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Review

Combination of niclosamide and current therapies to overcome resistance for cancer: New frontiers for an old drug

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ABSTRACT

Niclosamide is a drug used to treat parasitic infections. Recent studies have shown that niclosamide may have a wide range of clinical applications and can be used to treat cancer and other diseases. However, its application is also limited by its water solubility and safety, and drug resistance to cancer. To solve these problems, some studies have shown that niclosamide can be used in combination with chemotherapeutic drugs, targeted drugs, radiotherapy, and immunotherapy to enhance the anti-tumor effect. This review summarizes the drug combination strategies and therapeutic effect of niclosamide, to provide a reference for the combination therapy of niclosamide and wider application of antitumor drugs.

1. Introduction

Niclosamide is an FDA-approved anti-worm drug and exerts its anthelmintic effect by uncoupling oxidative phosphorylation [1,2]. In the past few years, niclosamide has been identified as a multifunctional drug through drug repurposing. It can regulate a variety of signaling pathways and biological processes, including Wnt/β-catenin [3], mTORC1 [4], STAT3 [5], nuclear factor-κB (NF-κB) [6], Notch [7], NS2B-NS3 interaction [8], and pH [9], indicating that it may treat human diseases, such as cancer [10], bacterial [11]and viral infection [12], and metabolic diseases [13].

It is worth noting that niclosamide has several weaknesses that cannot be ignored, such as cytotoxicity and limited water solubility, relatively low absorption rate, and low oral bioavailability, which may affect a variety of signal pathways and lead to side effects [14]. These factors may hinder its extensive clinical application as an antitumor or antiviral drug. Therefore, the development of new methods to use niclosamide will determine whether the drug repurposing of niclosamide can be successful.

At present, studies have shown that niclosamide can be used not only in one-way treatment but also in combination treatment [15]. Therefore, using the way of the drug combination to achieve a synergistic effect or improve its antitumor effect will be beneficial. Moreover, drug resistance and recurrence are the main challenges of cancer treatment, but combination therapy for different pathways may be able to meet these challenges. This review summarizes the drug combination strategies of niclosamide in the treatment of cancer, providing a clear understanding of drug repurposing of niclosamide to achieve better antitumor effects.

2. The effect of niclosamide on cancer therapy

In the previous review on niclosamide, it was mentioned that niclosamide has a wide range of drug activities in addition to antiparasitic activities, such as activities treating bacterial infection, viruses [16], metabolic diseases, artery constriction, endometriosis, neuropathic pain, rheumatoid arthritis, sclerodermatous graft-versus-host disease and systemic sclerosis [17,18]. Among them, the antitumor activity of niclosamide has attracted attention. Niclosamide's anticancer activity has been confirmed in human breast cancer [19], prostate

Abbreviations: Dox, Adriamycin; ARA-a, Cytarabine; DDP, Cisplatin; STAT, Signal transducers and activators of transcription; NF-κB, Nuclear factor-κB; HER2, Human epidermal growth factor receptor 2; EMT, Epithelial-mesenchymal transition; ER, Estrogen receptor; CS, Cisplatin sensitive cells; CR, Cisplatin-resistant cells; EGFR, Epidermal growth factor; VEGFR, Vascular endothelial growth factor receptor; PDGF, Platelet-derived growth factor; CDKs, Cyclin-dependent kinases; TKI, Tyrosine kinase inhibitor; P-gP, P-glycoprotein; NFAT, Nuclear factor of activated T cells; MDR, Multidrug resistance.

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cancer [20,21], colon cancer [22,23], ovarian cancer [24], multiple myeloma [25], acute myelogenous leukemia [26], glioblastoma [27], adrenocortical carcinoma [28], osteosarcoma [29–31], head and neck cancer [32], lung cancer [33], oral cancer [34]. Niclosamide can inhibit the proliferation of cancer cells and have minimal effect on normal cells and has no obvious toxicity to nonmalignant tumor cancer cells and can inhibit the migration and invasion of cancer cells [15,35]and the activity of cancer stem cells [36].

The anticancer activity of niclosamide is related to its ability to damage the mitochondria of tumor cells, block a variety of signal pathways controlling the beginning and progression of cancer, induce cancer cell cycle arrest, and induce the growth inhibition and apoptosis of cancer cells [37]. Niclosamide can inhibit a variety of abnormal cancer signaling pathways, including Wnt/β-catenin, mTORC1, STAT3, NF-κB, and Notch pathway [24,38–41].

3. Combination therapy of niclosamide

Clinical treatment methods for cancer mainly include the following: chemotherapy, targeted therapy, radiotherapy, immunotherapy, and surgery (Fig. 1). However, chemotherapy has limitations such as adverse drug reactions, toxicity, and cell line heterogeneity. Targeted drugs also have the characteristics of selectivity to patients and are easy to produce drug resistance. Meanwhile, the radiation tolerance of tumor-adjacent tissues affects the effectiveness of radiotherapy, immunotherapy is not yet a complete cure for tumors and needs to be explored, and surgery is high-risk and invasive. Therefore, it is very important to develop new therapies. The combination of niclosamide with chemotherapeutic drugs, targeted drugs, radiotherapy, and immunotherapy can restore drug sensitivity, and greatly enhance the antitumor effect. (Fig. 2).

3.1. Combined treatment of niclosamide with chemotherapeutic drugs

Chemotherapy is one of the main methods to treat tumors. Chemotherapeutic drugs can act on different stages of tumor cell growth and reproduction, and inhibit or kill tumor cells [42]. According to the source and chemical structure of drugs, they are divided into botanical drugs, alkylating agents, antimetabolic drugs, anticancer antibiotics, platinum anticancer drugs, and complex. The combination of niclosamide and chemotherapeutic drugs can have a synergistic anti-tumor effect (Fig. 3, Table 1).

