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Review on the application of ginsenosides and their pharmaceutical preparations in the treatment of breast cancer

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Abstract:

Ginsenosides, as the main active ingredients of ginseng, have shown great potential in the treatment of breast cancer. Studies have found that many types of ginsenosides, such as PPD ginsenosides Rh2, Rg3, CK and PPT ginsenosides Rg1, Rg2, have inhibitory effects on breast cancer cells. These components can effectively inhibit the development of breast cancer by directly inhibiting the proliferation of cancer cells, inducing apoptosis, enhancing the anticancer ability of NK cells, and remodeling the tumor microenvironment. In addition, the liposome and nanoparticle drug delivery system synthesized by ginsenoside showed great advantages in the application of drug formulations, providing a new strategy for the targeted transportation of antitumor drugs and improving the tumor killing ability. These research results not only provide a new strategy for breast cancer treatment, but also expand the application prospect of ginsenosides in cancer treatment. In the future, with the in-depth research, ginsenosides and their pharmaceutical preparations are expected to play a greater role in the treatment of breast cancer and bring more hope to patients.

Keywords: Ginsenosides, Breast Cancer Treatment, Pharmaceutical Preparations

1.Introduction

Ginseng is the dried root and rhizome of Panax ginseng C. A. mey. It was first published in Shennong materia medica classic and listed as the top grade.[1] It has been collected in all dynasties and has the effects of greatly tonifying vitality, restoring pulse and Strengthening Qi, tonifying spleen and lungs, generating fluid and nourishing blood, calming nerves and benefiting intelligence. Ginseng is a famous and precious medicinal material at home and abroad, and its research and application have received widespread attention at home and abroad. Modern research shows that ginseng contains ginsenosides, phytosterols, choline and other bioactive substances,[3] which have the effects of regulating immunity, relieving fatigue, delaying aging, inhibiting tumor, anti-inflammatory and so on.[2] Among them, ginsenosides are the most important active ingredients, which have inhibitory and therapeutic effects on many types of cancer.

Breast cancer is one of the most common types of cancer. In 2022, 357200 women with breast cancer will be newly diagnosed in China.[5] In addition, breast cancer has a high mortality rate, and breast cancer is the second leading cause of death for women with cancer[4]. There are several main types of breast cancer: Estrogen receptor (ER) positive, progesterone receptor (PR) positive, human epidermal growth factor receptor-2 (HER2) positive and triple negative breast cancer. Traditional treatments for breast cancer mainly include surgical resection, chemotherapy, immunotherapy and radiotherapy, However, these treatment methods have not shown significant improvement in the survival rate of breast cancer patients, and all have significant side effects. [6]

In recent years, more and more studies have found that ginsenosides have inhibitory growth and therapeutic effects on breast cancer. Ginsenosides are a series of glycosylated triterpenoid compounds belonging to the active compounds of the genus Panax, including protopanaxadiol (PPD), protopanaxatriol (PPT), otilol (OCT), and oleic acid (OA). They accumulate in the roots, stems, leaves, and flowers of plants.[15] The main components of ginsenosides can be divided into three categories: protopanaxadiol (PPD), protopanaxatriol (PPT), and others. Rb1, Rb2, Rb3, Rc, Rd, Rg3, and Rh2 belong to the protopanaxadiol (PPD) type of ginsenosides, whereas Re, Rf, Rg1, Rg2, and Rh1 belong to the protopanaxatriol (PPT) type; More than 90% of ginsenosides are derived from PPD and PPT types. The other two types are the oleanane group (Ro) and pseudoginsenosides of the ocotillol type (F11, R1, R2, and RT4). [7]

Many ginsenosides have inhibitory and therapeutic effects on breast cancer. Its action mode mainly includes inhibiting the proliferation, migration and invasion of breast cancer, and promoting autophagic apoptosis of breast cancer cells. Studies have also found that ginsenosides can be used in combination with other chemotherapy drugs as adjunctive therapy drugs to reduce the side effects of chemotherapy.

This article reviews the research and application of ginsenosides in inhibiting the progress of breast cancer in recent years.

