

Therapeutic Potential of Ion Carrier Antibiotics in Ovarian Cancer: Mechanisms and Prospects

Li Feng¹, Wang Wen², Yao Shujuan³

¹The First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, People's Republic of China; ²Tengzhou Central People's Hospital, Tengzhou, Shandong, People's Republic of China; ³Gynecology Department, The Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong, People's Republic of China

Correspondence: Wang Wen, Tengzhou Central People's Hospital, Tengzhou, Shandong, People's Republic of China, Email 925059557@qq.com; Yao Shujuan, The Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong, People's Republic of China, Email 13064017834@163.com

Abstract: With over two-thirds of cases diagnosed at advanced stages, ovarian cancer is the deadliest gynecological cancer. In 70% of patients receiving standardized treatment, recurrence happens within 12–24 months, leading to a 5-year survival rate below 35%. Patients with ovarian cancer now have a better outlook thanks to personalized precision treatment; however, treating advanced ovarian cancer remains challenging. The poor 5-year survival rate and disease recurrence in individuals with ovarian cancer are mainly caused by platinum resistance. Therefore, targeted screening for drugs that can not only inhibit the growth of ovarian cancer cells but also control their migration, invasion, and drug resistance is especially important to reduce the treatment challenges of ovarian cancer. Ionic carrier antibiotics have enhanced the resistance of several malignant tumors to chemotherapy and have shown anti-tumor properties. This article explores the development of ionic carrier antibiotic research in ovarian cancer to evaluate their potential role in the disease.

Keywords: ion carrier antibiotics, ovarian cancer, treatment, gynecology, cancer

Introduction

Ovarian cancer has long been the deadliest malignant tumor among gynecological tumors.^{1–5} Among gynecological tumors, ovarian cancer has historically been the deadliest type of cancer.⁶ The gold standard for treating ovarian cancer has been cytoreductive surgery plus systemic chemotherapy since the mid-1990s.^{6–8} Despite this, there has not been a noticeable improvement in the 5-year ovarian cancer survival rate during the previously mentioned two decades.^{9,10} The main reason for the low patient survival rate is the subtle symptoms of ovarian cancer, which are usually detected only after the disease has advanced. Additionally, most patients will eventually face a recurrence of the disease, even though many achieve complete clinical remission after initial treatment. Patients with ovarian cancer are experiencing shorter periods of remission or disease stabilization due to an increasing number of chemotherapy regimens that lead to multidrug resistance. This ultimately results in death.^{2,7,11} The main factors affecting the prognosis of ovarian cancer include metastasis, invasion, and tumor cell resistance to chemotherapy drugs. These characteristics are closely associated with the recurrence of ovarian cancer. Both carboplatin and paclitaxel, which are commonly used in clinical practice, have significant killing effects on a wide range of tumor types at the moment,^{12–14} many studies have demonstrated that different tumor types are susceptible to developing resistance to either cisplatin or paclitaxel,^{15–17} suggesting that these two first-line chemotherapy drugs may not be as effective at preventing cancer cell metastasis, invasion, and resistance. Therefore, to improve the prognosis for ovarian cancer patients, it is essential to identify and develop candidate drugs that can significantly lower medication resistance and reduce cancer cell invasion and metastasis. In recent years, research on anti-tumor drugs has been expanding steadily, and targeted therapy has made significant progress, such as with bevacizumab and PARP inhibitors. In a Phase III trial involving 806 patients with advanced ovarian cancer, Olaparib combined with bevacizumab improved progression-free survival compared to placebo plus bevacizumab in patients with tumors positive for homologous-recombination deficiency.¹⁸ Additionally, some

antibiotic drugs have shown promising anti-tumor activity and potential. The investigation of new anti-tumor drugs derived from these agents has opened new avenues for cancer treatment research.¹⁹

