proliferation, metabolism and survival, and its hyperactivation is often associated with sorafenib resistance (151). Targeting this pathway can restore sorafenib sensitivity and enhance apoptosis (152).

ii) Paris saponin (RPS). A natural compound from *Paris polyphylla*, RPS enhances sorafenib efficacy by regulating p53 expression. Although promising *in vitro* and *in vivo*, its pharmacokinetic profile and clinical feasibility remain to be fully elucidated (153).

iii) Curcumin. Curcumin inhibits aerobic glycolysis and sensitizes HCC cells to sorafenib. This approach addresses the Warburg effect, a metabolic reprogramming in which cancer cells preferentially rely on aerobic glycolysis rather than oxidative phosphorylation even in the presence of oxygen; however, the low bioavailability of curcumin remains a major obstacle to clinical translation (154).

iv) Artesunate (ART). ART disrupts the PI3K/AKT/mTOR and induces ferroptosis. The dual mechanism involving combining pathway inhibition and oxidative stress offers a promising strategy for multi-target synergy (155).

v) PI-103. A dual PI3K/mTOR inhibitor, PI-103 enhances the efficacy of sorafenib by simultaneously inhibiting the Ras/MAPK and PI3K pathways. This combined inhibition confers broad-spectrum cytotoxicity but may elevate the risk of systemic toxicity (102).

vi) LY3214996. LY3214996 is a selective ERK inhibitor which enhances apoptosis when combined with sorafenib by suppressing MAPK/ERK and PI3K pathways. However, reactivation of the ERK pathway is common, warranting further *in vivo* evaluation (156).

In summary, targeting the PI3K/AKT/mTOR axis effectively restores sorafenib sensitivity, although numerous studies remain preclinical and face translational limitations due to pharmacodynamics and toxicity concerns.

Increasing oxidative stress. Oxidative stress, through the accumulation of ROS, promotes cancer cell death. Several agents enhance sorafenib efficacy by disrupting redox homeostasis (157).

i) Metformin. Metformin, widely used in the treatment of diabetes, induces ferroptosis and elevates ROS levels when combined with sorafenib. While preclinical data are strong, optimal dosing and appropriate patient stratification remain necessary for clinical translation (63,158).

ii) Proteasome inhibitors. Proteasome inhibitors induce ER stress and DNA damage; sorafenib enhances their effects by modulating the UPR. Dual targeting of protein homeostasis and redox pathways may trigger synthetic lethality, but poses a risk of off-target effects (159).

iii) Diclofenac. As a non-steroidal anti-inflammatory drug (NSAID), diclofenac enhances ROS production via mitochondrial disruption. This mechanism is straightforward and cost-effective, but lacks specificity and supporting clinical evidence (160).

iv) HCQ. HCQ reverses sorafenib resistance by regulating autophagy and oxidative DNA damage through the toll like receptor 9/superoxide dismutase 1/hsa-miR-30a-5p/BECN1 axis. This multistep regulation highlights the role of immune-autophagy cross-talk but is mechanistically too complex for clinical validation (161).

Collectively, oxidative stress inducers sensitize tumors to sorafenib, but the precise ROS thresholds and potential off-target toxicities require further investigation.

Synergistic mechanism of small molecules and natural products. In addition to well-defined pathway-specific inhibitors, a number of natural products and small-molecule compounds have been shown to enhance the efficacy of sorafenib through multi-target or pleiotropic mechanisms. These agents often exert synergistic effects by simultaneously modulating multiple signaling pathways (such as PI3K/AKT,

Table I. Drug combinations and research stage.

Model	Drug/compound	Mechanism category	Combination purpose	Research stage	(Refs.)
Mouse	Paris Saponin (RPS)	PI3K/AKT/mTOR inhibition	Enhance efficacy	Preclinical (<i>in vitro/in vivo</i>)	(152)
Mouse	Curcumin	PI3K/AKT/mTOR inhibition	Enhance efficacy	Preclinical	(153)
Human liver cancer cells, nude mice	Artesunate	PI3K/AKT/mTOR inhibition, ferroptosis	Enhance efficacy	Preclinical	(154)
Human liver cancer cells, nude mice	PI-103	Dual PI3K/AKT and mTOR inhibition	Enhance efficacy	Preclinical	(155)
Human liver cancer cells	LY3214996	ERK inhibition	Enhance efficacy	Preclinical	(156)
Human liver cancer cells	Metformin	Oxidative stress, ferroptosis	Enhance efficacy	Preclinical and clinical	(63,158)
Human liver cancer cells	Metformin	Oxidative stress, ferroptosis	Enhance efficacy	Preclinical and clinical	(63,158)
Human liver cancer cells	Proteasome inhibitors	ER stress, ROS	Enhance efficacy	Preclinical	(159)
Human liver cancer cells, nude mice	Diclofenac	Mitochondrial ROS	Enhance efficacy	Preclinical	(160)
Human liver cancer cells	Hydroxychloroquine	Autophagy/oxidative DNA damage via TLR9	Overcome resistance	Preclinical	(161)
Human liver cancer cells	Wogonin	Autophagy inhibition	Enhance efficacy	Preclinical	(162)
MOGCCM, T98G	Quercetin	Hsp27/Hsp72 inhibition	Enhance efficacy	Preclinical	(163,164)
Kidney cancer cells	TRAIL + HDACi	Death receptor activation and HDAC inhibition	Enhance efficacy	Preclinical	(166,167)
Human liver cancer cells, rats	Crocin	Oxidative stress and apoptosis	Enhance efficacy	Preclinical	(168)
Human liver cancer cells	Biochanin A	Cell cycle and mitochondrial apoptosis	Enhance efficacy	Preclinical	(169)
Rats	Ascorbic acid	Ca ²⁺ homeostasis disruption	Enhance efficacy	Preclinical	(170)
Human liver cancer cells, mice, nude mice	Melatonin	Multiple: Apoptosis, autophagy, ROS	Enhance efficacy	Preclinical	(171-175)
Human liver cancer cells	Regorafenib	Inhibit EMT (ERK/STAT3)	Overcome resistance	Clinical (approved)	(176)
Human liver cancer cells	3-Methyladenine	Autophagy inhibition	Overcome resistance	Preclinical	(177)
Human liver cancer cells, mice	Aspirin	Glycolysis inhibition	Overcome resistance, reduce toxicity	Preclinical	(178)
Human liver cancer cells, mice	Dichloroacetate	OXPHOS activation	Overcome resistance	Preclinical	(179)
Human liver cancer cells, mice liver cancer cells, mice	Silybin	STAT3/ERK/AKT inhibition	Overcome resistance	Preclinical	(180)
Mouse	Apigenin	Antioxidant/anti-inflammatory	Reduce renal toxicity	Preclinical	(182)
Mouse, rat	ATF4	UPR/glutathione elevation	Reduce cardiotoxicity	Preclinical	(184)

Table I. Continued.

Model	Drug/compound	Mechanism category	Combination purpose	Research stage	(Refs.)
Mouse, rat	Nobiletin	Antioxidant, anti-cardiotoxic	Reduce cardiotoxicity	Preclinical	(135)
Rat myocardial cells, mice	Ferostatin-1	Ferroptosis inhibition	Reduce cardiotoxicity	Preclinical	(185)
Mouse	Lupeol	Antioxidant, redox homeostasis	Reduce hepatorenal toxicity	Preclinical	(186)

ER, endoplasmic reticulum; ROS, reactive oxygen species; TLR9, toll like receptor 9; Hsp, heat shock protein; HDAC, histone deacetylase; EMT, epithelial-mesenchymal transition; OXPHOS, mitochondrial oxidative phosphorylation; ATF4, activating transcription factor 4; UPR, unfolded protein response.

ERK and STAT3), redox homeostasis or cellular stress responses. Although their precise molecular targets may be less well-defined, their integrated biological effects make them promising candidates for combination therapy. This section discusses representative compounds with such multifaceted mechanisms.

i) Wogonin. Wogonin inhibits autophagy and promotes apoptosis with minimal toxicity to normal cells. However, it lacks *in vivo* validation for safety and systemic delivery (162).

ii) Quercetin. Quercetin blocks heat shock proteins (HSP) 27 and 72, enhancing sorafenib-induced apoptosis. Targeting HSPs provides a novel therapeutic angle, but greater specificity is required (163,164).

iii) SHP099. SHP099 inhibits SHP2, thereby blocking RTK feedback loops activated in response to sorafenib. This represents a rational combination strategy, especially in RTK-driven tumors, but clinical validation is still lacking (165).

iv) TRAIL and histone deacetylase (HDAC) inhibitors. TRAIL and HDAC inhibitors trigger activation of death receptors and modulate gene expression via epigenetic mechanisms. The synergy is mechanistically attractive, but clinical tolerability of HDAC inhibitors remains a concern (166,167).

v) Crocin. The carotenoid, Crocin, reduces oxidative stress and inflammation, thereby enhancing apoptosis. Its efficacy has been primarily validated in murine models, and data on its bioavailability remain limited (168).

vi) Biochanin A. The isoflavone biochanin A induces mitochondrial apoptosis and arrests the cell cycle. Isoflavones exhibit multitarget effects but lack pharmacokinetic studies in humans (169).

vii) Ascorbic acid (vitamin C). Ascorbic acid enhances calcium imbalance and membrane disruption in HCC cells. It is simple and safe, but dosage and delivery remain key issues (170).

viii) Melatonin. Melatonin is a physiological hormone primarily secreted by the pineal gland, with a wide range of biological functions, including physiological regulation, antioxidant activity, anti-inflammatory effects, immune modulation and antitumor properties. It shows potential as an adjunct chemotherapy agent for various cancers and modulates signaling pathways involved in cell proliferation, apoptosis, survival, ER stress and autophagy.

Melatonin has been shown to enhance the antitumor efficacy of sorafenib through multiple synergistic mechanisms. Firstly, melatonin promotes apoptosis in HCC cells by markedly downregulating the Bcl-2/Bax ratio in HepG2 cells, thereby increasing apoptotic rates (171). In parallel, it inhibits cytoprotective autophagy via the PERK-ATF4-BECN1 signaling axis, sensitizing HCC cells to sorafenib-induced cytotoxicity by disrupting autophagic flux (41). Additionally, melatonin potentiates sorafenib-induced apoptosis through the activation of the JNK/c-Jun pathway and cleavage of caspase-3, further amplifying apoptotic signaling cascades (172).

Moreover, under normoxic conditions, melatonin suppresses the mTORC1/p70S6K/HIF-1 α pathway in Hep3B cells, thereby reducing hypoxia-induced mitophagy and enhancing sorafenib's cytotoxicity (173). This effect is complemented by melatonin-induced early mitochondrial autophagy, which leads to excessive ROS production, mitochondrial membrane depolarization and ultimately increased apoptosis

Table II. Combinations to reduce sorafenib resistance.