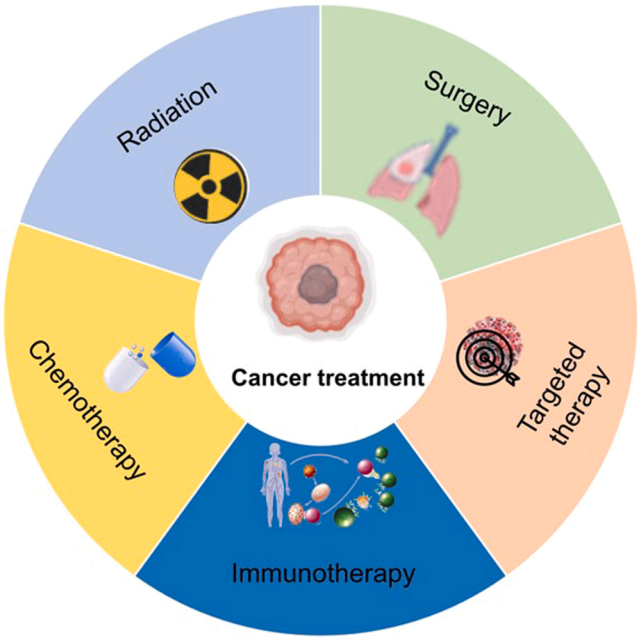

Fig. 1. The current strategies for tumor treatment. The treatment strategies for cancer mainly include chemotherapy, targeted therapy, radiotherapy, immunotherapy and surgery.

3.1.1. Botanical drugs

Botanical drugs are alkaloids and natural products. They can inhibit mitosis or the action of enzymes, to prevent the synthesis of proteins necessary for cell regeneration [43]. They are often used in combination with other anticancer drugs in the treatment of a variety of cancers.

Paclitaxel is a natural anticancer drug that inhibits mitosis and triggers apoptosis of cancer cells, and then effectively prevents the proliferation of cancer cells [44]. The treatment with the combination of niclosamide and paclitaxel is more effective than paclitaxel alone. Niclosamide inhibits the proliferation and induces apoptosis of paclitaxel-resistant esophageal cancer cells, enhances the efficacy of paclitaxel in vivo, and significantly inhibites the growth of paclitaxel-resistant esophageal cancer without toxicity to mice by targeting Wnt/β-catenin pathway [3]. Niclosamide can also increase the sensitivity of cervical cancer cells to paclitaxel by inhibiting the mTOR pathway that is modulated by oxidative stress [45]. Paclitaxel and niclosamide thermosensitive nanocrystal hydrogel can be used in chemotherapy for triple-negative breast cancer by decreasing the expression of Ki67 and CD44 to inhibit cell proliferation and migration and induce apoptosis [46].

3.1.2. Alkylating agent

Alkylating agents act directly on DNA to prevent cancer cell regeneration. Temozolomide is an antitumor drug that can spontaneously and quickly degrade in vivo to produce an antitumor effect [47]. Niclosamide and temozolomide can be combined to treat glioblastoma (GBM). This combined treatment significantly down-regulated the expression of epithelial-mesenchymal transition-related markers, Zeb1, N-cadherin, and β-catenin, which can effectively reduce the viability, stem cell characteristics, and invasiveness of GBM and prolong the survival time of patients, which indicates that this combination may be the choice of clinical treatment for GBM patients [48,49].

3.1.3. Antimetabolic chemotherapeutic drugs

Antimetabolic drugs interfere with DNA and RNA synthesis. Cytarabine (ARA-a) is a drug mainly used in leukemia [50]. Clinically, it is mainly used as a pyrimidine antimetabolic drug in the S phase. It interferes with cell proliferation by inhibiting the synthesis of DNA [51]. Etoposide is a cell cycle-specific antitumor drug that acts on DNA topoisomerase II to form a drug-blocking DNA repair [52]. Niclosamide has a synergistic effect with acute myeloid leukemia (AML) first-line chemotherapy drugs Ara-A and etoposide by inhibiting the CREB-dependent pathway and NF-κB pathway and increasing ROS levels [53] and has an inhibitory effect on cell proliferation in acute myeloid leukemia cells [54], which has been further confirmed in acute myeloid leukemia stem cells [55].

3.1.4. Antibiotic chemotherapeutic drugs

Antibiotics interfere with DNA by inhibiting the action of enzymes and mitosis or altering cell membranes [56]. Daunorubicin is mainly used in acute lymphocytic or granulocytic leukemia resistant to common antitumor drugs. It can embed DNA and inhibit the synthesis of RNA and DNA, but the remission period is short, so it needs to be combined with other drugs [57]. Niclosamide has a synergistic effect with Daunorubicin by inhibiting the NF-κB pathway and increasing ROS levels [53].

Adriamycin (Dox) is an anthracycline drug. It is used as a first-line treatment for many cancers in clinical practice and is the standard treatment for breast cancer [58]. Treatment with Dox and niclosamide induces apoptosis. In terms of mechanism, niclosamide downregulates the Wnt/β-catenin signaling pathway and makes cell cycle arrest in G0/G1 phase. The increase of reactive oxygen species by niclosamide and DOX, and the inherent cytotoxicity of DOX mediate the synergistic

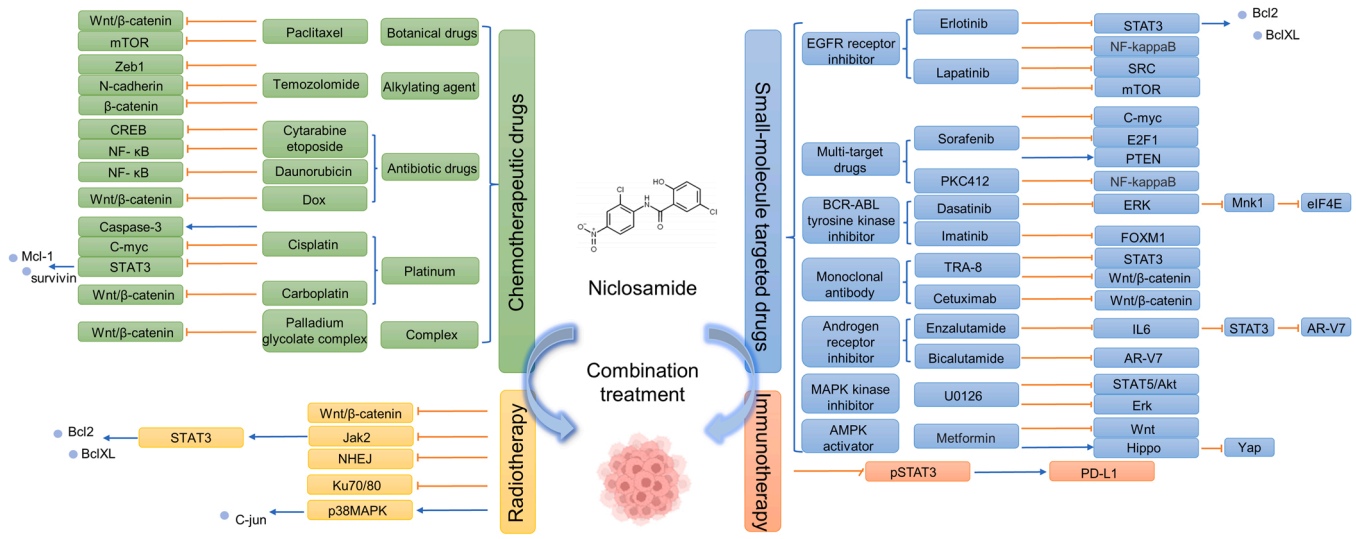

Fig. 2. The mechanism of niclosamide and chemotherapy, targeted therapy, radiotherapy and immunotherapy in the combination treatment of cancer.