First used in 1967, the term “ion carrier” describes a molecule’s capacity to bind metal ions and make it easier for them to pass through cell membranes.²⁰ This physicochemical property makes polyether ion carriers a valuable tool for studying cation transport mechanisms. The Gram(+) bacteria of the genus *Streptomyces* produce ion carrier antibiotics, a class of more than 120 structurally related fat-soluble drugs with similar building blocks and a shared mode of action. Polyether ion carrier antibiotics display a broad range of biological actions, including antiviral, antifungal, antibacterial, and antiparasitic effects, and these drugs were initially widely used as feed additives in industrial animal husbandry. The antimicrobial bioactivity of ion-carrier antibiotics is closely linked to the characteristics of their ion carriers. Originally, these medications were frequently added to feed in industrial animal husbandry. The antibacterial action of ion-carrier antibiotics is functionally linked to the properties of their ion carriers. They can selectively bind metal cations, mainly alkaline cations, and transfer them from the extracellular environment into the cell through the biofilm, where the transported cations are liberated.²¹ In clinical practice, ion carrier antibiotics such as monensin,^{22,23} salinomycin,^{24,25} nigericin,^{26,27} doxycycline,^{28,29} and ivermectin^{30,31} are frequently utilized. Ionophore antibiotics have been shown in studies to have anti-tumor properties when used to treat a variety of malignant tumors,³² although research on ovarian cancer remains relatively inadequate. This article discusses the recent advances in ion carrier antibiotic research related to ovarian cancer.

The Anti-Tumor Properties of Ion-Carrier Antibiotics

Inhibit Tumor Cell Proliferation

It has been found that ion carrier antibiotics inhibit the growth and multiplication of many tumor cell types; for instance, monensin prevents the growth of various tumor cell types. Only 5% of patients with pancreatic ductal adenocarcinoma (PDAC) survive for five years. In vitro, monensin caused apoptosis in pancreatic cancer cell lines PANC-1 and MiaPaCa-2 by suppressing their growth and cell cycle progression. And prevented PDAC xenograft tumors from growing in vivo.³³ Glioblastoma is a tumor with a terrible prognosis. Monensin not only prevents glioblastoma cells from proliferating and capillary formation in glioblastoma endothelial cells in vitro, but it also prevents tumor growth in glioblastoma cells mouse xenografts in vivo.³⁴ In terms of female morbidity, breast cancer ranks as the first malignant tumor. Studies have demonstrated that monensin can dramatically reduce the growth of breast cancer cells, speed up apoptosis, upregulate the expression of genes closely linked to apoptosis, like Bax2, Caspase3, and Caspase7, and downregulate the expression of anti-apoptosis Bcl-2. And prevent breast cancer cells from developing tumors.²² Additionally, research on prostate cancer has demonstrated that monensin disrupts Ca^{2+} homeostasis and induces the release of reactive oxygen species from mitochondria. Monensin also stops the cell cycle in the G1 phase and lowers the survival rate of the prostate cell line PC-3.³⁵ In human lymphoma cell lines, SNU-C1 colon cancer cells, and NCI-H929 myeloma cells, monensin alters mitochondrial transmembrane potential and induces G1 and/or G2-M phase arrest, which has antiproliferative effects.^{36,37} In addition, monensin can also inhibit the survival rate of lung cancer cells.³⁸

The antibiotic salinomycin, a polyether ion carrier, can kill tumor stem cells efficiently.³⁹ In addition, salinomycin can induce apoptosis in many tumor cells. The disruption of the Wnt/ β -catenin signaling pathway is closely related to tumor stem cell survival and metastasis. The formation of stem cells depends heavily on the Wnt/ β -linker signaling system, and cancer medications that target this pathway may act if it is abnormally activated (Figure 1). Research has shown that salinomycin inhibits Wnt1-induced signaling at nanomolar concentrations and promotes β -catenin degradation at micromolar concentrations, thereby blocking downstream activator-induced Wnt signaling. The Wnt/ β -catenin signaling system may be inhibited by salinomycin, which may result in the death of tumor stem cells.⁴⁰ Salinomycin was found to increase β -conjugated protein degradation at micromolar doses while inhibiting Wnt1-induced signaling at nanomolar concentrations, thereby blocking downstream activator-induced Wnt signaling. Consequently, different doses of salinomycin can inhibit Wnt signaling through distinct mechanisms. In subsequent experiments, salinomycin successfully induced apoptosis in malignant lymphocytes, whereas high concentrations of salinomycin failed to induce apoptosis in peripheral blood mononuclear cells under the same conditions. It was demonstrated that salinomycin was selectively cytotoxic to tumor cells reliant on Wnt signaling.⁴¹