Model	Active substance	Effect	Mechanism	(Refs.)
Human liver cancer cells	Regorafenib	Reduces resistance	Inhibits p-ERK and p-STAT3, blocks HGF-induced EMT	(176)
Human liver cancer cells	3-Methyladenine	Reduces resistance	Inhibits autophagosome formation	(177)
Human liver cancer cells, mice	Aspirin	Reduces resistance	Regulates glycolysis and apoptosis	(178)
Human liver cancer cells, mice	Dichloroacetate	Reduces resistance	Activates OXPHOS	(179)
Human liver cancer cells, mice liver cancer cells, mice	Silybin	Reduces resistance	Increases STAT3/ERK/AKT phosphorylation	(180)

HGF, hepatocyte growth factor; EMT, epithelial-mesenchymal transition; OXPHOS, mitochondrial oxidative phosphorylation.

and reduced cell viability (174). Finally, melatonin contributes to cell cycle regulation by activating the AKT/p27 signaling pathway, resulting in cell growth arrest and increased sensitivity to sorafenib (175).

Together, these findings underscore the potential of melatonin as a multifaceted adjuvant that not only enhances apoptosis and inhibits autophagy, but also modulates hypoxia and cell cycle pathways, thereby improving the overall efficacy of sorafenib in HCC. Melatonin demonstrates excellent synergistic effects in combination therapy, and further investigation into the mechanisms underlying its interaction with sorafenib is warranted.

In summary, although these natural products and small molecules do not target a single canonical pathway, their ability to exert synergistic effects through multi-level modulation of cellular signaling, stress responses and metabolic balance supports their therapeutic value. These agents represent a versatile class of adjuvants that complement the pathway-specific inhibitors discussed in previous sections. A more refined mechanistic understanding of these compounds could facilitate their integration into rational polytherapy regimens.

Combination therapies to reduce sorafenib resistance. This section focuses on combination therapies designed to mitigate sorafenib resistance. For an overview of key combination strategies targeting resistance mechanisms, Table II summarizes representative agents, their molecular targets and experimental stages.

Regorafenib. Regorafenib is an oral diphenylurea multi-kinase inhibitor that targets angiogenesis (VEGFR1-3, TEK receptor tyrosine kinase), tumor stroma (PDGFR- β , FGFR) and oncogenic receptor tyrosine kinases (KIT, RET and RAF). It reverses sorafenib resistance by inhibiting p-ERK and p-STAT3 signaling, thereby blocking HGF-induced EMT—a key mechanism in resistance development (176). These findings are primarily derived from *in vitro* and *in vivo* models; therefore, further clinical validation is warranted.

3-Methyladenine (3-MA). 3-MA is a classical autophagy inhibitor that functions by blocking PI3K. By preventing autophagosome formation, 3-MA reduces cytoprotective autophagy, which has been implicated in sorafenib resistance. Its combination with sorafenib enhances apoptosis and suppresses tumor viability in HCC cell models (177). However, this mechanism has yet to be validated in clinical studies.

Aspirin. Aspirin (acetylsalicylic acid) is a widely used NSAID with anti-inflammatory and antiplatelet properties. When combined with sorafenib, it enhances apoptosis in resistant HCC cell lines by downregulating glycolysis via the HIF-1 α /6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3/phosphofructokinase-1 signaling pathway. This metabolic reprogramming improves efficacy and may also mitigate sorafenib-induced adverse effects (178). However, supporting data from *in vivo* or clinical studies remain limited.

Dichloroacetate (DCA). DCA is a PDK inhibitor that shifts cancer cell metabolism from glycolysis toward mitochondrial oxidative phosphorylation. This metabolic reprogramming reverses resistance to sorafenib by restoring mitochondrial respiration, which is typically suppressed in resistant phenotypes. Preclinical data suggest strong synergy with sorafenib in overcoming resistance, although the underlying mechanistic details remain under investigation (179).

Silybin. Silybin is a bioactive flavonolignan derived from milk thistle, traditionally used as a hepatoprotective agent. Recent studies indicate that silybin can enhance sorafenib efficacy by modulating STAT3, ERK and AKT signaling pathways, which are frequently hyperactivated in resistant HCC cells and stem-like subpopulations (180,181). This dual targeting of both the bulk tumor and cancer stem cells suggests therapeutic potential, although no clinical data currently support this application (180).

Combination therapies to reduce sorafenib toxicity. In this section, combination therapies aimed at reducing sorafenib toxicity are explored. Table III summarizes various protective agents that mitigate organ damage associated with sorafenib,

Table III. Combinations to reduce sorafenib toxicity.

Model	Active substance	Effect	Mechanism	(Refs.)
Mouse	Apigenin	Reduces toxicity, protects liver	Antioxidant, reduces chromosomal abnormalities	(182)
Mouse, rat	ATF4	Reduces heart toxicity	Upregulates GSH to promote cell survival	(184)
Mouse, rat	Nobiletin	Reduces heart toxicity	Downregulates NLRP3/TLR4 signaling, inhibits apoptosis	(135)
Rat myocardial cells, mice	Ferrostatin-1	Reduces heart toxicity	Inhibits lipid peroxidation and damage in myocardial cells	(185)
Mouse	Lupeol	Reduces liver and kidney toxicity	Reduces oxidative stress, restores redox system	(186)

ATF4, activating transcription factor 4; GSH, glutathione; NLRP3, NLR family pyrin domain containing 3; TLR4, toll like receptor 4.

with a particular focus on renal, cardiac and hepatic protection. These strategies involve the use of antioxidants, anti-ferroptosis agents and stress response modulators that target key cellular damage pathways.

Apigenin. Apigenin, a common dietary flavonoid (4,5,7-trihydroxyflavone), exhibits antioxidant, anti-inflammatory and anticancer properties. Preclinical studies have shown that combining apigenin with sorafenib markedly reduces nephrotoxicity. Histological analysis of kidney slices revealed near-complete restoration of normal structure, suggesting a protective effect on renal tissues (182,183).

ATF4. ATF4 is a major transcriptional regulator of the UPR, responsible for cellular adaptation to stress. By upregulating solute carrier family 7 member 11 and enhancing intracellular glutathione synthesis, ATF4 counteracts sorafenib-induced ferroptosis in cardiomyocytes. This mechanism has been validated in *in vitro* cardiomyocyte models, highlighting ATF4 as a potential cardioprotective co-treatment strategy (184).

Nobiletin. Nobiletin, a polymethoxylated flavonoid primarily derived from citrus peel, exhibits cardioprotective and anti-inflammatory properties. When co-administered with sorafenib, Nobiletin markedly reduces cardiotoxicity, as evidenced by improved myocardial histology and normalization of oxidative stress biomarkers. These findings are currently limited to animal models and warrant further investigation (135).

Ferrostatin-1 (Fer-1). Fer-1 is a potent ferroptosis inhibitor that scavenges hydroperoxide radicals. Experimental studies in H9c2 myocardial cells have demonstrated that Fer-1 co-treatment effectively inhibited lipid peroxidation and cell death induced by sorafenib. These findings confirm that targeting ferroptosis is a viable strategy to prevent cardiomyocyte injury during therapy (185).

Lupeol. Lupeol is a lupane-type triterpene with well-established antioxidant and hepatoprotective properties. When combined with sorafenib, lupeol has been shown to restore redox homeostasis, modulate p53 signaling and repair hepatic and renal tissue damage. This synergistic effect has been validated in rodent models of sorafenib-induced toxicity, highlighting its potential for preserving organ function during treatment (186).

Novel combination strategies involving immunotherapy and nanotechnology. In previous years, notable progress has been made in combining sorafenib with immunotherapy and nanotechnology-based delivery systems, offering promising avenues for improving efficacy and overcoming resistance. These innovative strategies, mostly of which have emerged since 2023, address the limitations of conventional combination therapies by improving tumor specificity, minimizing off-target toxicity and activating antitumor immune responses. Immunotherapy-based combinations have emerged as a pivotal approach. A recent study demonstrated that combining sorafenib with an engineered DNA vaccine targeting α -fetoprotein notably enhanced the antitumor immune response by promoting CD8⁺ T-cell infiltration and down-regulating programmed death-ligand 1 expression in HCC models (187). This suggests a synergistic interaction between sorafenib and immune checkpoint modulation.

Simultaneously, nanotechnology-based delivery platforms have opened new avenues for precise and controlled drug administration. For instance, hybrid nanoparticles co-delivering sorafenib and the autophagy inhibitor 3-MA have demonstrated improved therapeutic efficacy in resistant HCC cells, attributed to enhanced intracellular uptake and inhibition of autophagic flux (188). Other nanocarriers, such as MnO₂-based nanosystems (189) and calcium carbonate nanoparticles functionalized with polyethylene glycol and folic acid (190), have exhibited TME-responsive release and improved bioavailability of sorafenib. Furthermore, pH-sensitive coordination nanostructures (191) and self-assembled nanocomplexes targeting mitochondria (192) have shown potential to enhance sorafenib cytotoxicity while minimizing systemic toxicity.

Taken together, these immuno-nanotechnological strategies represent a promising frontier for sorafenib combination therapy and warrant further investigation in both preclinical and clinical settings to facilitate a comprehensive understanding.

4. Clinical applications, advantages and future directions of sorafenib combination therapy

Potential clinical application value. Sorafenib is widely used in the clinically treatment of advanced HCC and

RCC. However, the limitations of monotherapy have become increasingly apparent, including the rapid emergence of resistance and notable side effects. By combining sorafenib with other agents, particularly those that regulate the PI3K/AKT/mTOR signaling pathway, increase oxidative stress or inhibit autophagy, its antitumor efficacy has been markedly enhanced. Specifically, drugs that inhibit the PI3K/AKT/mTOR signaling pathway, such as RPS and curcumin, effectively enhance tumor cell sensitivity to sorafenib when used in combination, thereby delaying or overcoming resistance. Additionally, these combination therapies synergistically inhibit tumor cell proliferation and promote apoptosis, thus improving patient survival rates. Moreover, agents that increase oxidative stress (such as metformin and proteasome inhibitors) can induce tumor cell death and reduce the development of resistance when combined with sorafenib. These compounds enhance the production of ROS, thereby disrupting the antioxidant defense mechanisms of tumor cells and further compromising their resistance and survival capacity (158,159).

Another important combination therapy strategy involves use of autophagy inhibitors, such as HCQ, which block the autophagy pathway in tumor cells used to evade treatment. By inhibiting autophagy, sorafenib's antitumor activity can be further enhanced, making tumor cells more susceptible to the drug's effects and effectively delaying the onset of resistance (161). Although combining sorafenib with other drugs has shown potential in preclinical studies, large-scale, long-term clinical trials are still required to confirm the safety and efficacy of these combination therapies. In the future, exploring more precise combination therapy strategies tailored to individual patient characteristics will be a key direction for enhancing the therapeutic efficacy of sorafenib. Such approaches not only have the potential to extend patient survival but also to improve their quality of life, thereby advancing cancer treatment.