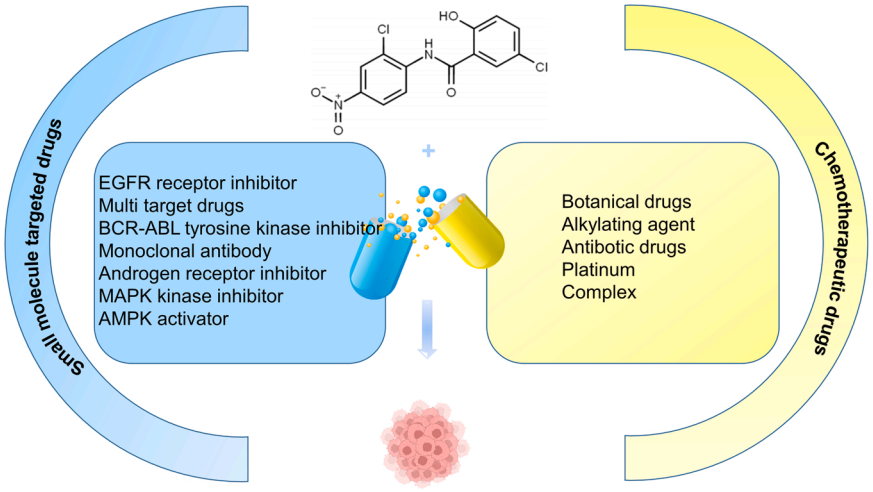

Fig. 3. Drug combination therapy of niclosamide. The combined treatment of niclosamide and drugs mainly includes chemotherapy drugs and targeted drugs. Among them, chemotherapy drugs can be divided into botanical drugs, alkylating agent, antibotic drugs, platinum and complex. Small molecular targeted drugs can be divided into EGFR receptor inhibitor, multi target drugs, BCR-ABL tyrosine kinase inhibitor, monoclonal antibody, androgen receptor inhibitor, MAPK kinase inhibitor, AMPK activator.

therapeutic effect of the two drugs [59].

3.1.5. *Platinum compounds*

Oxaliplatin is a third-generation platinum anticancer drug. It targets DNA and inhibits its replication and transcription [60]. However, neuropathic pain is a limiting factor of chemotherapy of platinum [61]. Studies have shown that niclosamide can improve the therapeutic effect of oxaliplatin by reducing the neurodegenerative side effects of oxaliplatin and enhancing the cytotoxicity to cancer cells, and can prevent oxaliplatin from inducing IL6 and TNF-α and elevating levels of advanced oxidized protein products [62]. In vitro and in vivo, it can have neuroprotective effects by limiting the ability of oxaliplatin to induce oxidative stress and neuroinflammation [62]. In addition, in HCT116, HT29, and Caco2 colorectal cancer cell lines, treatment with niclosamide increases the antiproliferative activity of oxaliplatin [23,62].

Cisplatin (DDP) is a cell nonspecific drug that can bind to DNA, cause cross-connection, disable the function of DNA and inhibit cell mitosis [63]. STAT3 activation is a critical signaling pathway to survive HER2 (Human epidermal growth factor receptor 2) resistant breast cancer patients [64]. Chung et al. reported that in HER2 overexpressing breast cancer, STAT3 activation can promote CSC (Cancer stem cell) characteristics [65], while niclosamide is an effective STAT3 inhibitor that inhibits STAT3 phosphorylation at Tyr705 [66], and this inhibition also affects other pathways, including Wnt/β-Catenin pathway associated with cancer progression and progression [67]. Therefore, niclosamide inhibits the growth and EMT (epithelial-mesenchymal transition) of ER (Estrogen receptor) and HER2-positive breast cancer cells by inhibiting STAT3 phosphorylation and inducing apoptosis by downregulation of Bcl-2 [68]. Meanwhile, niclosamide can induce mitochondrial disintegration and the production of mitochondrial superoxide [25,37]. Therefore, niclosamide combined with cisplatin can inhibit the invasion, EMT, and viability of breast cancer cells, and inhibit the resistance of HER2-positive breast cancer cells to cisplatin [68]. Triple-negative breast cancer (TNBC) is one of the most difficult breast cancers to treat. Because there is no targeted therapy. Traditional cytotoxic chemotherapy and adjuvant radiotherapy are the standard treatment for TNBC patients. Liu et al. found that niclosamide reverses the process of EMT, inhibits Akt, Erk, and Src signaling pathways significantly inhibits the expression of Ki67, and inhibits the proliferation of cisplatin sensitive cells (CS) and cisplatin-resistant cells (CR) in triple-negative breast cancers in vitro [69]. This suggests that niclosamide alone or in combination with cisplatin might be a new strategy for the treatment of cisplatin-resistant TNBC. Cisplatin-based chemotherapy is the basis for the treatment of most advanced non-small cell lung cancer patients. However, DDP resistance limits its clinical application. Niclosamide can

Table 1
Mechanism and function of drug combination treatment with niclosamide and chemotherapeutic drugs.