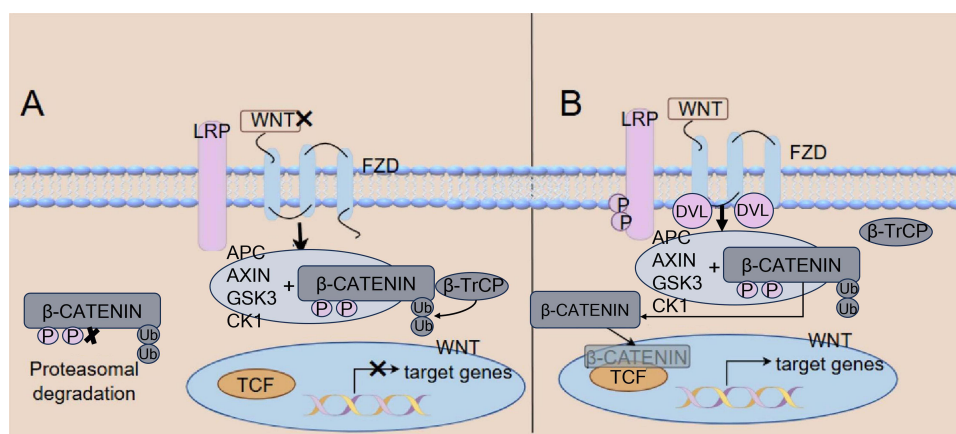


Figure 1 Wnt/β-catenin signalling pathway. **(A)** Free β-catenin attaches to its destruction complex (which includes APC, CK1, GSK-3β, and AXIN) in the absence of a WNT ligand. Phosphorylation of β-catenin causes ubiquitination, which is followed by proteasomal disintegration. **(B)** When WNT ligand is present, WNT + FZD receptor + receptor LRP binding results in LRP phosphorylation, which in turn attracts DVL, a destructive complex that stops β-catenin from degrading. β-catenin then accumulates and moves to the nucleus, where it interacts with TCF transcription factors to activate the transcription of WNT target genes.

Inhibit the Invasion and Migration of Tumor Cells

Current studies have demonstrated that monensin can prevent different tumor cells from spreading and invading other areas. In the field of breast cancer, studies have shown that monensin can inhibit the migration and invasion of breast cancer cells, and can inhibit the expression of matrix metalloproteinases-2 and -9, which is closely related to metastasis and invasion in cells. It is speculated that the mechanism of tumor suppression may be achieved by down-regulating the UBA2 gene.²² Studies on colorectal cancer have demonstrated that monensin can prevent the expression of Wnt/β-catenin in colorectal cancer cells.⁴² Due to Wnt/β-catenin being one of the core factors regulating the epithelial-mesenchymal transition (EMT) pathway,^{43,44} the EMT process is a factor that directly determines the ability of cells to metastasize and invade,^{45–47} therefore, it can be inferred that monensin can further inhibit the metastasis and invasion ability of colon cancer cells by suppressing the expression level of β-catenin. In addition, based on the close relationship between the EMT pathway and cancer metastasis and drug resistance, the EMT-selective compounds were screened by a high-content screening scheme of cell imaging. It was found that monensin has EMT selectivity and can induce apoptosis, cell cycle arrest, and reactive oxygen species release.⁴⁸ Tumor stem cells or stem cell-like tumor cells have high invasion and metastasis ability. Monensin also has a good inhibitory effect on tumor stem cells.^{23,49} The high metastasis and invasion characteristics of cancer stem cells and stem cell-like tumor cells are also related to the EMT process.^{50,51}

Human colon cancer cells treated with salinomycin exhibit decreased colony-forming capacity and cell motility, indicating that salinomycin not only selectively targets colon cancer stem cells but also inhibits colon cancer cell invasion and migration.⁵² Salinomycin decreases the viability of glioblastoma cells, according to studies.⁵³ Mycamycin targets the extracellular signal-regulated kinase-cyclin D1 and p38 pathways, respectively, to prevent endothelial cell migration and proliferation. This reduces the stimulatory impact of vascular endothelial growth factor. Additionally, inostamycin possesses anti-invasive and anti-proliferative properties.⁵⁴ The majority of cancer-related deaths are caused by invasion and metastasis, so this will provide new insights into the treatment of tumors.