Advantages and limitations of sorafenib combination therapy strategies

Advantages of sorafenib combination therapy strategies. The primary advantage of sorafenib combination therapy lies in overcoming the limitations of monotherapy, particularly in mitigating resistance and reducing toxicity. By combining sorafenib with various types of agents, its antitumor activity is notably enhanced. For example, inhibitors targeting the PI3K/AKT/mTOR pathway effectively suppress tumor cell proliferation, promote apoptosis and delay the onset of resistance when used in combination with sorafenib (193). These combination therapies have demonstrated notable synergistic effects in preclinical studies, suggesting promising potential for clinical applications.

Additionally, combination therapy can reduce the toxicity of sorafenib. For instance, combining sorafenib with antioxidants not only enhances its antitumor effects but also reduces side effects caused by oxidative stress, thereby improving patient tolerance and quality of life (194). By targeting different molecular pathways, these combination therapies offer a multi-angle, multi-level cancer treatment strategy, further improving therapeutic precision and efficacy.

Limitations of sorafenib combination therapy strategies.

Despite the notable advantages of sorafenib combination therapy, its clinical application faces several challenges and limitations. Firstly, the complexity of combination therapy can increase the risk of drug interactions, leading to unpredictable side effects (195). For example, overlapping metabolic pathways between different drugs may elevate the risk of liver and kidney toxicity (130). Therefore, careful drug selection and dose adjustments are necessary in clinical practice to avoid cumulative adverse effects. Secondly, numerous combination therapy strategies are still in the preclinical or early clinical trial stages, lacking large-scale, long-term follow-up data. Individual differences among patients, tumor heterogeneity and the complex interactions between different treatment regimens can result in varying outcomes across patients populations (196). Future research needs to further clarify the scope of these therapies and develop standardized treatment protocols. Lastly, the cost of combination therapy cannot be overlooked. The use of multiple drugs inevitably increases the financial burden of treatment, especially in cases requiring long-term therapy. Balancing enhanced efficacy with cost control remains an important issue that needs to be addressed (197).

In summary, sorafenib combination therapy strategies show great potential in improving tumor treatment outcomes, delaying the development of resistance and reducing toxicity. However, challenges such as drug interactions, limited long-term clinical data and high treatment costs must be addressed in future research and clinical practice. Ongoing studies and clinical trials will be essential to optimize these combination approaches, making them safer, more effective and tailored to individual patients (198).

Future directions for sorafenib combination therapy research.

Despite the notable potential of sorafenib combination therapy in overcoming tumor resistance and enhancing antitumor efficacy, a number of unresolved questions and research gaps remain. Future research should focus on the following key areas.

In-depth study of molecular mechanisms. Current understanding of the molecular mechanisms behind sorafenib combination therapy remains incomplete. Future studies should investigate how these combination therapies achieve synergistic effects through multiple signaling pathways and molecular targets. For example, exploring the interactions among the PI3K/AKT/mTOR pathway, autophagy and oxidative stress pathways will help clarify their roles in drug resistance. By applying molecular biology and systems biology approaches, new therapeutic targets can be identified to support the development of more effective combination therapies (199).

Development of personalized treatment strategies. Tumor heterogeneity and individual patient differences are key factors influencing treatment outcomes. Future research should aim to develop personalized treatment strategies based on biomarkers to precisely identify patient groups suitable for combination therapies (200). This requires comprehensive analysis of patient genomes, proteomes and the TME, using big data and artificial intelligence technologies to design personalized treatment plans that maximize efficacy and minimize side effects (201).

Accumulation of long-term clinical trials and real-world data. Numerous studies on sorafenib combination therapy are

still in the preclinical stage and lack large-scale, long-term clinical data. Future research should design and conduct multicenter, randomized controlled clinical trials to verify the safety and efficacy of these combination therapies. In addition, accumulating real-world data will provide important evidence for evaluating the actual efficacy of these therapies in clinical practice (202,203), helping to optimize treatment protocols and guide clinical applications.

Exploration of new combination therapy regimens. As new drugs are continuously developed and brought to market, future research should explore more innovative combination therapy regimens. In particular, combining sorafenib with drugs targeting novel molecular pathways may further improve treatment outcomes. For example, combining immune checkpoint inhibitors with sorafenib could enhance antitumor responses by activating the patient's immune system (204). Additionally, the combination of metabolism-regulating agents and antioxidants is worth further investigation (205).

Strategies for reducing treatment costs. Since combination therapies may lead to increased treatment costs, future research should also focus on strategies to reduce expenses by optimizing dosages, selectively using drugs and developing more cost-effective combinations (206). Exploratory studies can evaluate the effectiveness of low-dose combination therapy and investigate ways to minimize unnecessary drug use without compromising efficacy, thereby easing the financial burden on patients.

Interdisciplinary collaboration and application of new technologies. Research on sorafenib combination therapy requires collaboration among experts in pharmacology, oncology and related fields, as well as input from disciplines such as bioinformatics and materials science. For example, nanotechnology-based drug delivery systems and CRISPR gene editing for target validation could lead to breakthroughs in combination therapy research (207). Interdisciplinary collaboration will facilitate develop more precise and effective treatment strategies.

Future research should continue to explore the molecular mechanisms underlying sorafenib combination therapy, develop personalized treatment strategies, perform long-term clinical trials and investigate novel combination regimens. These efforts will not only improve cancer treatment outcomes but also provide new insights and tools for clinical practice, ultimately improving patient prognosis and quality of life.

5. Conclusions

The present article reviews the application and challenges of sorafenib combination therapy in cancer treatment. By analyzing the co-administration of various signaling pathway inhibitors, antioxidants and autophagy inhibitors with sorafenib, the study highlights the notable potential of these strategies to enhance its anticancer efficacy, delay the onset of resistance and reduce side effects. However, several challenges remain, including complex drug interactions and a lack of robust clinical application data. Future research should focus on further elucidating the molecular mechanisms underlying combination therapies, developing personalized treatment strategies based on biomarkers and validating safety and efficacy through large-scale clinical trials. These efforts

offer valuable insights into cancer therapy, and hold the potential to promote more precise and effective clinical practices, ultimately improving patient survival and quality of life.

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Availability of data and materials

Not applicable.

Authors' contributions

MYW, ZLC, LD and WW conducted the systematic literature search, analyzed and interpreted the retrieved studies, and curated the investigation records. MW, LSJ and LND performed study screening and data extraction, classified the literature and conducted thematic synthesis; they drafted the relevant sections and critically revised the manuscript for important intellectual content. MYW further integrated these materials and prepared the complete first draft of the manuscript. HS provided critical supervision and contributed to the revision of the manuscript for important intellectual content. MQZ contributed to the conceptual design of the review, secured funding, and gave final approval of the manuscript.. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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.

References

1. Leicht DT, Balan V, Kaplun A, Singh-Gupta V, Kaplun L, Dobson M and Tzivion G: Raf kinases: Function, regulation and role in human cancer. *Biochim Biophys Acta* 1773: 1196-1212, 2007.
2. McDonald OB, Chen WJ, Ellis B, Hoffman C, Overton L, Rink M, Smith A, Marshall CJ and Wood ER: A scintillation proximity assay for the Raf/MEK/ERK Kinase cascade: High-throughput screening and identification of selective enzyme inhibitors. *Anal Biochem* 268: 318-329, 1999.
3. Padala SA, Barsouk A, Thandra KC, Saginala K, Mohammed A, Vakiti A, Rawla P and Barsouk A: Epidemiology of renal cell carcinoma. *World J Oncol* 11: 79-87, 2020.

4. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, *et al*: Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 359: 378-390, 2024.
5. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, *et al*: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 10: 25-34, 2009.
6. Cheng AL, Guan Z, Chen Z, Tsao CJ, Qin S, Kim JS, Yang TS, Tak WY, Pan H, Yu S, *et al*: Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: Subset analyses of the phase III Sorafenib Asia-Pacific trial. *Eur J Cancer* 48: 1452-1465, 2012.
7. Gauthier A and Ho M: Role of sorafenib in the treatment of advanced hepatocellular carcinoma: An update. *Hepatol Res* 43: 147-154, 2013.
8. Yang S and Liu G: Targeting the Ras/Raf/MEK/ERK pathway in hepatocellular carcinoma (review). *Oncol Lett* 13: 1041-1047, 2017.
9. Kim MJ, Kim SM, Lee EK, Hwangbo Y, Lee YJ, Cho SW, Park DJ, Lee Y and Park YJ: Tumor doubling time predicts response to sorafenib in radioactive iodine-refractory differentiated thyroid cancer. *Endocr J* 66: 597-604, 2019.
10. Kontomanolis EN, Koutras A, Syllaios A, Schizas D, Mastoraki A, Garmpis N, Diakosavvas M, Angelou K, Tsatsaris G, Pagkalos A, *et al*: Role of oncogenes and tumor-suppressor genes in carcinogenesis: A review. *Anticancer Res* 40: 6009-6015, 2020.
11. Ishizawa R and Parsons SJ: c-Src and cooperating partners in human cancer. *Cancer Cell* 6: 209-214, 2004.
12. Myers MB, Wang Y, Mckim KL and Parsons BL: Hotspot oncomutations: Implications for personalized cancer treatment. *Expert Rev Mol Diagn* 12: 603-620, 2012.
13. Manzari MT, Shamay Y, Kiguchi H, Rosen N, Scaltriti M and Heller DA: Targeted drug delivery strategies for precision medicines. *Nat Rev Mater* 6: 351-370, 2021.
14. Kuczyński EA, Lee CR, Man S, Chen E and Kerbel RS: Effects of sorafenib dose on acquired reversible resistance and toxicity in hepatocellular carcinoma. *Cancer Res* 75: 2510-2519, 2015.
15. Fairfax BP, Pratap S, Roberts IS, Collier J, Kaplan R, Meade AM, Ritchie AW, Eisen T, Macaulay VM and Protheroe A: Fatal case of sorafenib-associated idiosyncratic hepatotoxicity in the adjuvant treatment of a patient with renal cell carcinoma. *BMC Cancer* 12: 590, 2012.
16. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M, *et al*: BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 64: 7099-7109, 2004.
17. Liu L, Cao Y, Chen C, Zhang X, McNabola A, Wilkie D, Wilhelm S, Lynch M and Carter C: Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. *Cancer Res* 66: 11851-11858, 2006.
18. Reiss KA, Yu S, Mamtani R, Mehta R, D'Addeo K, Wileyto EP, Taddei TH and Kaplan DE: Starting dose of sorafenib for the treatment of hepatocellular carcinoma: A retrospective, multi-institutional study. *J Clin Oncol* 35: 3575-3581, 2017.
19. Woo HY, Heo J, Yoon KT, Kim GH, Kang DH, Song GA and Cho M: Clinical course of sorafenib treatment in patients with hepatocellular carcinoma. *Scand J Gastroenterol* 47: 809-819, 2012.
20. Dahiya M and Dureja H: Sorafenib for hepatocellular carcinoma: Potential molecular targets and resistance mechanisms. *J Chemother* 34: 286-301, 2022.
21. Ashman LK and Griffith R: Therapeutic targeting of c-KIT in cancer. *Expert Opin Investig Drugs* 22: 103-115, 2013.
22. Lei J, Dai H, Zhang Y, Ou G, Liang Z, Lu Y and Li H: Prognostic impact of primary versus secondary resistance to sorafenib in patients with HCC. *Ther Adv Med Oncol* 17: 7588359241299678, 2025.
23. Carmeliet P and Jain RK: Molecular mechanisms and clinical applications of angiogenesis. *Nature* 473: 298-307, 2011.
24. Liu C, Chen Z, Chen Y, Lu J, Li Y, Wang S, Wu G and Qian F: Improving oral bioavailability of sorafenib by optimizing the 'Spring' and 'Parachute' Based on molecular interaction mechanisms. *Mol Pharm* 13: 599-608, 2016.
25. Ghassabian S, Rawling T, Zhou F, Doddareddy MR, Tattam BN, Hibbs DE, Edwards RJ, Cui PH and Murray M: Role of human CYP3A4 in the biotransformation of sorafenib to its major oxidized metabolites. *Biochem Pharmacol* 84: 215-223, 2012.
26. Ye L, Yang X, Guo E, Chen W, Lu L, Wang Y, Peng X, Yan T, Zhou F and Liu Z: Sorafenib metabolism is significantly altered in the liver tumor tissue of hepatocellular carcinoma patient. *PLoS One* 9: e96664, 2014.
27. Porta C, Paglino C, Imarisio I and Bonomi L: Uncovering pandora's vase: The growing problem of new toxicities from novel anticancer agents. The case of sorafenib and sunitinib. *Clin Exp Med* 7: 127-134, 2007.
28. Wei S, Wei F, Li M, Yang Y, Zhang J, Li C and Wang J: Target immune components to circumvent sorafenib resistance in hepatocellular carcinoma. *Biomed Pharmacother* 163: 114798, 2023.
29. Wu J, Chai H, Li F, Ren Q and Gu Y: SETD1A augments sorafenib primary resistance via activating YAP in hepatocellular carcinoma. *Life Sci* 260: 118406, 2020.
30. Zhu Y, Zheng B, Wang H and Chen L: New knowledge of the mechanisms of sorafenib resistance in liver cancer. *Acta Pharmacol Sin* 38: 614-622, 2017.
31. Sun T, Mao W, Peng H, Wang Q and Jiao L: YAP promotes sorafenib resistance in hepatocellular carcinoma by upregulating survivin. *Cell Oncol* 44: 689-699, 2021.
32. Faletti OD, Alsaadawe M, Long J, Luo Q, Hu L, Zhang Y, Deng S, Wu G, Fang W, He M and Lyu X: Dimethyl fumarate abrogates hepatocellular carcinoma growth by inhibiting Nrf2/Bcl-xL axis and enhances sorafenib's efficacy. *Sci Rep* 15: 16724, 2025.
33. Tutusaus A, Stefanovic M, Boix L, Cucarull B, Zamora A, Blasco L, de Frutos PG, Reig M, Fernandez-Checa JC, Marí M, *et al*: Antiapoptotic BCL-2 proteins determine sorafenib/regorafenib resistance and BH3-mimetic efficacy in hepatocellular carcinoma. *Oncotarget* 9: 16701-16717, 2018.
34. Chen KF, Chen HL, Tai WT, Feng WC, Hsu CH, Chen PJ and Cheng AL: Activation of phosphatidylinositol 3-Kinase/Akt signaling pathway mediates acquired resistance to sorafenib in hepatocellular carcinoma cells. *J Pharmacol Exp Ther* 337: 155-161, 2011.
35. Maurer U, Charvet C, Wagman AS, Dejardin E and Green DR: Glycogen synthase Kinase-3 regulates mitochondrial outer membrane permeabilization and apoptosis by destabilization of MCL-1. *Mol Cell* 21: 749-760, 2006.
36. Gilley J, Coffey PJ and Ham J: FOXO transcription factors directly activate bim gene expression and promote apoptosis in sympathetic neurons. *J Cell Biol* 162: 613-622, 2003.
37. Chong C, Tan L, Lim L and Manser E: The mechanism of PAK activation: Autophosphorylation events in both regulatory and kinase domains control activity. *J Biol Chem* 276: 17347-17353, 2001.
38. Xie L, Zeng Y, Dai Z, He W, Ke H, Lin Q, Chen Y, Bu J, Lin D and Zheng M: Chemical and genetic inhibition of STAT3 sensitizes hepatocellular carcinoma cells to sorafenib induced cell death. *Int J Biol Sci* 14: 577-585, 2018.
39. Dai Z, Wang X, Peng R, Zhang B, Han Q, Lin J, Wang J, Lin J, Jiang M, Liu H, *et al*: Induction of IL-6Rα by ATF3 enhances IL-6 mediated sorafenib and regorafenib resistance in hepatocellular carcinoma. *Cancer Lett* 524: 161-171, 2022.
40. Zang M, Hayne C and Luo Z: Interaction between Active Pak1 and Raf-1 is necessary for phosphorylation and activation of Raf-1. *J Biol Chem* 277: 4395-4405, 2002.
41. Zhou B, Lu Q, Liu J, Fan L, Wang Y, Wei W, Wang H and Sun G: Melatonin increases the sensitivity of hepatocellular carcinoma to sorafenib through the PERK-ATF4-Beclin1 pathway. *Int J Biol Sci* 15: 1905-1920, 2019.
42. Rodríguez-Hernández MA, González R, de la Rosa AJ, Gallego P, Ordóñez R, Navarro-Villarán E, Contreras L, Rodríguez-Arribas M, González-Gallego J, Álamo-Martínez JM, *et al*: Molecular characterization of autophagic and apoptotic signaling induced by sorafenib in liver cancer cells. *J Cell Physiol* 234: 692-708, 2019.
43. Shi YH, Ding ZB, Zhou J, Hui B, Shi GM, Ke AW, Wang XY, Dai Z, Peng YF, Gu CY, *et al*: Targeting autophagy enhances sorafenib lethality for hepatocellular carcinoma via ER stress-related apoptosis. *Autophagy* 7: 1159-1172, 2011.
44. Shimizu S, Takehara T, Hikita H, Kodama T, Tsunematsu H, Miyagi T, Hosui A, Ishida H, Tatsumi T, Kanto T, *et al*: Inhibition of autophagy potentiates the antitumor effect of the multikinase inhibitor sorafenib in hepatocellular carcinoma. *Int J Cancer* 131: 548-557, 2012.
45. van Malenstein H, Dekervel J, Verslype C, Van Cutsem E, Windmolders P, Nevens F and van Pelt J: Long-term exposure to sorafenib of liver cancer cells induces resistance with epithelial-to-mesenchymal transition, increased invasion and risk of rebound growth. *Cancer Lett* 329: 74-83, 2013.
46. Chow AK, Ng L, Lam CS, Wong SK, Wan TM, Cheng NS, Yau TC, Poon RT and Pang RW: The enhanced metastatic potential of hepatocellular carcinoma (HCC) cells with sorafenib resistance. *PLoS One* 8: e78675, 2013.