Drug type	Cancer type	Treatment	Mechanism	Function	Reference
Botanical drugs	Esophageal cancer	Paclitaxel	The target of the Wnt/β-catenin signaling pathway	Inhibition of cell proliferation, induction of apoptosis, enhancement of efficacy of paclitaxel	[3]
Botanical drugs	Cervical carcinoma	Paclitaxel	Inhibition of the mTOR pathway	Increase in drug sensitivity	[45]
Botanical drugs	Breast cancer	Paclitaxel	Decrease of the expression of Ki67 and CD44	Paclitaxel and niclosamide nanocrystal thermosensitive hydrogel can be used inhibit cell proliferation and migration and induce apoptosis.	[46]
Alkylating agent	Glioblastoma	Temozolomide	Downregulation of Zeb1, N-cadherin, and β-catenin	Inhibition of survival and invasion ability	[48,49]
Antimetabolic drugs	Leukemia	Cytarabine, etoposide,	Inhibition of CREB-dependent pathway and NF-κB pathway, increase of ROS levels	Synergistic effect with niclosamide that inhibits cell proliferation	[53–55]
Antibiotic	Leukemia	Daunorubicin	Inhibition of the NF-κB pathway, increase of ROS levels	Synergistic effect with niclosamide that inhibits cell proliferation	[53]
Antibiotic	Breast cancer	Dox	Downregulation of Wnt/β-catenin signal, arrestment of the cycle in the G0/G1 phase, increase of reactive oxygen species, and cytotoxicity	Induction of cell death	[59]
Platinum anticancer drugs	Colorectal cancer	Oxaliplatin	Induction of IL6 and TNF-α	Inhibition of cell proliferation and neuroinflammation	[23,62]
Platinum anticancer drugs	Breast cancer	Cisplatin	Inhibition of STAT3, Akt, Erk and ERC, downregulation of Bcl-2	Inhibition of cell proliferation, EMT and invasion, induction of apoptosis	[68,69]
Platinum anticancer drugs	NSCLS	Cisplatin	Activation of caspase-3, inhibition of the expression of lung resistance-related protein and c-myc	Induction of apoptosis, enhancement of the cytotoxicity	[70]
Platinum anticancer drugs	HCC	Cisplatin	Inhibition of STAT3 pathway, block of the anti-apoptotic function of Mcl-1, and Survivin	Promotion of cell apoptosis, inhibition of cell growth, enhancement of drug sensitivity	[40]
Platinum anticancer drugs	Ovarian cancer	Carboplatin	Abolishment of Wnt/β-catenin signal transduction	Induction of cell death	[72,73]
Complex	Breast cancer	Palladium glycolate complex	Interference of Wnt signal pathway	Enhancement of the activity of inducing apoptosis of breast cancer stem cells	[74]

induce apoptosis by activating caspase-3, inhibit the expression of drug-resistant related protein and c-myc, and enhance the cytotoxicity of cisplatin on cisplatin-resistant human lung cancer cells. It is expected to become a candidate drug for the treatment of lung cancer [70]. Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor in the world, with high late mortality. Niclosamide enhanced cisplatin-induced cell apoptosis by inhibiting the STAT3 signal pathway and blocking the anti-apoptotic function of Mcl-1 and Survivin, which indicates that niclosamide has synergistic effects with cisplatin to increase the drug sensitivity of HCC cells [40].

Carboplatin is a cell cycle nonspecific drug that can combine with DNA, destroy the function of DNA, make it unable to replicate and synthesize, and kill cancer cells at all stages of growth [71]. Ovarian cancer is a malignant tumor. Niclosamide induces cell death by abolishing Wnt7a/β-signal transduction, inhibiting the transcriptional activity of β-catenin, oral niclosamide can inhibit the growth and progression of xenograft ovarian cancer tumors in animal models, and combination treatment produced increased cytotoxicity compared to single agent treatment [72,73].

3.1.6. Complex

The palladium (II) saccharide complex of terpyridine ([PdCl (terpy)] (SAC) 2H2O) enhances the cytotoxicity of niclosamide that induces apoptosis of breast cancer stem cells [74]. The Wnt signaling pathway is one of the most critical signaling pathways of cancer stem cells. It is reactivated in CSCs and has an important role in the survival, self-renewal, and proliferation of these cells. Niclosamide is an inhibitor of the Wnt signaling pathway associated with breast cancer stem cells [74]. Since its good cytotoxic effect on cancer stem cells that cause breast cancer recurrence, the application of this combination therapy may be regarded as a new effective way to treat breast cancer.

3.2. Combined treatment of niclosamide with small molecule targeted drugs

The action pathways of molecular targeted drugs include signal pathways that regulate cell proliferation and angiogenesis and transduction of tumor suppressor genes that lose their function. Molecular targeted therapy will be more effective and have fewer side effects than chemotherapy, and it is a very promising cancer treatment strategy. Limitations such as drug resistance can be overcome when targeted drugs are used in combination with niclosamide [75] (Fig. 3, Table 2).

3.2.1. Epidermal growth factor (EGFR) receptor inhibitor

Erlotinib is a small molecule targeted therapeutic drug and an inhibitor of epidermal growth factor tyrosine kinase [76]. Erlotinib inhibits the expression of EGFR and induces the activation of STAT3, which leads to the generation of drug resistance. Niclosamide can overcome erlotinib resistance by inhibiting the STAT3 signaling pathway [77]. The combined inhibition of epidermal growth factor receptor and STAT3 by erlotinib and niclosamide can synergistically induce the apoptosis of colon cancer cell lines and have the effect of inhibiting cell proliferation [77]. In non-small cell lung cancer, they also have synergistic effects, which can effectively inhibit the growth of allografted tumors that are resistant to erlotinib and increase apoptosis in tumor tissues [78]. The possible mechanism is to inhibit STAT3 and block the STAT3/Bcl-2/Bcl-XL pathway. EGFR is widely expressed in head and neck cancer. However, the efficacy of EGFR targeted therapy in head and neck cancer is not obvious, because the inhibition of EGFR by erlotinib stimulates the phosphorylation and activation of STAT3, increasing Bcl-2 and Bcl-XL levels. Niclosamide has a blocking effect on STAT3/ Bcl-2 /Bcl-XL pathway [79]. Erlotinib combined with niclosamide inhibits EGFR and STAT3 and more effectively induces apoptosis of tumor tissues, is non-toxic to normal tissues, which may be a new and

Table 2
Mechanism and function of drug combination treatment with niclosamide and small-molecule targeted drugs.