Reduce Tumor Cell Resistance

During chemotherapy, drug resistance is a common clinical issue for cancer patients. Thus, discovering novel medications for cancer treatment is a significant challenge, and polyether ion carrier antibiotics are potential candidates. These ion-carrier antibiotics can reverse multidrug resistance in human cancer and increase chemosensitivity to cancer cells. In an effort to find potential new treatment targets, studies have looked at how polyether ion carrier antibiotics affect colchicine resistance in human cancer multidrug-resistant KB-C410 cells. The findings of these investigations demonstrated that a range of polyether ion carrier antibiotics might overcome colchicine resistance. Lethalomycin had good efficacy, increasing the cytotoxicity of colchicine in KB-C700 cells by approximately one-fold at a dosage of 4 μg/m.⁵⁵

Salinomycin can decrease the emergence of drug resistance in cancer cells treated with anticancer medications such as vincristine, paclitaxel, docetaxel, and colchicine. Furthermore, salinomycin made cancer cells more susceptible to the apoptotic effects of adriamycin and etoposide. Salinomycin has been shown to increase DNA damage and lower the amount of the anti-apoptotic protein p21 in cancer cells, increasing their vulnerability to the effects of etoposide and adriamycin.⁵⁶ The combination of salinomycin with other chemotherapeutic agents will result in less resistance in glioblastoma cells.⁵³

The antibiotic natamycin, a polyether ion carrier, also reduced the multidrug resistance exhibited by KB-C4 human cancer cells. Inostamycin increased periwinkle accumulation in a dose-dependent way in multidrug-resistant KB-C4 cells. The active efflux of periwinkle from KB-C4 cells was blocked by inostamycin, but the vincristine efflux from KB-3-1 cells was not affected. At a concentration of 1 µg/mL natamycin, the 4-hour increase in periwinkle accumulation in KB-C4 cells was roughly double. Although natamycin bonded to the KB plasma membrane irreversibly, according to mechanistic investigations, the binding capacity did not correspond with the levels of P-glycoprotein in the three KB cell lines, and natamycin could irreversibly bind to the plasma membrane via phosphatidylethanolamine, thereby irreversibly inhibiting P-glycoprotein.^{57,58} When inostamycin and paclitaxel were administered together, the capacity to cause apoptosis in Ms-1 cells was enhanced. MS-1 cells treated with natamycin required less paclitaxel to induce apoptosis. Consequently, inostamycin is an effective treatment for small-cell lung cancer when used in conjunction with paclitaxel.⁵⁹ However, in both KB parental and KB/multidrug-resistant cells, monensin was a strong inhibitor of proliferation. Monensin intervention boosted the intracellular accumulation of Adriamycin in KB/multidrug-resistant cells by approximately two to three times, but the phenomenon was absent in KB parental cells. Additionally, monensin dramatically decreased the efflux of Adriamycin from KB/multidrug-resistant cells. These findings imply that monensin may reverse multidrug resistance by promoting drug transport and, in turn, increasing DNA damage in cells. The concept that monensin works directly on P-glycoprotein in multidrug-resistant cells is supported by mechanistic investigations that showed it decreased drug efflux but did not change the subcellular distribution of zorubicin.^{60–62}