2 Ginsenoside PPD

According to its skeleton, ginsenosides can be categorized into the dammarane type and the oleanol type. Among them, protopanaxadiol (PPD) belongs to the dammarane type of ginsenosides.[17] PPD exhibits excellent antioxidant, anti-inflammatory, anti-cancer, and other biological activities. Currently, there are numerous papers reporting on the anti-tumor activity of PPD.[16] The main active ingredients against breast cancer in PPD include Rh2, Rg3, CK, etc.

2.1 Ginsenoside Rh2

Ginsenoside Rh2 possesses the biological activity of directly inhibiting the proliferation of breast cancer cells. Ginsenoside Rh2 is a potential estrogen receptor ligand with moderate estrogenic activity. Studies have discovered that ginsenoside Rh2 can induce apoptosis and the G1/S phase of MCF-7 cells. The treatment of cells with ginsenoside Rh2 can down-regulate the protein level of ER-α and up-regulate the mRNA level of ER-β, promoting the overexpression of TNF-a to induce apoptosis and cell cycle arrest in MCF-7 cells.[8]

Ginsenoside Rh2 can also indirectly facilitate the killing and inhibition of breast cancer cells by enhancing the immune system's ability. Yang C et al disclosed that Rh2 played a significant role in delaying cancer growth and metastasis by enhancing the cytotoxic function of NK cells and promoting the release of perforin, Granzyme B, and interferon -γ(IFN-γ). Rh2 was capable of reducing the expression of Erp5 and directly binding to Erp5 in MDA-MB-231 cells and at the level of recombinant protein. Rh2 prevented the formation of soluble MICA (sMICA) and upregulated the expression level of MICA in vivo and in vitro. They demonstrate for the first time that Rh2 plays a key role in enhancing NK cell activity by directly binding to Erp5 to regulate the NKG2D-MICA signaling axis.[35]

In recent years, numerous new studies have concentrated on the interaction between ginsenosides and non-coding RNA, thereby achieving the inhibition of breast cancer cell proliferation. Ginsenoside Rh2 can mediate breast cancer cell proliferation through gene methylation. In a study, a new long non-coding RNA, C3orf67-AS1, was reported. When C3orf67-AS1 was down-regulated by siRNA, the cell growth rate decreased, demonstrating the oncogenic activity of C3orf67-AS1. Therefore, cancer patients showed lower methylation and higher expression levels of C3orf67-AS1. C3orf67-AS1 is highly methylated at the CpG site of the promoter identified by Rh2 in MCF-7 cancer cells, thereby inhibiting its expression by Rh2 and mediating the inhibition of cancer cell proliferation.[9] Ginsenoside Rh2 down-regulated the regulatory activity of long non-coding RNA (lncRNA) CFAP20DC-AS1. The dysregulation of CFAP20DC-AS1 attenuated the expression of miR-3614-3p, but miR-3614-3p could be up-regulated by Rh2, inhibiting the proliferation of MCF-7 cells and stimulating apoptosis. The Rh2/CFAP-20DC-AS1/miR-3614-3p/ target gene axis contributes to the anti-proliferative activity of Rh2 in cancer cells.[10] Park Je et al studied that Rh2 regulates competing endogenous RNAs (ceRNAs) within cancer cells. The lncRNAs whose promoter DNA methylation level was significantly changed by Rh2 were screened from methylation array data: STXBP5-AS1, miR-4425, and RNF217. The results showed that the inhibition of STXBP5-AS1 decreased the apoptosis of MCF-7 cells but stimulated the growth of cells, which indicated that lncRNA had tumor suppressive activity. miR-4425 was identified as having a binding site on STXBP5-AS1 and proved to be down-regulated by STXBP5-AS1 and Rh2. Among them, miR-4425 showed pro-proliferative activity by inducing decreased apoptosis but increased growth of MCF-7 cells. Further screening of the target genes of miR-4425 and Rh2 revealed that Rh2, STXBP5-AS1, and miR-4425 consistently regulated the tumor suppressor RNF217 at the RNA and protein levels. Therefore, LncRNA STXBP5-AS1 is up-regulated by Rh2 through promoter hypomethylation, and as a ceRNA, it absorbs oncogenic miR-4425. Therefore, Rh2 controls the STXBP5-AS1 /miR-4425/RNF217 axis to inhibit breast cancer cell growth.[36] The interaction between ginsenosides and non-coding RNAs has become a current research hotspot, mainly because ginsenosides can be used to regulate the promoter methylation of targeted genes and then regulate the interaction between non-coding RNAs, so as to achieve the inhibition of breast cancer cell proliferation and the promotion of apoptosis.