47. Bao MH and Wong CC: Hypoxia, metabolic reprogramming, and drug resistance in liver cancer. *Cells* 10: 1715, 2021.
48. Dong N, Shi X, Wang S, Gao Y, Kuang Z, Xie Q, Li Y, Deng H, Wu Y, Li M and Li JL: M2 macrophages mediate sorafenib resistance by secreting HGF in a feed-forward manner in hepatocellular carcinoma. *Br J Cancer* 121: 22-33, 2019.
49. Arrondeau J, Mir O, Boudou-Rouquette P, Coriat R, Ropert S, Dumas G, Rodrigues MJ, Rousseau B, Blanchet B and Goldwasser F: Sorafenib exposure decreases over time in patients with hepatocellular carcinoma. *Invest New Drugs* 30: 2046-2049, 2012.
50. Gao R, Buechel D, Kalathur RKR, Morini MF, Coto-Llerena M, Ercan C, Piscuoglio S, Chen Q, Blumer T, Wang X, *et al*: USP29-mediated HIF1 α stabilization is associated with Sorafenib resistance of hepatocellular carcinoma cells by upregulating glycolysis. *Oncogenesis* 10: 52, 2021.
51. Zeng Z, Lu Q, Liu Y, Zhao J, Zhang Q, Hu L, Shi Z, Tu Y, Xiao Z, Xu Q and Huang D: Effect of the hypoxia inducible factor on sorafenib resistance of hepatocellular carcinoma. *Front Oncol* 11: 641522, 2021.
52. Wang S, Cai L, Zhang F, Shang X, Xiao R and Zhou H: Inhibition of EZH2 attenuates sorafenib resistance by targeting NOTCH1 Activation-dependent liver cancer stem cells via NOTCH1-related MicroRNAs in hepatocellular carcinoma. *Transl Oncol* 13: 100741, 2020.
53. Azumi J, Tsubota T, Sakabe T and Shiota G: miR-181a induces sorafenib resistance of hepatocellular carcinoma cells through down-regulation of RASSF1 expression. *Cancer Sci* 107: 1256-1262, 2016.
54. Hutson TE, Figlin RA, Kuhn JG and Motzer RJ: Targeted therapies for metastatic renal cell carcinoma: An overview of toxicity and dosing strategies. *Oncologist* 13: 1084-1096, 2008.
55. Tovar V, Cornella H, Moeini A, Vidal S, Hoshida Y, Sia D, Peix J, Cabellos L, Alsinet C, Torrecilla S, *et al*: Tumour initiating cells and IGF/FGF signalling contribute to sorafenib resistance in hepatocellular carcinoma. *Gut* 66: 530-540, 2017.
56. Jang JW, Song Y, Kim SH, Kim JS, Kim KM, Choi EK, Kim J and Seo HR: CD133 confers cancer stem-like cell properties by stabilizing EGFR-AKT signaling in hepatocellular carcinoma. *Cancer Lett* 389: 1-10, 2017.
57. Hagiwara S, Kudo M, Nagai T, Inoue T, Ueshima K, Nishida N, Watanabe T and Sakurai T: Activation of JNK and high expression level of CD133 predict a poor response to sorafenib in hepatocellular carcinoma. *Br J Cancer* 106: 1997-2003, 2012.
58. Wang M, Wang Z, Zhi X, Ding W, Xiong J, Tao T, Yang Y, Zhang H, Zi X, Zhou W and Huang G: SOX9 enhances sorafenib resistance through upregulating ABCG2 expression in hepatocellular carcinoma. *Biomed Pharmacother* 129: 110315, 2020.
59. Giovannini C, Baglioni M, Baron Toaldo M, Ventrucci C, D'Adamo S, Cipone M, Chieco P, Gramantieri L and Bolondi L: Notch3 inhibition enhances sorafenib cytotoxic efficacy by promoting GSK3 β phosphorylation and p21 down-regulation in hepatocellular carcinoma. *Oncotarget* 4: 1618-1631, 2013.
60. Wang S, Wang Y, Xun X, Zhang C, Xiang X, Cheng Q, Hu S, Li Z and Zhu J: Hedgehog signaling promotes sorafenib resistance in hepatocellular carcinoma patient-derived organoids. *J Exp Clin Cancer Res* 39: 22, 2020.
61. Leung HW, Leung CON, Lau EY, Chung KPS, Mok EH, Lei MML, Leung RWH, Tong M, Keng VW, Ma C, *et al*: EPHB2 activates β -catenin to enhance cancer stem cell properties and drive sorafenib resistance in hepatocellular carcinoma. *Cancer Res* 81: 3229-3240, 2021.
62. Guan D, Shi J, Zhang Y, Zhao JS, Long LY, Chen TW, Zhang EB, Feng YY, Bao WD, Deng YZ, *et al*: Sorafenib enriches epithelial cell adhesion molecule-positive tumor initiating cells and exacerbates a subtype of hepatocellular carcinoma through TSC2-AKT cascade. *Hepatology* 62: 1791-803, 2015.
63. Hu Z, Zhao Y, Li L, Jiang J, Li W, Mang Y, Gao Y, Dong Y, Zhu J, Yang C, *et al*: Metformin promotes ferroptosis and sensitivity to sorafenib in hepatocellular carcinoma cells via ATF4/STAT3. *Mol Biol Rep* 50: 6399-6413, 2023.
64. Ahmed TA, Adamopoulos C, Karoulia Z, Wu X, Sachidanandam R, Aaronson SA and Poulikakos PI: SHP2 drives adaptive resistance to ERK signaling inhibition in molecularly defined subsets of ERK-dependent tumors. *Cell Rep* 26: 65-78.e5, 2019.
65. Kane RC, Farrell AT, Saber H, Tang S, Williams G, Jee JM, Liang C, Booth B, Chidambaram N, Morse D, *et al*: Sorafenib for the treatment of advanced renal cell carcinoma. *Clin Cancer Res* 12: 7271-7278, 2006.
66. Han T, Xiang DM, Sun W, Liu N, Sun HL, Wen W, Shen WF, Wang RY, Chen C, Wang X, *et al*: PTPN11/Shp2 overexpression enhances liver cancer progression and predicts poor prognosis of patients. *J Hepatol* 63: 651-660, 2015.
67. Ichikawa K, Watanabe Miyano S, Minoshima Y, Matsui J and Funahashi Y: Activated FGF2 signaling pathway in tumor vasculature is essential for acquired resistance to anti-VEGF therapy. *Sci Rep* 10: 2939, 2020.
68. Kanzaki H, Chiba T, Ao J, Koroki K, Kanayama K, Maruta S, Maeda T, Kusakabe Y, Kobayashi K, Kanogawa N, *et al*: The impact of FGF19/FGFR4 signaling inhibition in antitumor activity of multi-kinase inhibitors in hepatocellular carcinoma. *Sci Rep* 11: 5303, 2021.
69. Gao L, Wang X, Tang Y, Huang S, Hu CAA and Teng Y: FGF19/FGFR4 signaling contributes to the resistance of hepatocellular carcinoma to sorafenib. *J Exp Clin Cancer Res* 36: 8, 2017.
70. Allen E, Walters IB and Hanahan D: Brivanib, a dual FGF/VEGF inhibitor, is active both first and second line against mouse pancreatic neuroendocrine tumors developing adaptive/evasive resistance to VEGF inhibition. *Clin Cancer Res* 17: 5299-5310, 2011.
71. Huynh H, Ngo VC, Fagnoli J, Ayers M, Soo KC, Koong HN, Thng CH, Ong HS, Chung A, Chow P, *et al*: Brivanib alaninate, a dual inhibitor of vascular endothelial growth factor receptor and fibroblast growth factor receptor tyrosine kinases, induces growth inhibition in mouse models of human hepatocellular carcinoma. *Clin Cancer Res* 14: 6146-6153, 2008.
72. Abou-Alfa GK: Selection of patients with hepatocellular carcinoma for sorafenib. *J Natl Compr Canc Netw* 7: 397-403, 2009.
73. Donnem T, Hu J, Ferguson M, Adighib O, Snell C, Harris AL, Gatter KC and Pezzella F: Vessel co-option in primary human tumors and metastases: An obstacle to effective anti-angiogenic treatment? *Cancer Med* 2: 427-436, 2013.
74. Bridgeman VL, Wan E, Foo S, Nathan MR, Welter JC, Frenz S, Vermeulen PB, Preece N, Springer CJ, Powles T, *et al*: Preclinical evidence that trametinib enhances the response to antiangiogenic tyrosine kinase inhibitors in renal cell carcinoma. *Mol Cancer Ther* 15: 172-183, 2016.
75. Ma L, Chen Z, Erdjument-Bromage H, Tempst P and Pandolfi PP: Phosphorylation and functional inactivation of TSC2 by Erk implications for tuberous sclerosis and cancer pathogenesis. *Cell* 121: 179-193, 2005.
76. Mills JR, Hippo Y, Robert F, Chen SM, Malina A, Lin CJ, Trojahn U, Wendel HG, Charest A, Bronson RT, *et al*: mTORC1 promotes survival through translational control of Mcl-1. *Proc Natl Acad Sci* 105: 10853-10858, 2008.
77. Dufies M, Verbiest A, Cooley LS, Ndiaye PD, He X, Nottet N, Souleyreau W, Hagege A, Torrino S, Parola J, *et al*: Plk1, upregulated by HIF-2, mediates metastasis and drug resistance of clear cell renal cell carcinoma. *Commun Biol* 4: 166, 2021.
78. Mazumder S, Higgins PJ and Samarakoon R: Downstream targets of VHL/HIF- α signaling in renal clear cell carcinoma progression: Mechanisms and therapeutic relevance. *Cancers (Basel)* 15: 1316, 2023.
79. Ge Y, Weygant N, Qu D, May R, Berry WL, Yao J, Chandrasekaran P, Zheng W, Zhao L, Zhao KL, *et al*: Alternative splice variants of DCLK1 mark cancer stem cells, promote self-renewal and drug-resistance, and can be targeted to inhibit tumorigenesis in kidney cancer. *Int J Cancer* 143: 1162-1175, 2018.
80. Lagas JS, van Waterschoot RAB, Sparidans RW, Wagenaar E, Beijnen JH and Schinkel AH: Breast cancer resistance protein and P-glycoprotein limit sorafenib brain accumulation. *Mol Cancer Ther* 9: 319-326, 2010.
81. Huang WC, Hsieh YL, Hung CM, Chien PH, Chien YF, Chen LC, Tu CY, Chen CH, Hsu SC, Lin YM and Chen YJ: BCRP/ABCG2 inhibition sensitizes hepatocellular carcinoma cells to sorafenib. *PLoS One* 8: e83627, 2014.
82. Singh A, Wu H, Zhang P, Happel C, Ma J and Biswal S: Expression of ABCG2 (BCRP) is regulated by Nrf2 in cancer cells that confers side population and chemoresistance phenotype. *Mol Cancer Ther* 9: 2365-2376, 2010.
83. Wang H, Luo F, Zhu Z, Xu Z, Huang X, Ma R, He H, Zhu Y, Shao K and Zhao J: ABCG2 is a potential prognostic marker of overall survival in patients with clear cell renal cell carcinoma. *BMC Cancer* 17: 222, 2017.
84. Shibayama Y, Nakano K, Maeda H, Taguchi M, Ikeda R, Sugawara M, Iseki K, Takeda Y and Yamada K: Multidrug resistance protein 2 implicates anticancer Drug-resistance to sorafenib. *Biol Pharm Bull* 34: 433-435, 2011.
85. Colombo F, Trombetta E, Cetrangolo P, Maggioni M, Razini P, De Santis F, Torrente Y, Prati D, Torresani E and Porretti L: Giant lysosomes as a chemotherapy resistance mechanism in hepatocellular carcinoma cells. *PLoS One* 9: e114787, 2014.
86. Zheng B, Zhu H, Gu D, Pan X, Qian L, Xue B, Yang D, Zhou J and Shan Y: MiRNA-30a-mediated autophagy inhibition sensitizes renal cell carcinoma cells to sorafenib. *Biochem Biophys Res Commun* 459: 234-239, 2015.