A variety of antibiotics with antitumor activity can inhibit the resistance of tumor cells to chemotherapeutic drugs; for example, salinomycin can block NF-κB nuclear translocation in cisplatin-resistant breast cancer cells, down-regulate the expression of Survivin, XIAP, and Bcl-2 genes, which are positively correlated with cell survival, and further inhibit the proliferation and metastasis of cisplatin-resistant breast cancer cells;⁶³ Nigericin inhibits the Wnt/β-catenin signaling system, which lowers the lifespan of lung malignancies and multidrug-resistant lung cancer cells;⁶⁴ By binding to the extracellular domain of the epidermal growth factor receptor (EGFR) on tumor cell membranes, ivermectin can inhibit the ERK/AKT/NF-κB signaling pathway, which is closely linked to the growth and metastasis of tumor cells and further inhibit the expression of P-glycoprotein, which has the function of keeping drugs out of the cell. Thereby overcoming some tumor cells' treatment resistance.⁶⁵ In drug-resistant pancreatic cancer cell lines, studies have demonstrated that monensin increases apoptosis and inhibits cell proliferation, cell cycle progression, and cell metastasis, most likely via lowering tumor cells' levels of EGFR expression.³³ In another study, non-small cell lung cancer (NSCLC) cells were constructed with EGFR-tyrosine kinase inhibitor resistance induced by modulation of the EMT pathway. The addition of monensin markedly inhibited the EMT process in drug-resistant lung cancer cells, and the EGFR-tyrosine kinase inhibitor restored the inhibition of drug-resistant lung cancer cells. Growth and apoptosis-promoting effects on drug-resistant lung cancer cells.⁶⁶ Another study showed that monensin was able to restore the sensitivity of tumor necrosis factor-related apoptosis-induced ligand (TRAIL)-resistant glioma cells to the apoptosis-inducing effects of TRAIL, possibly by inducing the endoplasmic reticulum stress reaction. Up-regulation of death receptor 5 and down-regulation of Fas-related death domain-like interleukin-1β-converting enzyme inhibitory protein increased the efficiency of tumor cells in receiving and processing apoptotic signals.⁶⁷

Ion carrier antibiotics can directly induce apoptosis in cancer cells, preventing tumor invasion and growth. When combined with other anticancer drugs, they can help overcome drug resistance and enhance the effectiveness of therapy. Therefore, ion carrier antibiotics have strong anti-tumor properties, which are valuable for managing tumor disorders and developing new anti-tumor drugs, showing broad potential for research and development.

The Inhibitory Effect of Ion Carrier Antibiotics on Ovarian Cancer Monensin

Monensin is a natural lipid-soluble bioactive ion carrier produced by *Streptomyces cinnamonensis*, with a molecular weight of 670 and a formula of $C_{36}H_{61}O_{11}$, whose antimicrobial activity is mediated by its function of exchanging Na^+ and K^+ ions across cellular membranes, which disrupts the ionic gradient and alters cellular physiology. The US Food and Drug Administration has authorized monensin as a veterinary antibiotic for the treatment of coccidiosis.^{68–70} In addition to its use as a veterinary drug, monensin exhibits broad-spectrum activity against human conditionally pathogenic bacteria, viruses, fungi, and parasites in both drug-sensitive and drug-resistant strains.⁶⁸ Another study found that monensin sodium salt may be able to treat new coronavirus infections by blocking SARS-CoV-2S protein-mediated cell fusion.⁷¹ More and more studies are finding that monensin has anti-tumor activity.

Monensin inhibits the proliferation of various ovarian cells to varying degrees and mostly functions during the G1/S phase of the cell cycle. It also inhibits ovarian cell invasion and migration, which has a strong correlation with the expression of key kinases like MEK and ERK as well as signaling molecules linked to EMT.^{72,73} Monensin attenuates the activity of MEK1 by enhancing SUMO1 modification of MEK1 and inhibiting its activation, which in turn negatively regulates the ERK pathway and ultimately inhibits cell overgrowth.⁷⁴ Additionally, Deng et al investigated the potential of the antibiotic monensin as an anti-ovarian cancer medication using the human ovarian cancer lines HeyA8 and SKOV3. It has been discovered that monensin efficiently induces apoptosis and inhibits the growth, migration, and cell cycle progression of human ovarian cancer cells. This is mostly because monensin can lower the expression of EGFR in ovarian cancer cells and inhibit cancer-related pathways such as Elk1/SRF, AP1, NF κ B, and STAT. When combined with oxaliplatin and EGFR inhibitors, monensin can stop the growth of ovarian cancer cells and cause them to undergo apoptosis.⁷⁵