Ginsenoside Rh2 can also synergize with chemotherapeutic drugs and effectively reduce the side effects of chemotherapy as an adjuvant treatment. As a commonly used chemotherapeutic drug, doxorubicin cannot selectively target tumorigenic cells with high proliferation rate, and often causes side effects. Experiments have demonstrated that clinical doses of doxorubicin (100nm) induce cellular senescence and senescence associated secretory phenotype (SASP) of breast tumor cell MDA-MB-231 and normal epithelial cell MCF-10A. SASP of both cells can effectively promote cell migration and cell invasion of MDA-MB-231 cells. However, SASP of senescent cells treated with Rh2 greatly attenuated the bystander effect described above. Rh2 is also expected to be developed as a drug input therapy to reduce the bystander effect of chemotherapy drugs.[11]

2.2 Ginsenoside Rg3

Breast cancer stem cells (BCSCs) are responsible for cancer metastasis, recurrence, and treatment resistance, making BCSCs a potential driver of breast cancer invasion. Studies have shown that Rg3 inhibits mammosphere formation and reduces the expression of stemness-related transcription factors. Rg3 accelerates the degradation of Myc mRNA mainly by enhancing the expression of let-7 family, and inhibits the stem like properties of breast cancer by inhibiting the expression of Myc.[13] Rg3 inhibits breast cancer metastasis by inhibiting BCSC stemness.

Rg3 can inhibit breast cancer by remodeling the tumor microenvironment, affecting changes in cancer stem-like cells (CSCs) and epithelial-mesenchymal transition (EMT). Joong Hyun song Et al found that bone marrow-derived suppressor cells (MDSCs) can cause changes in cancer stem like cells (CSCs) and epithelial mesenchymal transition (EMT). Rg3 was evaluated using various methods to downregulate MDSC and inhibit MDSC-induced cancer stemness and EMT through the inhibition of STAT3 dependent pathway and Notch signaling pathway at a dose without obvious cytotoxicity. In an FM3A mouse breast cancer model, Rg3 delayed tumor growth.[18]

Previous studies have shown that ginsenosides exist in the form of stereoisomers, which depend on the position of the hydroxyl groups on carbon 20; 20 (R) - ginsenoside and 20 (s) - ginsenoside are epimers. Sang Min Jeong Et al showed that the mixture of 20 (R) - and 20 (s) - ginsenosides regulates ion channel activity. It was demonstrated that only 20 (s) -Rg3 inhibited Ca2 +, K +, and Na + channel currents in a dose - and voltage-dependent manner. However, 20 (R) -Rg3 exhibited no significant activity.[20] Ginsenoside 20 (S, R) -Rg3 was also isolated. It was found that ginsenoside 20 (S) -Rg3 could induce apoptosis by activating Caspase-3, Caspase-8 and caspase-9 and regulating the expression of Bcl-2 and Bax. However, no tumor suppressor activity of 20 (R) -Rg3 was found.[21]

The above studies all suggest that ginsenosides have two epimers, R and S, and different isomers may have different inhibitory effects on cancer. Since then, studies have demonstrated the potential of the Rg3 epimer for the treatment of triple-negative breast cancer. Maryam nakhjavani Et al optimized the combination of Ginsenoside Rg3 (Rg3) epimers to exert anti-angiogenic effects. The optimized combination of 50μm SRg3 and 25μm RRg3 (C3) was found to shrink the primary tumor and reduce the metastatic burden in a mouse model of triple negative breast cancer bearing mda-mb-231-luc cells.[22] Maryam Nakhjavani Et al showed that Rg3 interacts with aquaporin 1 (AQP1) water channel through molecular docking. The expression of AQP1 in TNBC cell lines was compared using quantitative polymerase chain reaction (PCR). The results showed that only SRg3 inhibited AQP1 water flux and arrested the cell cycle at the G0/G1 phase, thereby inhibiting the proliferation of MDA-MB-231 (100μm). In addition, SRg3 inhibited the chemoattractant-induced migration of MDA-MB-231 cells. While RRg3 has greater potency to inhibit the migration and invasion of MDA-MB-231 cells. Rg3 has a stereoselective anticancer effect in the AQP1 high-expression cell line MDA-MB-231.[23] These studies remind us that while paying attention to the anticancer activity of different ginsenosides, we need to pay more attention to the differences in the effects of molecular isomers.