87. He J, He J, Min L, He Y, Guan H, Wang J and Peng X: Extracellular vesicles transmitted miR-31-5p promotes sorafenib resistance by targeting MLH1 in renal cell carcinoma. *Int J Cancer* 146: 1052-1063, 2020.
88. Xu Z, Yang F, Wei D, Liu B, Chen C, Bao Y, Wu Z, Wu D, Tan H, Li J, *et al*: Long noncoding RNA-SRLR elicits intrinsic sorafenib resistance via evoking IL-6/STAT3 axis in renal cell carcinoma. *Oncogene* 36: 1965-1977, 2017.
89. Liu F, Chen N, Gong Y, Xiao R, Wang W and Pan Z: The long non-coding RNA NEAT1 enhances epithelial-to-mesenchymal transition and chemoresistance via the miR-34a/c-Met axis in renal cell carcinoma. *Oncotarget* 8: 62927-62938, 2017.
90. Amato RJ, Flaherty AL and Stepankiw M: Phase I trial of everolimus plus sorafenib for patients with advanced renal cell cancer. *Clin Genitourin Cancer* 10: 26-31, 2012.
91. Jin Y, Huang R, Xia Y, Huang C, Qiu F, Pu J, He X and Zhao X: Long noncoding RNA KIF9-AS1 regulates transforming growth Factor- β and autophagy signaling to enhance renal cell carcinoma chemoresistance via microRNA-497-5p. *DNA Cell Biol* 39: 1096-1103, 2020.
92. Qin C, Cao Q, Li P, Wang S, Wang J, Wang M, Chu H, Zhou L, Li X, Ye D, *et al*: The influence of genetic variants of sorafenib on clinical outcomes and toxic effects in patients with advanced renal cell carcinoma. *Sci Rep* 6: 20089, 2016.
93. Escudier B, Rini BI, Motzer RJ, Tarazi J, Kim S, Huang X, Rosbrook B, English PA, Loomis AK and Williams JA: Genotype correlations with blood pressure and efficacy from a randomized Phase III trial of Second-line axitinib versus sorafenib in metastatic renal cell carcinoma. *Clin Genitourin Cancer* 13: 328-337.e3, 2015.
94. Han KS, Raven PA, Frees S, Gust K, Fazli L, Ettinger S, Hong SJ, Kollmannsberger C, Gleave ME and So AI: Cellular adaptation to VEGF-targeted antiangiogenic therapy induces evasive resistance by overproduction of alternative endothelial cell growth factors in renal cell carcinoma. *Neoplasia* 17: 805-816, 2015.
95. Sarbasov DD, Guertin DA, Ali SM and Sabatini DM: Phosphorylation and regulation of Akt/PKB by the Rictor-mTOR complex. *Science* 307: 1098-1101, 2005.
96. Zhao CX, Luo CL and Wu XH: Hypoxia promotes 786-O cells invasiveness and resistance to sorafenib via HIF-2 α /COX-2. *Med Oncol* 32: 419, 2014.
97. Bielecka ZF, Malinowska A, Brodaczewska KK, Klemba A, Kieda C, Krasowski P, Grzesiuk E, Piwowarski J, Czarnecka AM and Szczylik C: Hypoxic 3D in vitro culture models reveal distinct resistance processes to TKIs in renal cancer cells. *Cell Biosci* 7: 71, 2017.
98. Bae T, Hallis SP and Kwak MK: Hypoxia, oxidative stress, and the interplay of HIFs and NRF2 signaling in cancer. *Exp Mol Med* 56: 501-514, 2024.
99. Chang K, Chen Y, Zhang X, Zhang W, Xu N, Zeng B, Wang Y, Feng T, Dai B, Xu F, *et al*: DPP9 stabilizes NRF2 to suppress ferroptosis and induce sorafenib resistance in clear cell renal cell carcinoma. *Cancer Res* 83: 3940-3955, 2023.
100. Siska PJ, Beckermann KE, Rathmell WK and Haake SM: Strategies to overcome therapeutic resistance in renal cell carcinoma. *Urol Oncol* 35: 102-110, 2017.
101. Tang S, Tan G, Jiang X, Han P, Zhai B, Dong X, Qiao H, Jiang H and Sun X: An artificial lncRNA targeting multiple miRNAs overcomes sorafenib resistance in hepatocellular carcinoma cells. *Oncotarget* 7: 73257-73269, 2016.
102. Gedaly R, Angulo P, Hundley J, Daily MF, Chen C, Koch A and Evers BM: PI-103 and Sorafenib inhibit hepatocellular carcinoma cell proliferation by blocking Ras/Raf/MAPK and PI3K/AKT/mTOR pathways. *Anticancer Res* 30: 4951-4958, 2010.
103. Weygant N, Qu D, May R, Tierney RM, Berry WL, Zhao L, Agarwal S, Chandrakesan P, Chinthalapally HR, Murphy NT, *et al*: DCLK1 is a broadly dysregulated target against epithelial-mesenchymal transition, focal adhesion, and stemness in clear cell renal carcinoma. *Oncotarget* 6: 2193-2205, 2015.
104. Patel TV, Morgan JA, Demetri GD, George S, Maki RG, Quigley M and Humphreys BD: A preeclampsia-like syndrome characterized by reversible hypertension and proteinuria induced by the multitargeted kinase inhibitors sunitinib and sorafenib. *J Natl Cancer Inst* 100: 282-284, 2008.
105. Schmidinger M, Zielinski CC, Vogl UM, Bojic A, Bojic M, Schukro C, Ruhsam M, Hejna M and Schmidinger H: Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 26: 5204-5212, 2024.
106. Altena R, Perik PJ, van Veldhuisen DJ, de Vries EGE and Gietema JA: Cardiovascular toxicity caused by cancer treatment: Strategies for early detection. *Lancet Oncol* 10: 391-399, 2009.
107. Wu S, Chen JJ, Kudelka A, Lu J and Zhu X: Incidence and risk of hypertension with sorafenib in patients with cancer: A systematic review and meta-analysis. *Lancet Oncol* 9: 117-123, 2008.
108. Winnik S, Lohmann C, Siciliani G, von Lukowicz T, Kuschnerus K, Kraenkel N, Brokopp CE, Enseleit F, Michels S, Ruschitzka F, *et al*: Systemic VEGF inhibition accelerates experimental atherosclerosis and disrupts endothelial homeostasis-implications for cardiovascular safety. *Int J Cardiol* 168: 2453-2461, 2013.
109. Pomej K, Scheiner B, Park D, Bauer D, Balcar L, Meischl T, Mandorfer M, Reiberger T, Müller C, Trauner M and Pinter M: Vascular complications in patients with hepatocellular carcinoma treated with sorafenib. *Cancers (Basel)* 12: 2961, 2020.
110. Choueiri TK, Schutz FAB, Je Y, Rosenberg JE and Bellmunt J: Risk of arterial thromboembolic events with sunitinib and sorafenib: A systematic review and Meta-analysis of clinical trials. *J Clin Oncol* 28: 2280-2285, 2010.
111. Pearson JD: Endothelial cell function and thrombosis. *Best Pract Res Clin Haematol* 12: 329-341, 1999.
112. Herrmann J, Yang EH, Iliescu CA, Cilengiroglu M, Charitakis K, Hakeem A, Toutouzas K, Leeser MA, Grines CL and Marmagkiolis K: Vascular toxicities of cancer therapies. *Circulation* 133: 1272-1289, 2016.
113. Brose MS, Frenette CT, Keefe SM and Stein SM: Management of Sorafenib-related adverse events: A clinician's perspective. *Semin Oncol* 41 (Suppl 2): S1-S16, 2014.
114. Je Y, Schutz FAB and Choueiri TK: Risk of bleeding with vascular endothelial growth factor receptor tyrosine-kinase inhibitors sunitinib and sorafenib: A systematic review and Meta-analysis of clinical trials. *Lancet Oncol* 10: 967-974, 2009.
115. Dai C, Zhou F, Shao JH, Wu LQ, Yu X and Yin XB: Bleeding risk in cancer patients treated with sorafenib: A meta-analysis of randomized controlled trials. *J Cancer Res Ther* 14 (Suppl 1): S948-S956, 2018.
116. Chu D, Lacouture ME, Fillos T and Wu S: Risk of hand-foot skin reaction with sorafenib: A systematic review and meta-analysis. *Acta Oncol (Madr)* 47: 176-186, 2008.
117. Yeh CN, Huang WK, Lu CW, Chen CP, Lin SH, Pan YR and Wu CE: A potential association of zinc deficiency and tyrosine kinase Inhibitor-induced Hand-foot skin reaction. *Biol Trace Elem Res* 201: 5540-5545, 2023.
118. Luo P, Yan H, Chen X, Zhang Y, Zhao Z, Cao J, Zhu Y, Du J, Xu Z, Zhang X, *et al*: s-HBEGF/SIRT1 circuit-dictated crosstalk between vascular endothelial cells and keratinocytes mediates sorafenib-induced hand-foot skin reaction that can be reversed by nicotinamide. *Cell Res* 30: 779-793, 2020.
119. Lacouture ME, Reilly LM, Gerami P and Guitart J: Hand foot skin reaction in cancer patients treated with the multikinase inhibitors sorafenib and sunitinib. *Ann Oncol* 19: 1955-1961, 2008.
120. Shah VH, Supekar BB, Singh RP and Mukhi JI: Sorafenib induced Hand-Foot skin reaction at low dose. *Indian Dermatol Online J* 11: 997-1000, 2020.
121. Wang P, Tan G, Zhu M, Li W, Zhai B and Sun X: Hand-foot skin reaction is a beneficial indicator of sorafenib therapy for patients with hepatocellular carcinoma: A systematic review and meta-analysis. *Expert Rev Gastroenterol Hepatol* 12: 1-8, 2018.
122. Wang E, Xia D, Bai W, Wang Z, Wang Q, Liu L, Wang W, Yuan J, Li X, Chen H, *et al*: Hand-foot-skin reaction of grade ≥ 2 within sixty days as the optimal clinical marker best help predict survival in sorafenib therapy for HCC. *Invest New Drugs* 37: 401-414, 2019.
123. Mir O, Coriat R, Blanchet B, Durand JP, Boudou-Rouquette P, Michels J, Ropert S, Vidal M, Pol S, Chaussade S and Goldwasser F: Sarcopenia predicts early Dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. *PLoS One* 7: e37563, 2012.
124. Escudier B, Szczylik C, Eisen T, Stadler WM, Schwartz B, Shan M and Bukowski RM: Randomized phase III trial of the Raf kinase and VEGFR inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC). *J Clin Oncol* 23: LBA4510-LBA4510, 2025.
125. FAN L and Iseki S: Immunohistochemical localization of vascular endothelial growth factor in the endocrine glands of the rat. *Arch Histol Cytol* 61: 17-28, 1998.
126. Zheng W, Kuhlicke J, Jäckel K, Eltzschig HK, Singh A, Sjöblom M, Riederer B, Weinhold C, Seidler U, Colgan SP and Karhausen J: Hypoxia inducible factor-1 (HIF-1)-mediated repression of cystic fibrosis transmembrane conductance regulator (CFTR) in the intestinal epithelium. *FASEB J* 23: 204-213, 2009.
127. Xu Y, Mo Y, Zhou W, Qin M, Li M, Yin G, Yu H, Chen Y, Du H, Jin Y, *et al*: Sorafenib induces intestinal toxicity by disturbing gut microbiota and activating the LPS/TLR4/NF- κ B signaling pathway in mice. *Toxicology* 517: 154220, 2025.
128. Izzedine H, Massard C, Spano JP, Goldwasser F, Khayat D and Soria JC: VEGF signalling inhibition-induced proteinuria: Mechanisms, significance and management. *Eur J Cancer* 46: 439-448, 2010.