Besides preventing tumor cells from proliferating, migrating, and invading, ovarian cancer drugs must also possess strong resistance, which is a major obstacle to using traditional chemotherapy agents like paclitaxel and platinum.^{76–79} Monensin can inhibit the proliferation, metastasis, and other tumor cell features of more than one type of drug-resistant cells,^{33,66} and also selectively inhibits the growth of tumor cells with an active EMT process,²³ and it is also effective against drug-resistant cells prone to drug resistance with the characteristics of a tumor stem cell,^{23,49} so monensin also can play a more significant role in overcoming cancer cells' resistance. Thus, monensin may be able to fulfill the need for effective drug functionality in the treatment of ovarian cancer.

Salinomycin

Streptomyces albus is the source of the monocarboxylic polyether antibiotic salinomycin. Originally, it was employed as an agricultural antimicrobial agent for poultry and nutrition. In animal trials, Gupta et al particularly inhibited breast cancer stem cells by reducing tumor size and boosting apoptosis and necrosis, proving for the first time that salinomycin is the most effective medication against breast cancer stem cells.³⁹ Current data indicate that salinomycin can target cells that resemble cancer stem cells in a variety of human malignancies,³⁹ causing effects including apoptosis induction, suppression of tumor cell proliferation, angiogenesis, autophagy, etc., as well as targeting the Wnt and EMT pathways to prevent tumor invasion and migration.^{80–87} As an anticancer agent, salinomycin has significant therapeutic potential.

By blocking the Wnt/ β -catenin pathway and preventing EMT from forming, salinomycin decreases cell invasion and migration and prevents the growth of epithelial ovarian cancer cells.⁸⁸ Fuat Kaplan et al treated ovarian cancer cells and ovarian epithelial cells with eight various concentrations of salinomycin, including 0.1, 1, and 40 μ M, in order to further examine the apoptotic and cytotoxic effects of salinomycin on the human ovarian cancer cell line (OVCAR-3) and then cultured them separately. It was discovered that incubating human OVCAR-3 cells with 0.1 μ M salinomycin for 24 hours could trigger apoptosis and kill 40% of the cancer cells by up-regulating the expression of the apoptotic Bax gene, down-regulating the expression of the anti-apoptotic Bcl-2 gene, and increasing the expression of active caspase-3 protein, while not affecting normal cells⁸⁹ (Figure 2). Additionally, salinomycin, a possible chemotherapeutic drug for the treatment of cisplatin-resistant ovarian cancer, can cause the death of cisplatin-resistant ovarian cancer cells by blocking Akt/NF- κ B and activating p38 MAPK.^{90,91}