2.3 Ginsenoside CK

Ginsenoside CK (CK) can effectively inhibit triple-negative cancer (TNBC), and its occurrence and development are associated with glutamine dependence. Bo Zhang Et al found that TNBC cells addicted to high glutamine were particularly sensitive to CK treatment. CK inhibits glutamine consumption and glutamate production by downregulating the expression of glutaminase 1 (Gls1), thereby exerting antitumor activity on TNBC. CK can induce glutathione (GSH) depletion and reactive oxygen species (ROS) accumulation, thereby triggering TNBC apoptosis. In addition, CK decreased the expression of Gls1 in mammary tumors of SUM159 xenograft mice and significantly inhibited tumor growth.[24]

2.4 Ginsenoside F2

Fayeza MD Siraj Et al found that F2 induces apoptosis in breast CSCs by activating the intrinsic apoptotic pathway and mitochondrial dysfunction. At the same time, F2 induced the formation of acidic vesicular organelles, the recruitment of GFP-LC3-II to autophagosomes, and the increase of Atg-7 levels, suggesting that F2 initiates autophagy in breast CSCs.[25] Ginsenoside F2 is also promising for further research and application in promoting the apoptosis of breast cancer cells.

3 Ginsenoside PPT

Protopanaxatriol (PPT) is also classified as a dammarane ginsenoside according to its skeleton structure. Ginsenosides can be divided into dammarane type and oleanol type according to its skeleton, among which protopanaxadiol (PPD) belongs to dammaran-type ginsenoside.[17] More than 50 different types of PPTs have been reported.[42] The promising ppts applied in the treatment of breast cancer include Rg1, Rg2, Rh1, etc. Among them, Rg1, Rg2 and Rh1 have similarities. All three ginsenosides can regulate the proliferation and apoptosis of breast cancer cells by regulating the level of reactive oxygen species (ROS).

3.1 Ginsenoside Rg1

Yan Chu Et al discovered that ginsenoside Rg1 induced cytotoxicity and apoptosis in triple-negative breast cancer cells (MDA-MB-MD-231 cell line) by generating reactive oxygen species (ROS) and altering mitochondrial membrane potential (MMP).

Ginsenoside Rg1 can also prevent the expression of markers related to cell proliferation and survival, regulate apoptosis markers, down-regulate invasion and angiogenesis markers, and regulate EMT markers to exert anticancer effects.[28]

Rg1 can also serve as an adjuvant to chemotherapy. Rg1 collaborates with doxorubicin to enhance the apoptotic cell ability of doxorubicin. Shengcui Liu Et al determined the chemosensitizing effect of Ginsenoside Rg1 in the triple-negative MDA-MB-231 breast cancer cell line. Breast cancer cells treated with Ginsenoside Rg1 (10μm) were exposed to 8nm doxorubicin, and the chemosensitization potential was measured through a cell-based assay. The treatment of Ginsenoside Rg1 (10μm) reduced the IC50 value of doxorubicin to 0.01nm. The number of apoptotic cells increased in cells treated with ginsenoside Rg1 plus doxorubicin. The treatment of Ginsenoside Rg1 activated DNA damage response elements (ATM, H2AX, Rad51, and XRCC1) and subsequent patterns of apoptosis-related gene expression (p21, TP53, Apaf1, Bax, CASP3, and CASP9). Moreover, Rg1 can inhibit the activation of mitogen-activated protein kinase (MAPK) gene expression (Akt, ERK and MAPK) caused by doxorubicin alone.[27]