129. Tufro A and Veron D: VEGF and podocytes in diabetic nephropathy. *Semin Nephrol* 32: 385-393, 2012.
130. Azad NS, Posadas EM, Kwitkowski VE, Steinberg SM, Jain L, Annunziata CM, Minasian L, Sarosy G, Kotz HL, Premkumar A, *et al*: Combination targeted therapy with sorafenib and bevacizumab results in enhanced toxicity and antitumor activity. *J Clin Oncol* 26: 3709-3714, 2024.
131. Kuroda D, Hayashi H, Nitta H, Imai K, Abe S, Hashimoto D, Chikamoto A, Ishiko T, Beppu T and Baba H: Successful treatment for sorafenib-induced liver dysfunction: A report of case with liver biopsy. *Surg Case Rep* 2: 4, 2016.
132. Van Hootegeem A, Verslype C and Van Steenberghe W: Sorafenib-induced liver failure: A case report and review of the literature. *Case Rep Hepatol* 2011: 941395, 2011.
133. Fernando J, Sancho P, Fernández-Rodríguez CM, Lledó JL, Caja L, Campbell JS, Fausto N and Fabregat I: Sorafenib sensitizes hepatocellular carcinoma cells to physiological apoptotic stimuli. *J Cell Physiol* 227: 1319-1325, 2012.
134. Stepniak J, Krawczyk-Lipiec J, Lewiński A and Karbownik-Lewińska M: Sorafenib versus lenvatinib causes stronger oxidative damage to membrane lipids in noncancerous tissues of the thyroid, liver, and kidney: Effective protection by melatonin and Indole-3-Propionic acid. *Biomedicines* 10: 2890, 2022.
135. Zaafer D, Khalil HMA, Rasheed RA, Eltelbany RFA and Zaitone SA: Hesperetin mitigates sorafenib-induced cardiotoxicity in mice through inhibition of the TLR4/NLRP3 signaling pathway. *PLoS One* 17: e0271631, 2022.
136. Qiu X, Li M, Wu L, Xin Y, Mu S, Li T and Song K: Severe Fatigue is an important factor in the prognosis of patients with advanced hepatocellular carcinoma treated with Sorafenib. *Cancer Manag Res* 12: 7983-7992, 2020.
137. Tamaskar I, Bukowski R, Elson P, Ioachimescu AG, Wood L, Dreicer R, Mekhail T, Garcia J and Rini BI: Thyroid function test abnormalities in patients with metastatic renal cell carcinoma treated with sorafenib. *Ann Oncol* 19: 265-268, 2008.
138. Beukhof CM, van Doorn L, Visser TJ, Bins S, Visser WE, van Heerebeek R, van Kemenade FJ, de Rijke YB, de Herder WW, Chaker L, *et al*: Sorafenib-induced changes in thyroid hormone levels in patients treated for hepatocellular carcinoma. *J Clin Endocrinol Metab* 102: 2922-2929, 2017.
139. Biondi B and Cooper DS: The clinical significance of subclinical thyroid dysfunction. *Endocr Rev* 29: 76-131, 2008.
140. Antoun S, Birdsell L, Sawyer MB, Venner P, Escudier B and Baracos VE: Association of skeletal muscle wasting with treatment with sorafenib in patients with advanced renal cell carcinoma: Results from a Placebo-controlled study. *J Clin Oncol* 28: 1054-1060, 2010.
141. Mir-Bonafé JF, Saceda-Corrado D and Vañó-Galván S: Adverse hair reactions to new targeted therapies for cancer. *Actas Dermosifiliogr (Engl Ed)* 110: 182-192, 2019.
142. Kim KI, Jung KE, Shin YB, Kim CD and Yoon TJ: Sorafenib induces pigmentation via the regulation of β -catenin signalling pathway in melanoma cells. *Exp Dermatol* 31: 57-63, 2022.
143. Li W, Man XY, Li CM, Chen JQ, Zhou J, Cai SQ, Lu ZF and Zheng M: VEGF induces proliferation of human hair follicle dermal papilla cells through VEGFR-2-mediated activation of ERK. *Exp Cell Res* 318: 1633-1640, 2012.
144. Hartmann JT and Kanz L: Sunitinib and periodic hair depigmentation due to temporary c-KIT inhibition. *Arch Dermatol* 144: 1525-1526, 2008.
145. Gole P, Madke B, Khopkar U, Kumar P, Noronha V and Yadav M: Side effects of Sorafenib and sunitinib: A new concern for dermatologist and oncologist. *Indian Dermatol Online J* 5: 89-91, 2014.
146. Jeong SM and Yoon TJ: Development of pigmentation-regulating agents by drug repositioning. *Int J Mol Sci* 22: 3894, 2021.
147. Hansen T, Little AJ, Miller JJ and Ioffreda MD: A case of inflammatory nonscarring alopecia associated with the tyrosine kinase inhibitor nilotinib. *JAMA Dermatol* 149: 330-332, 2013.
148. Galanis A and Levis M: Inhibition of c-Kit by tyrosine kinase inhibitors. *Haematologica* 100: e77-e79, 2015.
149. Ibrahim N, Yu Y, Walsh R. W and Yang JL: Molecular targeted therapies for cancer: Sorafenib monotherapy and its combination with other therapies (Review). *Oncol Rep* 27: 1303-1311, 2012.
150. Hsu CH, Shen YC, Shao YY, Hsu C and Cheng AL: Sorafenib in advanced hepatocellular carcinoma: Current status and future perspectives. *J Hepatocell Carcinoma* 1: 85-99, 2014.
151. Gedaly R, Angulo P, Chen C, Creasy KT, Spear BT, Hundley J, Daily MF, Shah M and Evers BM: The role of PI3K/mTOR inhibition in combination with sorafenib in hepatocellular carcinoma treatment. *Anticancer Res* 32: 2531-2536, 2012.
152. Dai N, Ye R, He Q, Guo P, Chen H and Zhang Q: Capsaicin and sorafenib combination treatment exerts synergistic anti-hepatocellular carcinoma activity by suppressing EGFR and PI3K/Akt/mTOR signaling. *Oncol Rep* 40: 3235-3248, 2018.
153. Yao J, Man S, Dong H, Yang L, Ma L and Gao W: Combinatorial treatment of Rhizoma Paridis saponins and sorafenib overcomes the intolerance of sorafenib. *J Steroid Biochem Mol Biol* 183: 159-166, 2018.
154. Man S, Yao J, Lv P, Liu Y, Yang L and Ma L: Curcumin-enhanced antitumor effects of sorafenib via regulating the metabolism and tumor microenvironment. *Food Funct* 11: 6422-6432, 2020.
155. Li ZJ, Dai HQ, Huang XW, Feng J, Deng JH, Wang ZX, Yang XM, Liu YJ, Wu Y, Chen PH, *et al*: Artesunate synergizes with sorafenib to induce ferroptosis in hepatocellular carcinoma. *Acta Pharmacol Sin* 42: 301-310, 2021.
156. Ma Y, Xu R, Liu X, Zhang Y, Song L, Cai S, Zhou S, Xie Y, Li A, Cao W and Tang X: LY3214996 relieves acquired resistance to sorafenib in hepatocellular carcinoma cells. *Int J Med Sci* 18: 1456-1464, 2021.
157. Chiou JF, Tai CJ, Wang YH, Liu TZ, Jen YM and Shiau CY: Sorafenib induces preferential apoptotic killing of a drug- and radio-resistant hep G2 cells through a mitochondria-dependent oxidative stress mechanism. *Cancer Biol Ther* 8: 1904-1913, 2009.
158. Tang K, Chen Q, Liu Y, Wang L and Lu W: Combination of metformin and sorafenib induces ferroptosis of hepatocellular carcinoma through p62-Keap1-Nrf2 pathway. *J Cancer* 13: 3234-3243, 2022.
159. Honma Y and Harada M: Sorafenib enhances proteasome inhibitor-mediated cytotoxicity via inhibition of unfolded protein response and keratin phosphorylation. *Exp Cell Res* 319: 2166-2178, 2013.
160. Duval AP, Troquier L, de Souza Silva O, Demartines N and Dormond O: Diclofenac potentiates Sorafenib-based treatments of hepatocellular carcinoma by enhancing oxidative stress. *Cancers (Basel)* 11: 1453, 2019.
161. Chen MY, Yadav VK, Chu YC, Ong JR, Huang TY, Lee KF, Lee KH, Yeh CT and Lee WH: Hydroxychloroquine (HCQ) modulates autophagy and oxidative DNA damage stress in hepatocellular carcinoma to overcome sorafenib resistance via TLR9/SOD1/hsa-miR-30a-5p/Beclin-1 axis. *Cancers (Basel)* 13: 3227, 2021.
162. Rong LW, Wang RX, Zheng XL, Feng XQ, Zhang L, Zhang L, Lin Y, Li ZP and Wang X: Combination of wogonin and sorafenib effectively kills human hepatocellular carcinoma cells through apoptosis potentiation and autophagy inhibition. *Oncol Lett* 13: 5028-5034, 2017.
163. Jakubowicz-Gil J, Langner E, Bądziul D, Wertel I and Rzeski W: Quercetin and sorafenib as a novel and effective couple in programmed cell death induction in human gliomas. *Neurotox Res* 26: 64-77, 2014.
164. Abdu S, Juaid N, Amin A, Moulay M and Miled N: Effects of sorafenib and quercetin alone or in combination in treating hepatocellular carcinoma: In vitro and in vivo approaches. *Molecules* 27, 2022 doi: 10.3390/molecules27228082.
165. Leung CON, Tong M, Chung KPS, Zhou L, Che N, Tang KH, Ding J, Lau EYT, Ng IOL, Ma S and Lee TKW: Overriding adaptive resistance to sorafenib through combination therapy with src homology 2 Domain-containing phosphatase 2 blockade in hepatocellular carcinoma. *Hepatology* 72: 155-168, 2020.
166. Nojiri K, Sugimoto K, Shiraki K, Tameda M, Inagaki Y, Ogura S, Kasai C, Kusagawa S, Yoneda M, Yamamoto N, *et al*: Sorafenib and TRAIL have synergistic effect on hepatocellular carcinoma. *Int J Oncol* 42: 101-108, 2013.
167. Jiang Z and Dai C: Potential treatment strategies for hepatocellular carcinoma cell sensitization to sorafenib. *J Hepatocell Carcinoma* 10: 257-266, 2023.
168. Abdu S, Juaid N, Amin A, Moulay M and Miled N: Therapeutic effects of crocin alone or in combination with sorafenib against hepatocellular carcinoma: In vivo & in vitro insights. *Antioxidants* 11: 1645, 2022.
169. Youssef MM, Tolba MF, Badawy NN, Liu AW, El-Ahwany E, Khalifa AE, Zada S and Abdel-Naim AB: Novel combination of sorafenib and biochanin-A synergistically enhances the anti-proliferative and pro-apoptotic effects on hepatocellular carcinoma cells. *Sci Rep* 6: 30717, 2016.
170. Rouleau L, Antony AN, Bisetto S, Newberg A, Doria C, Levine M, Monti DA and Hoek JB: Synergistic effects of ascorbate and sorafenib in hepatocellular carcinoma: New insights into ascorbate cytotoxicity. *Free Radic Biol Med* 95: 308-322, 2016.
171. Liu Y, Liu J, Cheng L, Fan L, Wang F, Yu H, Li Y, Bu L, Li X, Wei W, *et al*: Melatonin increases the anti-tumor effects of sorafenib on human hepatoma cell lines via down-regulating autophagy. *Int J Clin Exp Med* 10: 14109-14120, 2017.