Drug type	Cancer type	Treatment	Mechanism	Function	Reference
EGFR receptor inhibitor	Colon cancer	Erlotinib	Inhibition of STAT3 signaling pathway	Overcome of the resistance to erlotinib, induction of apoptosis, inhibition of cell proliferation	[77]
EGFR receptor inhibitor	NSCLC	Erlotinib	Inhibition of STAT3 signal, block of STAT3/Bcl-2/Bcl-XL signal pathway	Inhibition of tumor growth, induction of cancer cell apoptosis	[78]
EGFR receptor inhibitor	Head and neck cancer	Erlotinib	Inhibition of STAT3 signal, block of STAT3/Bcl-2/Bcl-XL signal pathway	Synergistic therapy	[79]
EGFR receptor inhibitor	Breast cancer	Lapatinib	Interference with NF-κB, SRC, and mTOR signal pathways	Inhibition of tumor growth	[68,82]
Multi-target drugs	Renal cell carcinoma	Sorafenib	Inhibition of the expression of c-myc and E2F1, induction of the expression of PTEN	Synergistic inhibition of cancer cell proliferation and survival	[85]
Multi-target drugs	EMAIL	PKC412	Inhibition of NF-κB pathway	Synergistic induction of cancer cell apoptosis	[53]
BCR-ABL tyrosine kinase inhibitor	CML	Dasatinib	Inhibition of Erk/mnk1/eIF4E pathway	Enhancement of the drug sensitivity to dasatinib, inhibition of cell proliferation, induction of apoptosis, and target of BP-CML CD34 stem cells	[88]
BCR-ABL tyrosine kinase inhibitor	CML	Imatinib	Block of the interaction between p65 and FoxM1/B-18, inhibition of the transcription of the BCR-ABL gene by inhibiting SP1	Eradication of the role of leukemia stem cells in chronic myeloid leukemia and induction of cancer cell death	[91]
Monoclonal antibody drugs	Breast cancer	TRA-8	Inhibition of Wnt/β-catenin and STAT3 signals	Inhibition of tumor growth	[93]
Monoclonal antibody drugs	CRC	Cetuximab	Inhibition of Wnt/β-catenin signal	Restore the drug sensitivity of CRC	[95,96]
Androgen receptor inhibitor	Prostatic cancer	Abiraterone	Inhibition of AR-V7	Reverse of the resistance to abiraterone	[99]
Androgen receptor inhibitor	Prostatic cancer	Enzalutamide	Downregulation of the expression of AR-V7 protein through the proteasome-dependent pathway, the target of the IL6-STAT3-AR signaling pathway	Overcome of the enzalutamide resistance and inhibition of the migration and invasion of advanced prostate cancer	[100, 101]
Androgen receptor inhibitor	Prostatic cancer	Bicalutamide	Target of AR-V7	Overcome of bicalutamide and enzalutamide drug resistance, enhancement of the therapeutic effect of bicalutamide, and inhibition of the growth of drug-resistant tumors	[103, 104]
CDKs	Lymphoma	Alvocidib		Synergistic effects with niclosamide	[107]
MAPK kinase inhibitor	CML	U0126	Diminishment an enrichment of Sp1, decrease of WT- and T315I-BCR-ABL transcription, and STAT5 and Akt	Synergistic induction of apoptosis and inhibition of cell proliferation	[91]
MAPK kinase inhibitor	Osteosarcoma	U0126	Inhibition of the TGFBI expression via ERK pathway	Inhibition of the migratory ability	[30]
AMPK activator	Colorectal cancer	Metformin	Inhibition of Wnt and YAP signal and activate Hippo signal	Synergistic antitumor effect	[108, 109]

effective treatment strategy to improve the prognosis of patients with head and neck cancer. Reversal of drug resistance by niclosamide in bladder cancer is also confirmed [80].

Lapatinib is a receptor tyrosine kinase inhibitor that inhibits epidermal growth factor receptor (ErbB1) and human epidermal factor receptor 2 (ErbB2) [81]. Niclosamide reverses epithelial-mesenchymal transformation, induces apoptosis, and inhibits the growth of growth factor receptor 2 positive breast cancer cells by interfering with the abnormal signal pathway (NF-κB, Src, and mTOR) [68,82].

3.2.2. *Multitarget small-molecule targeted drugs*

Sorafenib is a new multi-target antitumor drug with dual antitumor effects: it can not only directly inhibit the proliferation of tumor cells by blocking the cell signal transduction pathway mediated by Raf/MEK/ERK [83], but also block the formation of tumor neovascularization by inhibiting Vascular Endothelial Growth Factor Receptor (VEGFR) and platelet-derived growth factor (PDGF) receptor, and indirectly inhibit the growth of tumor cells [84]. Niclosamide shows strong anticancer activity in human renal cell carcinoma cells and cooperates with sorafenib to inhibit the proliferation and survival of renal cell carcinoma cells by inhibiting the expression of c-myc and E2F1 while inducing the expression of PTEN in RCC cells [85], which suggests that niclosamide may be reused as an effective anticancer agent and may enhance the anticancer activity of other targeted therapies in the treatment of human renal cell carcinoma.

PKC412 is a multi-target protein kinase inhibitor. Niclosamide and PKC412 have synergistic effects in AML cells, and the mechanism is to inhibit the NF-κB pathway, which increases the level of ROS and induces apoptosis of AML cells [53].

3.2.3. *BCR ABL tyrosine kinase inhibitor (TKI)*

Dasatinib is a second-generation BCR-ABL TKI, which inhibits BCR-ABL kinase and Src family kinase, as well as many other selective carcinogenic kinases [86]. It is used in adult patients with all stages of chronic myeloid leukemia (chronic stage, accelerated stage, lymphoid cell blast stage, and myeloid cell blast stage) [87]. Chronic myeloid leukemia (CML) responded well to TKI but develops resistance to TKIs after progression to the outbreak (BP). Niclosamide can enhance the sensitivity of chronic myeloid leukemia cells to dasatinib by inhibiting the Erk/mnk1/eIF4E pathway, inhibiting the proliferation of the CML cell line, and inducing its apoptosis. It also selectively targets BP-CML CD34 stem/progenitor cells while retaining normal bone marrow (NBM) counterparts [88].