3.2 Ginsenoside Rg2

Hyesu Jeon Et al studied the anticancer effect of ginsenoside Rg2 in breast cancer (BC) cells and its potential signaling pathways. Rg2 significantly induced cytotoxicity and reactive oxygen species (ROS) production in MCF-7 cells. Rg2 significantly inhibited the protein and mRNA expression of cell cycle G1/S phase regulators (including p-RB, cyclin D1, CDK4 and Cdk6), and enhanced the protein and mRNA expression of cell cycle arrest and apoptotic molecules (including cleaved PARP, p21, p27, p53 and Bak) through the production of ROS. In addition, Rg2 has a similar effect as Rg: It induces mitochondrial damage by reducing membrane potential, further activates ROS sensor proteins, AMPK and downstream targets of AMPK activation, and down regulates mTOR activation. It mediates anticancer effects by activating cell cycle arrest and signaling pathways related to mitochondrial damage induced ROS production and apoptosis.[29]

Rg2 also has the potential to be developed as a drug assisted biotherapy. Trastuzumab (TZM) is a monoclonal antibody drug targeting epidermal growth factor 2 for the treatment of HER2 positive breast cancer, but it has significant cardiotoxicity. Guang Liu Et al found that Rg2 could alleviate TZM induced cardiotoxicity.

When primary human cardiomyocytes (HCMs) were treated with TZM, the colony forming ability of HCMs was significantly reduced in TZM treated cells, but recovered after pretreatment with Rg2. The apoptosis rate of HCMs was significantly higher in TZM treated cells, but significantly lower after pretreatment with Rg2. In addition, the protein levels of Caspase-3, caspase-9 and Bax were significantly higher in TZM treated cells, but significantly lower after pretreatment with Rg2. The inhibitory effect of ginsenoside Rg2 on TZM induced cardiotoxicity may be related to the down-regulation of the expression of Pro apoptotic proteins Caspase-3, caspase-9 and Bax and the inhibition of cardiomyocyte apoptosis caused by TZM. Ginsenoside Rg2 has the potential to be applied in cancer patients to prevent cardiac toxicity caused by TZM. [30]

3.3 Ginsenoside Rh1

The research on the anticancer mechanism of Rh1 mainly focuses on its induction of increasing the level of reactive oxygen species (ROS) to regulate cell cycle arrest and apoptosis. Jin y Et al found that Rh1 treatment induced less than 50% cytotoxicity at 50μM. In addition, Rh1 induces apoptosis in triple negative breast cancer (TNBC) cells through cleaved caspase-3 activation and G1/S period. Rh1 treated TNBC cells showed a significant increase in mitochondrial ROS (mtROS), which in turn increased the protein expression of mitochondrial molecules, such as Bak and cytochrome c, and led to changes in mitochondrial membrane potential. [39] Rh1 treatment of MDA-MB-231 cells significantly inhibited TNBC metastasis by inhibiting the protein and mRNA levels of MMP2, MMP9 and VEGF-a. Effective anticancer effects on TNBC migration and invasion through mtROS mediated inhibition of STAT3 and NF-κB signaling. [40] Huynh DTN Et al found that Rh1 enhanced ROS generation inhibited the activation of PI3K/AKT pathway. Consistently, Rh1 treatment significantly reduced tumor growth in vivo, increased ROS production and protein expression of lc3b and cleaved Caspase-3, but decreased Akt and retinoblastoma (RB) phosphorylation in tumor tissues. In conclusion, Rh1 exerts potential anticancer effects on BC cells by inhibiting ROS mediated PI3K/AKT pathway to induce cell cycle arrest, apoptosis and autophagy. [41]

4 Pharmaceutical Preparations

In addition to the above ginsenosides regulating intracellular signal transduction, the immune system, and gene expression, ginsenosides can be prepared in various ways. In the past five years, many studies have shown that ginsenosides have great advantages in the synthesis of drug delivery carriers. Ginsenosides can be prepared as liposomes, nanoparticles, and other drug delivery vehicles, which significantly improve the targeting ability of drugs, improve the killing efficiency of cancer cells, and reduce their impact on normal tissues. In research on various ginsenosides, the application of Rh2, RB1, and Rg3 showed great advantages.