172. Lin S, Hoffmann K, Gao C, Petrulionis M, Herr I and Schemmer P: Melatonin promotes sorafenib-induced apoptosis through synergistic activation of JNK/c-jun pathway in human hepatocellular carcinoma. *J Pineal Res* 62: e12398, 2017.
173. Prieto-Domínguez N, Méndez-Blanco C, Carbajo-Pescador S, Fondevila F, García-Palomo A, González-Gallego J and Mauriz JL: Melatonin enhances sorafenib actions in human hepatocarcinoma cells by inhibiting mTORC1/p70S6K/HIF-1 α and hypoxia-mediated mitophagy. *Oncotarget* 8: 91402, 2017.
174. Prieto-Domínguez N, Ordóñez R, Fernández A, Méndez-Blanco C, Baulies A, García-Ruiz C, Fernández-Checa JC, Mauriz JL and González-Gallego J: Melatonin-induced increase in sensitivity of human hepatocellular carcinoma cells to sorafenib is associated with reactive oxygen species production and mitophagy. *J Pineal Res* 61: 396-407, 2016.
175. Long F, Dong C, Jiang K, Xu Y, Chi X, Sun D, Liang R, Gao Z, Shao S and Wang L: Melatonin enhances the anti-tumor effect of sorafenib via AKT/p27-mediated cell cycle arrest in hepatocarcinoma cell lines. *RSC Adv* 7: 21342-21351, 2017.
176. Chen W, Yang J, Zhang Y, Cai H, Chen X and Sun D: Regorafenib reverses HGF-induced sorafenib resistance by inhibiting epithelial-mesenchymal transition in hepatocellular carcinoma. *FEBS Open Bio* 9: 335-347, 2019.
177. Zhao F, Feng G, Zhu J, Su Z, Guo R, Liu J, Zhang H and Zhai Y: 3-Methyladenine-enhanced susceptibility to sorafenib in hepatocellular carcinoma cells by inhibiting autophagy. *Anticancer Drugs* 32: 386-393, 2021.
178. Li S, Dai W, Mo W, Li J, Feng J, Wu L, Liu T, Yu Q, Xu S, Wang W, *et al*: By inhibiting PFKFB3, aspirin overcomes sorafenib resistance in hepatocellular carcinoma. *Int J Cancer* 141: 2571-2584, 2017.
179. Shen YC, Ou DL, Hsu C, Lin KL, Chang CY, Lin CY, Liu SH and Cheng AL: Activating oxidative phosphorylation by a pyruvate dehydrogenase kinase inhibitor overcomes sorafenib resistance of hepatocellular carcinoma. *Br J Cancer* 108: 72-81, 2013.
180. Mao J, Yang H, Cui T, Pan P, Kabir N, Chen D, Ma J, Chen X, Chen Y and Yang Y: Combined treatment with sorafenib and silibinin synergistically targets both HCC cells and cancer stem cells by enhanced inhibition of the phosphorylation of STAT3/ERK/AKT. *Eur J Pharmacol* 832: 39-49, 2018.
181. Gu HR, Park SC, Choi SJ, Lee JC, Kim YC, Han CJ, Kim J, Yang KY, Kim YJ, Noh GY, *et al*: Combined treatment with silibinin and either sorafenib or gefitinib enhances their growth-inhibiting effects in hepatocellular carcinoma cells. *Clin Mol Hepatol* 21: 49-59, 2015.
182. Singh D, Khan MA, Akhtar K, Arjmand F and Siddique HR: Apigenin alleviates cancer drug Sorafenib induced multiple toxic effects in Swiss albino mice via anti-oxidative stress. *Toxicol Appl Pharmacol* 447: 116072, 2022.
183. Sharma A, Sinha S and Shrivastava N: Apigenin and kaempferol as novel renoprotective agent against cisplatin-induced toxicity: An in vitro study. *Nat Prod Res* 36: 6085-6090, 2022.
184. Jiang H, Wang C, Zhang A, Li Y, Li J, Li Z, Yang X and Hou Y: ATF4 protects against sorafenib-induced cardiotoxicity by suppressing ferroptosis. *Biomed Pharmacother* 153: 113280, 2022.
185. Li Y, Yan J, Zhao Q, Zhang Y and Zhang Y: ATF3 promotes ferroptosis in sorafenib-induced cardiotoxicity by suppressing SLC7A11 expression. *Front Pharmacol* 13: 904314, 2022.
186. Fatma H, Jameel M, Akhtar K, Ansari MA and Siddique HR: Implication of Lupeol in compensating Sorafenib-induced perturbations of redox homeostasis: A preclinical study in mouse model. *Life Sci* 322: 121647, 2023.
187. Sargazi S, Arshad R, Ghamari R, Rahdar A, Bakhshi A, Karkan SF, Ajalli N, Bilal M and Díez-Pascual AM: siRNA-based nanotherapeutics as emerging modalities for immune-mediated diseases: A preliminary review. *Cell Biol Int* 46: 1320-1344, 2022.
188. Fathi-karkan S, Zeeshan M, Qindeel M, Eshaghi Malekshah R, Rahdar A and Ferreira LFR: NPs loaded with zoledronic acid as an advanced tool for cancer therapy. *J Drug Deliv Sci Technol* 87: 104805, 2023.
189. Pourmadadi M, Gerami SE, Ajalli N, Yazdian F, Rahdar A, Fathi-karkan S and Aboudzadeh MA: Novel pH-responsive hybrid hydrogels for controlled delivery of curcumin: Overcoming conventional constraints and enhancing cytotoxicity in MCF-7 cells. *Hybrid Adv* 6: 100210, 2024.
190. Fathi-Karkan S, Qindeel M, Arshad R, Moafian Z, Ghazy E, Rahdar A and Ghotekar S: Recent advancements in Irinotecan-loaded nanomaterials as a smart drug delivery system for cancer therapy: A state-of-art-review. *Inorg Chem Commun* 161: 112028, 2024.
191. Naderi J, Valizadeh N, Banimohamad-Shotorbani B, Shahgolzari M, Shayegh F, Maleki-baladi R, Sargazi S and Sargazi S: Exploring the biomedical potential of iron vanadate Nanoparticles: A comprehensive review. *Inorg Chem Commun* 157: 111423, 2023.
192. Pourmadadi M, Abdouss H, Memarzadeh A, Abdouss M, Fathi-karkan S, Rahdar A and Díez-Pascual AM: Innovative chitosan-polyacrylic acid-MoS₂ nanocomposite for enhanced and pH-responsive quercetin delivery. *Mater Today Commun* 39: 108724, 2024.
193. Yi H, Ye X, Long B, Ye T, Zhang L, Yan F, Yang Y and Li L: Inhibition of the AKT/mTOR pathway augments the anticancer effects of sorafenib in thyroid cancer. *Cancer Biother Radiopharm* 32: 176-183, 2017.
194. Hamza R: Protective effect of antioxidants combinations (Vit A, C, E and Selenium) (Antox Drug) against oxidative stress and cellular toxicity induced by sorafenib in male albino rats. *J Chem Pharmaceutical Res* 10: 43-50, 2018.
195. Schott E, Ebert MP and Trojan J: Treatment of hepatocellular carcinoma with Sorafenib-focus on special populations and adverse event management. *Z Gastroenterol* 50: 1018-1027, 2012.
196. Faivre S, Rimassa L and Finn RS: Molecular therapies for HCC: Looking outside the box. *J Hepatol* 72: 342-352, 2020.
197. Wen F, Zheng H, Zhang P, Liao W, Zhou K and Li Q: Atezolizumab and bevacizumab combination compared with sorafenib as the first-line systemic treatment for patients with unresectable hepatocellular carcinoma: A cost-effectiveness analysis in China and the United states. *Liver Int* 41: 1097-1104, 2021.
198. Li J, Zhang F, Yang J, Zhang Y, Wang Y, Fan W, Huang Y, Wang W, Ran H and Ke S: Combination of individualized local control and target-specific agent to improve unresectable liver cancer managements: A matched case-control study. *Target Oncol* 10: 287-295, 2015.
199. Galmiche A, Chauffert B and Barbare JC: New biological perspectives for the improvement of the efficacy of sorafenib in hepatocellular carcinoma. *Cancer Lett* 346: 159-162, 2014.
200. Huang A, Zhao X, Yang XR, Li FQ, Zhou XL, Wu K, Zhang X, Sun QM, Cao Y, Zhu HM, *et al*: Circumventing intratumoral heterogeneity to identify potential therapeutic targets in hepatocellular carcinoma. *J Hepatol* 67: 293-301, 2017.
201. Rani S, Kataria A, Bhambri P, Pareek PK and Puri V: Artificial Intelligence in Personalized Health Services for Better Patient Care BT-revolutionizing Healthcare: AI Integration with IoT for Enhanced Patient Outcomes. Gupta SK, Karras DA and Natarajan R (eds). Springer Nature Switzerland, Cham, pp89-108, 2024.
202. Fung AS, Tam VC, Meyers DE, Sim HW, Knox JJ, Zaborska V, Davies J, Ko YJ, Batuyong E, Samawi H, *et al*: Second-line treatment of hepatocellular carcinoma after sorafenib: Characterizing treatments used over the past 10 years and real-world eligibility for cabozantinib, regorafenib, and ramucirumab. *Cancer Med* 9: 4640-4647, 2020.
203. Rallis KS, Makrakis D, Ziogas IA and Tsoulfas G: Immunotherapy for advanced hepatocellular carcinoma: From clinical trials to real-world data and future advances. *World J Clin Oncol* 13: 448, 2022.
204. Zheng L, Fang S, Wu F, Chen W, Chen M, Weng Q, Wu X, Song J, Zhao Z and Ji J: Efficacy and safety of TACE combined with sorafenib plus immune checkpoint inhibitors for the treatment of intermediate and advanced TACE-refractory hepatocellular carcinoma: A retrospective study. *Front Mol Biosci* 7: 609322, 2021.
205. Turcios L, Vilchez V, Acosta LF, Poyil P, Butterfield DA, Mitov M, Marti F and Gedaly R: Sorafenib and FH535 in combination act synergistically on hepatocellular carcinoma by targeting cell bioenergetics and mitochondrial function. *Dig Liver Dis* 49: 697-704, 2017.
206. Abbadessa G, Rimassa L, Pressiani T, Carrillo-Infante C, Cucchi E and Santoro A: Optimized management of advanced hepatocellular carcinoma: Four Long-lasting responses to sorafenib. *World J Gastroenterol* 17: 2450, 2011.
207. Chen F, Fang Y, Chen X, Deng R, Zhang Y and Shao J: Recent advances of sorafenib nanoformulations for cancer therapy: Smart nanosystem and combination therapy. *Asian J Pharm Sci* 16: 318-336, 2021.