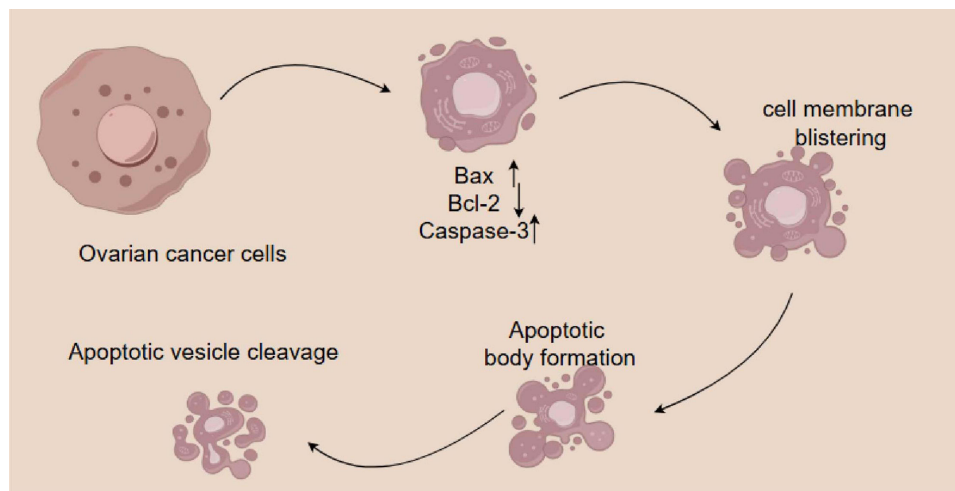


Figure 2 Apoptotic processes in ovarian cancer cells. Ovarian cancer cells treated with drugs can trigger apoptosis by up-regulating the expression of the apoptotic Bax gene, down-regulating the expression of the anti-apoptotic Bcl-2 gene, and increasing the expression of active caspase-3 protein. In the process of apoptosis, the cell volume is reduced, the nuclear chromosome is concentrated and condensed, the nucleus is cracked into multiple fragments, the cell membrane is blistered, and the fragments are wrapped. The cells are cut into multiple bodies, that is, apoptotic bodies, and finally apoptotic vesicles are cleaved.

An *in vitro* study by Michalak et al on the effectiveness of salinomycin and its derivatives in overcoming platinum drug resistance in ovarian cancer revealed that salinomycin and its derivatives, along with the widely used anticancer drugs 5-fluorouracil, gemcitabine, and cisplatin, can significantly overcome platinum drug resistance in patients with ovarian cancer. The study also suggests that combining salinomycin with anticancer medications like gemcitabine or 5-fluorouracil may provide new treatment options for patients with ovarian cancer.⁹² Similarly, a study found that the combination of salinomycin and paclitaxel also enhanced the inhibition of ovarian cancer stem cells.⁸¹

Nigericin

Nigericin is an acid polyether potassium ion carrier antibiotic, which is widely used in the treatment of chicken coccidiosis. In 2009, it was first reported that nigericin has a cytotoxic effect on breast cancer tumor stem cells. In 2011, the University of California, USA, confirmed using the HEK293 cell line that nigericin can selectively inhibit the Wnt signaling pathway at nanomolar concentration levels. In 2012, researchers from Shanghai Jiao Tong University confirmed that nigericin can inhibit colorectal cancer metastasis by affecting epithelial-mesenchymal transition. At the same time, ovarian cancer cells are somewhat inhibited by nigericin. In terms of preventing tumor cell metastasis and invasion, Wang et al used two ovarian cancer cell lines, A2780 and SKOV3, to examine the mechanism and inhibitory effect of nigericin on human epithelial ovarian cancer cells. The study found that nigericin can affect EMT by regulating the Wnt/ β -catenin signaling pathway, thereby inhibiting the proliferation, migration, and invasion ability of epithelial ovarian cancer, and having a specific function in preventing the angiogenesis of ovarian epithelial cancer cells.⁹³

According to research, nigericin may be a novel chemotherapeutic candidate for epithelial ovarian cancer. Zhou et al conducted further research on the effects and potential mechanisms of the combination chemotherapy of nigericin and cisplatin on epithelial ovarian cancer. Research has found that the inhibitory effect of cisplatin on the migration and colony formation of epithelial ovarian cancer cells can be strengthened when nigericin and cisplatin are combined. The mechanism may be due to nigericin inhibiting slug expression by promoting slug-like ubiquitination modification and inhibiting the Wnt/ β -catenin signaling pathway from being activated.⁹⁴ Nissin has an advantageous impact on the growth and metastasis of ovarian cancer cells, whether it is employed alone or in conjunction with cisplatin, and may improve the outcome of ovarian cancer treatment.

Conclusion

Ovarian cancer has a high recurrence rate and poor prognosis, posing a significant threat to women's health. Developing new medications is essential for treating ovarian cancer. The potential of ion-carrier antibiotics in anti-tumor therapy is

gradually being recognized, and they have shown some promise in ovarian cancer treatment. Overall, the use of ionophore antibiotics for ovarian cancer is still not well understood. Further experiments are needed to explore their application and therapeutic mechanisms, which could lead to innovative approaches and insights for developing new treatments for ovarian cancer.

Abbreviations

EGFR, Epidermal growth factor receptor; TRAIL, Tumor necrosis factor-related apoptosis-induced ligand; EMT, Epithelial-mesenchymal transition; PDAC, Pancreatic ductal adenocarcinoma.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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