Hong C Et al developed a multifunctional liposome system (Rh2 lipo) based on Ginsenoside Rh2, which uses Rh2 to replace cholesterol and peg in liposomes. Rh2 simultaneously acts as a membrane stabilizer, active targeting ligand, and chemotherapy adjuvant. Rh2 guarantees the stability of liposomes and prolongs their action time. Rh2 lipo can also remodel the structure of the TME and reverse the immunosuppressive environment, solving the problems of the complexity of the tumor microenvironment (TME) and the limitation of insufficient accumulation at the tumor site. When tested in 4T1 breast cancer xenograft model, paclitaxel loaded Rh2 lipo achieved efficient tumor growth inhibition.[38] Hong C Et al further studied the preparation of Rh2 liposomes using ethanol water system, replacing cholesterol and peg with Rh2, and loading paclitaxel Rh2 lipo (PTX-Rh2-lipo) can act on tumor models. Rh2 lipos have many advantages and solve the limitations of current liposome formulations against large tumors, such as enhancing uptake, high targeting and penetration ability of tumor-associated fibroblasts (TAFs) and tumor cells. In an in vivo study, PTX-Rh2-lipo effectively inhibited the growth of advanced breast tumors.[12] Both studies demonstrated the advantages of Rh2 in liposome preparation.

Kim YJ Et al. Prepared a Rh2 conjugated HA-ZnO nanocomposite was prepared to form Rh2-HA-ZnO based on the application of zinc oxide nanoparticles (ZnO NPs) in targeted, low-toxicity cancer therapy and the photocatalytic performance of hyaluronic acid (HA) to resist cancer cells. It was confirmed that Rh2-HA-ZnO had anticancer effects on MCF-7 breast cancer cells, and intracellular reactive oxygen species (ROS) were observed in cancer cell lines. Further studies showed that the potential anticancer activity of the novel Rh2-HA-ZnO nanoparticles may be related to ROS generation and apoptosis induction through activation of the caspase-9/p38 MAPK pathway.[37] Gu h Et al synthesized an EGFR-targeted nanoliposome with ginsenoside Rh2 as a wall material (LTL-Rh2-Lipo-ge11), in which GE11 acted as an EGFR-binding peptide to deliver more ginsenoside RH 2 and luteolin into triple-negative breast cancer (TNBC). It can be used in TNBC epidermal growth factor receptor (EGFR) - targeted therapies. It showed high specificity and significant ability to inhibit tumor progression and metastasis for cells expressing EGFR.[34]

Ginsenoside Rb1 has similar functions as ginsenoside Rh2 and enhances the anticancer ability of drugs through the modification of carbon nanotubes (CNTs). Lahiani MH constructed a conjugate of ginsenoside Rb1 and carbon nanotubes (CNTs) (RB CNTs). This conjugate allows the use of ginsenosides at low doses but achieves higher cancer lethality. Studies have proved that ginsenoside CNT conjugate can reduce the cell viability of breast cancer cells (MCF-7) by up to 62%. The total transcriptome profile of MCF-7 cells treated with ginsenoside CNT conjugate showed that many cells, apoptosis and response to stimulation process were affected.[31] In addition, ginsenoside Rb1 has attracted considerable attention because of its good solubility and hydrophilicity. The self-assembly behavior of RB1 was observed in the study by Lu L's al. RB1 nanoassemblies can further stabilize or encapsulate hydrophobic drugs, such as protopanaxadiol (PPD) and paclitaxel (PTX), to form nanoparticles, thereby stabilizing ginsenoside Rb1 and PTX/PPD co-loaded nanoparticles (GPP NPs). The nanoparticles had a small particle size, narrow size distribution, and good stability. Both PTX and PPD existed in the GPP NPs in an amorphous state and were released in sustained mode. The tumor inhibition rate of GPP NPs is much higher than that of PTX injection and has certain tumor targeting ability.[32] Moveover, Zuo S Et al used the amphiphilic nature of ginsenosides as building blocks for biomaterials to prepare carrier-free nanomedicines composed of ginsenosides Rg3 and RB1 without any additional carriers using the nanoprecipitation method. It was observed that Rg3-Rb1 nanoparticles (NPS) exhibited stronger antitumor and anti-invasive effects on TNBCs than free ginsenoside mediated triple-negative breast cancer (TNBC) in vitro. And there is no obvious systemic toxicity in vivo.[33]