Imatinib, a tyrosine kinase inhibitor, is clinically used in the treatment of chronic myeloid leukemia and malignant gastrointestinal stromal tumors [89]. Treatment with imatinib may develop resistance, leading to disease recurrence and progression. The resistance to imatinib is attributed to a variety of mechanisms. For example, about 50% of imatinib-resistant cases acquire point mutations in the BCR-ABL gene (such as T315I, F317L, F359C/V, G250E, Q252H, and E255K/V). Other factors may involve the presence of CML stem cells, overexpression of Src family kinases and Lyn kinases, etc [90]. Recently, studies have

shown that niclosamide can eradicate the role of leukemia stem cells (LSCs) in chronic myeloid leukemia by blocking the interaction between p65 and FoxM1/β-18, indicating it eliminates imatinib resistance caused by leukemia stem cells. Niclosamide inhibited the transcription of the BCR-ABL gene by inhibiting Sp1 in imatinib-resistant CML cells with the T315I mutation, eliminated the downstream signal molecules of BCR-ABL, such as STAT5 and Akt, enhanced the role of TKIs in mice, induced cell death in cells with the T315I mutation, and retained normal WBC [91]. The above information shows the synergistic effect of niclosamide and imatinib in reducing cell proliferation and inducing apoptosis, and the risk of cross-resistance is small when niclosamide and imatinib are used together.

3.2.4. Monoclonal antibody drugs

TRA-8 is an agonistic monoclonal antibody (McAb) that tracks death receptor 5 (DR5) [92]. Niclosamide and TRA-8 monoclonal antibody that inhibits the growth of basal-like breast cancer have a synergistic effect, and inhibit the growth of xenograft basal-like breast cancer cells by inhibiting Wnt/β- Catenin, and STAT3 signals [93].

Cetuximab is an anti-tumor-targeted drug, which is a monoclonal antibody against the EGFR [94]. The activation of the Wnt signaling pathway is related to the drug resistance of cetuximab. Therefore, niclosamide inhibiting Wnt/β-catenin signaling pathway can restore the sensitivity of coloretal cancer (CRC) to cetuximab [95,96].

3.2.5. Androgen receptor (AR) inhibitor

Prostate cancer is the most common cancer in men and the main cause of cancer death in men [97]. Abiraterone is an antiandrogen drug used to treat prostate cancer, but one-third of patients show primary resistance to abiraterone treatment[98]. Niclosamide treatment makes abiraterone-resistant cells sensitive to abiraterone by inhibiting AR-V7 [99]. It shows that the combined treatment of niclosamide and abiraterone is effective in the treatment of castrated prostate cancer. It is particularly important to find that niclosamide can produce an effect in vivo by oral administration and support the combination of abiraterone and niclosamide is effective in the treatment of advanced prostate cancer.

Enzalutamide is an anticancer-targeted drug for the treatment of advanced prostate cancer. It belongs to an androgen receptor inhibitor. It is a new treatment for androgen metastatic and castration-resistant prostate cancer (CRPC). The activation of several potential drug resistance pathways leads to the eventual inevitability of drug resistance to enzalutamide [98]. Liu et al. demonstrated that niclosamide significantly reduced the expression of AR-V7 protein, inhibited the transcriptional activity of AR-V7, and reduced the recruitment of AR-V7 to prostate specific antigen (PSA) promoter through a proteasome-dependent pathway [100]. Overcoming drug resistance through this mechanism significantly enhances the therapeutic effect of enzalutamide on prostate cancer cells, showing that niclosamide can be used alone or in combination with existing anti-androgen therapy to treat patients with advanced prostate cancer, especially those resistant to enzalutamide. Overexpression of IL6 in prostate cancer cells leads to resistance to enzalutamide. Niclosamide may target the IL6-STAT3-AR pathway, overcome enzalutamide resistance and inhibit the migration and invasion of advanced prostate cancer [101].-

Bicalutamide is a nonsteroidal anti-androgen drug, which is used in the clinical treatment of prostate cancer and effectively blocks AR activity and tumor growth in androgen-responsive prostate cancer [102]. AR variants, especially AR-V7, drive bicalutamide resistance. Targeting AR-V7 with niclosamide can resensitize bicalutamide-resistant cells [103]. The combined treatment of niclosamide and bicalutamide overcomes the prostate cancer resistance to enzalutamide and bicalutamide, can significantly enhance the therapeutic effect of bicalutamide, and inhibit the growth of enzalutamide-resistant tumors [104]. This suggests that the combination of niclosamide and bicalutamide may be a potentially cost-effective strategy for the treatment of patients with advanced prostate cancer, including those who are ineffective with enzalutamide.

Due to the poor oral availability, Mamta Parikh and others reconstituted niclosamide powder into capsules and conducted a phase IB test. It was found that the combination of pdmx1001/niclosamide, abiraterone, and prednisone was well tolerated, and could be safely used in patients with CRPC [105]. Michael T. Schweizer et al. initiated a phase I study to test the effect of oral niclosamide combined with enzalutamide. They found that niclosamide did not produce a good antitumor effect within the acceptable toxicity range, and the pharmacokinetics of niclosamide had moderate variability, so it could not be used as a drug for the treatment of CRPC [106]. Therefore, as an anti-tumor drug, the oral preparation of niclosamide can't be used in the clinic for the time being. We should turn our attention to finding niclosamide derivatives with higher bioavailability or better anti-tumor ability, or develop new combined drug regimens.

3.2.6. Other types of drugs

Alvocidib, an inhibitor of cyclin-dependent kinases (CDKs), was found to have synergistic effects with niclosamide in cutaneous T-cell lymphoma [107]. U0126 is a selective and non-competitive MAPK kinase inhibitor. U0126 and niclosamide resulted in the intensive inhibition of the TGFBI expression via the Erk pathway and the migratory ability in osteosarcoma cells [30]. Niclosamide diminished such an enrichment of Sp1, and decreased WT- and T315I-BCR-ABL transcription and its downstream signaling molecules such as STAT5 and Akt [91]. Niclosamide and U0126 have synergistic effects on inhibiting cell proliferation and inducing apoptosis, indicating that the combination of niclosamide and MEK inhibitor may be a potential method for the treatment of T315I-BCR-ABL chronic myeloid leukemia. Metformin is an AMPK activator. Niclosamide effectively inhibited Wnt, but it also inhibited Hippo and increased nuclear Yap activity, limiting its potential for the treatment of colorectal cancer [108]. However, when metformin and niclosamide act synergistically, they can inhibit Wnt and Yap in APC mutant colorectal cancer, activate Hippo, and achieve an antitumor effect [109]. It is suggested that metformin can be selected as a clinically available AMPK activator to overcome the therapeutic limitations of niclosamide in APC mutant CRC.

3.3. Combined treatment of niclosamide with radiotherapy

Radiotherapy is an effective treatment for cancer, which is combined with chemotherapy to improve the curative effect [110]. Acquired radiation resistance is a major clinical obstacle to breast cancer patients receiving radiotherapy [111]. Niclosamide is an effective radiosensitizer. Duru et al. showed that HER2-STAT3 crosstalk increased the aggressiveness and radiation resistance of breast cancer stem cells [112]. HER2 promotes radiation resistance in HER2-positive breast cancer through STAT3 and survivin regulation [113]. Yin et al. [114] reported that niclosamide not only inhibited IR-induced Wnt-3a expression and Wnt/β-Catenin signal activation in TNBC cells but also inhibited the expression of downstream target survivin and makes TNBC cells sensitive to IR. In addition, niclosamide can also increase the production of ROS in TNBC cells and xenograft tumors by inhibiting STAT3 and Bcl-2, to achieve the effect of radiosensitization. The combination of niclosamide and radiotherapy may provide an effective method to restore the sensitivity of anti-radiation TNBC cells to IR, which can improve the therapeutic effect and curative effect [115].

Lung cancer is the leading cause of cancer-related death worldwide. Niclosamide can significantly reduce the malignant potential of primary lung tumors by inhibiting intracellular Wnt/β-Catenin, Notch, mTORC1, and NF-κB signal cascade. Niclosamide may be a promising radiosensitizer in patients with lung cancer by activating the p38 MAPK-c-jun axis [116]. Inhibition of STAT3/Bcl-2/Bcl-XL pathway by niclosamide effectively overcomes acquired radiation resistance in vivo and in vitro. Niclosamide alone or in combination with radiotherapy overcomes the

radiation resistance of xenograft lung cancer, and its mechanism includes inhibiting radiation-induced jak2-STAT3 activity [117]. Additionally, Lee et al. used cell viability screening to determine that niclosamide enhances the radiosensitivity of non-small cell lung cancer cell line H1299. Niclosamide alone or combined with radiotherapy may be a new and more effective method for the treatment of lung cancer, especially for those patients who are resistant to radiotherapy.

The incidence rate of nasopharyngeal carcinoma is the leading cause of otorhinolaryngological malignancies. Radiotherapy is the first choice for nasopharyngeal carcinoma (NPC) [118]. Niclosamide inhibits the NHEJ pathway by inhibiting the transcription of Ku70/80, thus inhibiting the growth of NPC cells and making nasopharyngeal carcinoma cells sensitive to radiation [119]. The results show that niclosamide may be a candidate radiation sensitizer for the treatment of NPC (Fig. 4).

3.4. Combined treatment of niclosamide with immunotherapy

PD-1/PD-L1 blockade has received approval for clinical application due to its encouraging benefit in improving prognosis in selected populations[120]. Unfortunately, the response to immunotherapy for many patients remains unsatisfactory. Niclosamide can enhance the PD-L1 antibody effect and inhibit non-small cell lung cancer (NSCLC) growth in vitro and in vivo, which was involved in the blockage of p-STAT3 binding to the promoter of PD-L1 and finally downregulation of PD-L1 expression [121]. These encourage the combination therapy of niclosamide and PD-1/PD-L1 blockade to be further studied in clinics.

4. Overcoming drug resistance to cancer by drug combination of niclosamide

Drug resistance is one of the main obstacles to the success of cancer treatment [122,123]. The causes of drug resistance are multifactorial, including changes in the biological and biochemical characteristics of cancer cells [124], increased drug outflow by ATP-dependent pump

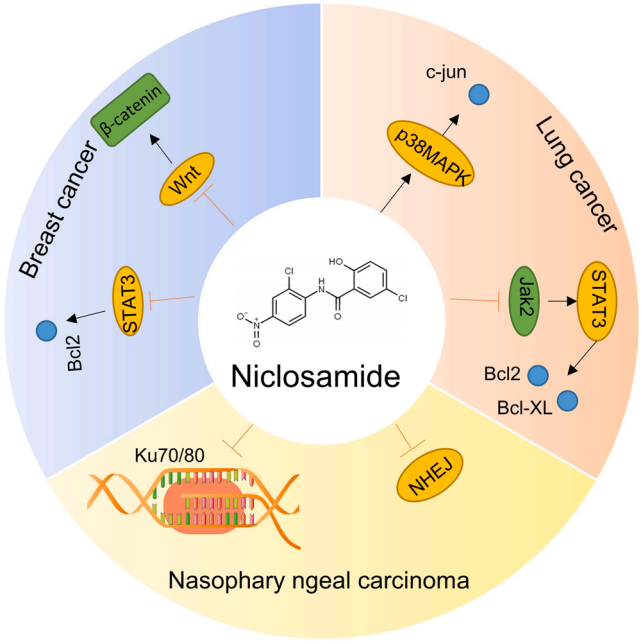

Fig. 4. The combined therapy of niclosamide with radiotherapy. In breast cancer, niclosamide inhibits Wnt/β-catenin or STAT3 and Bcl-2, to achieve the effect of radiosensitization. In lung cancer, niclosamide be a promising radiosensitizer by activating the p38 mapk-c-jun axis or inhibiting of STAT3/Bcl-2/Bcl-XL pathway. In nasopharyngeal carcinoma cells, niclosamide inhibits the NHEJ pathway by inhibiting the transcription of Ku70/80, thus making nasopharyngeal carcinoma cells sensitive to radiation.

[125], enhanced DNA repair, inactivation of the apoptotic pathway, changes in intracellular drug targets, and mutations in cell surface targets [126]. Drug resistance includes two typical cellular mechanisms: (1) Genetic and epigenetic changes, such as p53 mutation and overexpression of anti-apoptotic Bcl-2 and Bcl-XL proteins; (2) Overexpression of ATP binding (ABC) transporter leads to drug outflow and reduces intracellular drug accumulation [127].

It is worth noting that different mechanisms regulating drug resistance are controlled by different cellular signaling pathways. Therefore, drug resistance is a gene-driven and signal pathway-mediated process. Various pathways such as PI3K/AKT/mTOR [128], Notch [129], Hedgehog [130], NF-κB [131], TFG-β [132], Ras/MAPK [133], JAK/-STAT [134], and Wnt [135] are dysregulated in cancer. In addition to drug resistance, these dysregulated signaling pathways are also considered to be the root cause of tumorigenesis, progression, and maintenance [135]. Therefore, targeting dysregulated signaling pathways will help to overcome the drug resistance of cancer cells. When treated with anticancer drugs, chemotherapy-sensitive cells with reduced carcinogenic potential are expected to have more apoptosis and obtain better treatment results [136,137]. The complexity of the cancer genome, the heterogeneity of cancer cells and tumor microenvironment, and cancer drug resistance make monotherapy inefficient [138]. Therefore, the combination of use of drugs that target dysregulated signal pathways may be an effective method to improve the treatment results of cancer patients. The purpose of the drug combination is to block the signal pathway vertically and horizontally. Different drug combination schemes have been evaluated in various clinical experiments, including EGFR inhibitor plus VEGF inhibitor/MEK inhibitor/-BRAF inhibitor [139], PD-1 blocker plus CTLA-4 blocker, PD1 blocker plus EGFR inhibitor, etc [140]. Multidrug resistance needs to be solved by developing new drugs. The reuse of existing drugs is a promising way to solve this problem [141].