Rg3 can also construct a nanodrug delivery system to mediate targeted drug delivery to achieve tumor inhibition. In recent years, some studies have focused on Rg3 based nanodrug delivery systems coupled with doxorubicin in the treatment of breast cancer to improve the targeting of doxorubicin while reducing its toxicity. Doxorubicin (DOX) is one of the most effective chemotherapeutic drugs, which can induce immunogenic cell death (ICD), thus triggering an immune response and effectively treating breast cancer, especially triple-negative breast cancer. Chitosan and cell-penetrating peptide (r6f3) - loaded Ginsenoside Rg3 (Rg3) - modified nanoparticles (PNPs) were prepared by self-assembly technology, and then co-encapsulated with DOX based on a thermosensitive hydrogel, which was found to maximize the ICD effect induced by DOX. In addition, the hydrogel co loaded with Rg3 PNPs and DOX can be combined with PD-L1 blockers to obtain significant antitumor effect due to the recruitment of memory T cells and the decline of adaptive PD-L1 enrichment.[14] In order to improve the delivery of DOX and reduce its side effects, Shadi Rahimi Et al designed a pH-responsive delivery system based on graphene oxide (GO), which is capable of targeted drug release in an acidic tumor microenvironment. The coupling of go with Rg3 and loading DOX can effectively eliminate the reactive oxygen species (ROS) produced by go, weaken the activation of JAK-STAT signaling pathway mediated by go, so as to achieve the targeted delivery of DOX, significantly reduce the viability of cancer cells, and exhibit tumor suppressive activity in MDA-MB-231 breast cancer cells through the down regulation of transcriptional regulatory genes and the upregulation of apoptotic genes.[19]

In the study of Rg1, it was found that Rg1 can also be used as a drug delivery carrier to achieve targeted delivery of doxorubicin. Li C Et al developed Dox-Rg1 cardiotoxicity reducing nanoparticles to expand its application in cancer. Dox-Rg1 developed nanoparticles by encapsulating Doxorubicin (DOX) in self-assembled Rg1. The antitumor effect of the nanoparticles was evaluated in 4T1 tumor-bearing mice. It was found that the cytotoxicity of DOX-Rg1 nanoparticles on tumor cells was increased, and DOX-Rg1 nanoparticles had good tumor targeting ability, which improved the antitumor effect.[26]

5 Discussion and Prospect

In clinical breast cancer treatment, both traditional and new antitumor drugs may produce side effects, reduce the quality of life of the patients, and increase the risk of treatment resistance. Natural compounds are natural anti-tumor agents that provide an alternative approach. By identifying potential antitumor drugs from informative data containing natural compounds, these compounds have the potential to become a class of antitumor therapeutics with fewer side effects, significant therapeutic benefits, and relative affordability.[43] In recent years, a variety of studies have shown that different types of ginsenosides can inhibit breast cancer in various ways, including affecting the DNA expression of breast cancer cells, inhibiting the cell cycle, promoting apoptosis, inhibiting cell proliferation, regulating the tumor microenvironment, and promoting the immune system to kill cancer cells. In addition, ginsenosides can have more significant advantages in being prepared into drug delivery carrier preparations: they can target anti-tumor drugs to breast cancer cells, improve the killing ability of tumor cells while significantly reducing the toxicity to normal tissue cells, and inhibit cancer more stably and for a long time.[44]

Currently, research on ginsenosides in breast cancer is mostly focused on basic research at the molecular and cellular levels and related preparations. In view of the significant anticancer efficacy of ginsenosides, we need to strengthen the efficacy of animal experiments and accelerate clinical practice. Because modern research has gradually proven the curative effect of traditional Chinese medicine on a variety of diseases, ginsenosides have medicinal value in the development of anticancer drugs and related preparations. Ginsenosides have great developmental and clinical application prospects.[42]

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