Human EGFR is overexpressed in various gastrointestinal cancer types, which is related to poor prognosis and early disease progression [142]. In addition, cancer cells also upregulate other important downstream genes, such as STAT3, which contributes to cancer cell proliferation, cell survival, and angiogenesis, so that cancer cells can obtain resistance to anti-EGFR therapy [143]. Therefore, the STAT3 signaling pathway is an attractive therapeutic target that can avoid drug resistance [144]. Niclosamide may reverse drug resistance by blocking the STAT3 cell pathway through molecular targeted therapy. Niclosamide can also inhibit Wnt signal transduction, which provides another possible mechanism for overcoming EGFR inhibitor resistance [66]. Some studies have also shown that because of the interaction between Wnt and Ras signal pathway, niclosamide can also block the signal pathway related to Ras-mediated drug resistance by inhibiting the expression of GSK-3, a key kinase in Wnt signal transduction [145]. Although there is no direct evidence that niclosamide enhances the therapeutic response of anti-EGFR drugs, it may be a potential drug for repositioning anti-EGFR treatment.

Many prostate tumors are androgen-dependent, so anti-androgen is an important treatment. It is well known that targeted drugs (including anti-androgen drugs), chemotherapeutic drugs, and radiotherapy induce neural cell differentiation of prostate cancer cells. These differentiated cells lack androgen receptors and prostate-specific antigens and are resistant to treatment [146]. CRPC is characterized by increased activation and/or overexpression of AR, leading to downstream target gene transcription and tumor progression [147]. At this stage of prostate cancer progression, several drugs are currently used to prevent or reverse tumor growth. Niclosamide has the activity of treating CRPC in the clinical model. Potential mechanisms of action include degradation of constitutively activated mutant androgen receptor splice variants (AR-VS) or inhibition of other drug resistance pathways (such as Wnt signaling) [106]. AR contains three main functional domains: N-terminal domain (NTD), DNA binding domain (DBD), and ligand-binding domain (LBD) [148]. At present, almost all hormone therapies for

prostate cancer target the AR signal pathway. AR-V7 lacks LBD and has constitutive activity, which makes prostate cancer cells resistant to drugs targeting the classical AR signal pathways [149]. Studies have found that niclosamide targets AR-V7, which is one of the characteristics of fatal prognosis and the main mechanism of resistance to abiraterone and enzalutamide [150], reverses the drug resistance of prostate cancer cells to androgen AR pathway drugs in vitro and in vivo, and prolongs the survival time of mice carrying drug-resistant prostate cancer xenografts [99–101,105].

Wnt/β-Catenin signaling pathway is one of the signaling pathways abnormally expressed in a variety of cancers, which is known to be related to the development of therapeutic drug resistance [151,152]. In addition, abnormal Wnt signals initiate tumorigenesis by maintaining tumor stem cells (CSCs) and lead to immune escape and EMT, all of which are related to disease progression and failure of treatment methods [153]. The combination of Wnt signaling inhibitors and conventional anticancer drugs may improve the therapeutic effect. Recent research shows that FDA-approved niclosamide has shown a good effect as an inhibitor of Wnt signaling and anticancer agents [154]. Niclosamide can effectively downregulate the Wnt signals in many cancer cells, such as breast cancer, prostate cancer, colorectal cancer, lung cancer, and ovarian cancer [31]. In addition, as an FDA-approved anti-worm drug, the safety and pharmacokinetic characteristics of the drug have been previously determined. Therefore, from the perspective of translation, the reuse of niclosamide for cancer treatment is less challenging, which makes it a good choice to target the Wnt signal.

Niclosamide can also inhibit the STAT3 signaling pathway [155]. Studies have found that niclosamide has antitumor activity against sensitive and multidrug-resistant (P-glycoprotein overexpression) leukemia cells, which may be due to its rapid absorption and effective bypass of P-gP resulting in higher intracellular accumulation and effectiveness [36]. The cytotoxic activity of niclosamide is due to its inhibition of glutathione (GSH) synthesis and Nuclear Factor of Activated T cells (NFAT) signal against several signal pathways in cancer cells, which is also related to lipid metabolism [21]. Therefore, it is reasonable to use niclosamide as a clinical candidate for the treatment of refractory multidrug resistance (MDR) cancer.

5. Conclusions and future perspectives

At present, the treatment strategies for cancer mainly include chemotherapy, targeted therapy, radiotherapy, immunotherapy, and surgery, but these single treatment strategies have limitations and risks. However, many studies have shown that niclosamide has an antitumor effect. When combined with chemotherapeutic drugs, small molecule targeted drugs, radiotherapy, and immunotherapy, niclosamide can make cancer cells sensitive to these treatments, improve the therapeutic effect of these treatments, induce cell apoptosis, and inhibit cell proliferation. Therefore, it is expected to become a powerful drug for the treatment of tumors.

Although the above results are encouraging, there are still problems to be solved. First of all, there are few clinical trials, the sample size included in clinical studies is small, and the research results lack the support of large-scale clinical trial data, which can't fully reflect the real situation. Secondly, there is still a lack of strong evidence to support the long-term efficacy and safety of the combination of niclosamide and the above drugs. It is impossible to determine whether the toxicity of niclosamide within the therapeutic effective dose will have side effects on patients. In addition, the combination of niclosamide and antitumor drugs has synergistic or additive effects in the treatment of tumors, but some of its specific mechanisms are not clear and need to be further studied. It is necessary to improve the clinical trials and randomized controlled trials of the above-mentioned drugs, to provide the best clinical effects for patients with tumors.

Ethics approval and consent to participate

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Author statement

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Data Availability

All data generated during and/or analyzed during the current study are available.

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