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Effect of Resveratrol on Major Gynecological Tumors

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Abstract. Breast cancer (BC), cervical cancer (CC), endometrial cancer (EC), and ovarian cancer (OC) are the four most common tumors in women, which seriously threaten women's lives. However, the current mainstream treatment approaches are accompanied by great side effects, and related drugs are scarce. In recent years, researchers have discovered that RES has multiple biological functions and can intervene in the occurrence and development of common gynecological tumors through various pathways, such as inducing cell apoptosis, regulating cell autophagy, affecting cell migration and invasion, and reversing treatment tolerance. However, the instability of RES limits its clinical application, and clinical studies are relatively limited. This paper summarizes and analyzes the mechanism of RES against common gynecological tumors and concludes that RES has great research prospects but certain limitations in its application. It can also provide relevant personnel with a certain theoretical basis and research direction reference, as well. At present, the problems of RES stability and lack of clinical research have not been solved. In the future, we can start with drug development and clinical trials.

Keywords: Resveratrol; Gynecology; Tumor.

1. Introduction

Breast cancer (BC), cervical cancer (CC), endometrial cancer (EC), and ovarian cancer (OC) are the four most common tumors in women. According to relevant statistical reports, there were 2.297 million new cases of breast cancer in 2022 alone, ranking second among all cancers in the population, and its mortality rate ranked fourth among all cancers in the population; For the female population, whether it was the number of cases or the number of deaths, it ranked first among all cancers [1]. Moreover, in 2020, three types of malignant tumors in the female reproductive system, CC, EC, and OC, caused a total of approximately 646,000 deaths, ranked in descending order of proportion as CC (53%)>OC (32%)>EC (15%) [2]. Unfortunately, cancer has always been a difficult problem, although tumor resection, radiation therapy, and chemotherapy are often used as treatments. However, these methods can also cause significant damage to the normal function of the patients, such as bone marrow suppression. If treated with medication, it can reduce the damage to the normal function of the patients to a certain extent. However, currently, there are no specific drugs. However, in recent years, with the research on phytochemicals, many functions have been discovered, such as anti-oxidation, anti-inflammatory, anti-tumor, etc. Therefore, researchers have favored phytochemicals as a new research direction. Resveratrol (RES) is a polyphenol compound widely found in fruits such as grapes. In addition to the above-mentioned biological effects, it also has antibacterial, immune regulatory, cardiovascular, and cerebrovascular protective functions. In addition to hydroxyl groups, the chemical structure of RES also contains a stilbene structure, which provides greater possibilities for modification and gives it other biological functions. Therefore, this paper focuses on RES among phytochemicals and summarizes its anti-tumor effects on common gynecological tumors, aiming to provide a systematic theoretical basis for subsequent studies on the effects of RES on common gynecological tumors.

2. RES Biological Functions

The chemical name of RES is 3,4',5-trihydroxy-1,2-distyrene, which is a class of non-flavonoid polyphenolic compounds. Its main chemical structures for biological action are phenol and resorcinol,

and it is a bioactive ingredient in fruits and vegetables such as grapes and mulberries. The content of RES in fruits and vegetables is not prominent, and the cost of natural extraction is relatively high, so the use of biological, chemical, and other synthetic methods to prepare RES has become the mainstream means of obtaining it. Regarding the current application of RES, there are no extensive reports on related drugs in China.

The main biological functions of RES are as follows: 1) Reducing the generation of reactive oxygen species (ROS) and lipid peroxidation to prevent oxidation. It mainly relies on scavenging free radicals, increasing the activity of antioxidant enzymes, and inducing the body's non-enzymatic antioxidant system to play a role. 2) Acting on related cytokines such as inhibiting tumor necrosis factor-α (TNF-α), regulating nitric oxide (NO) levels, etc., to exert anti-inflammatory effects. 3) Interfering with bacterial biofilm formation, inhibition of the expression of fission protein FtsZ and Z-ring formation, for antibacterial purposes; inhibiting virus replication while enhancing the host's ability to resist viruses for antiviral purposes. 4) Improving the levels of natural immunity, humoral immunity, and cellular immunity in the body, as well as intervening in the secretion of cytokines, thereby enhancing the body's immune function. 5) Intervening in the AMPK-SIRT1-PGC-1α signaling pathway to regulate lipid metabolism and inhibit fat deposition. 6) Protecting the cardiovascular system: through calcium channels, it acts on endothelial vasodilator factor and multiple signaling pathways to relax blood vessels; lower blood lipid levels, and maintain the stability of thromboxane, prostaglandin, and calcium ions inside and outside cells to reduce platelet aggregation. 7) Inducing apoptosis and necrosis of cancer cells, inhibiting tumor cell angiogenesis, promoting the expression of junction proteins to enhance bystander effects, and achieving anti-tumor goals [3].

3. Effect of RES on Common Gynecological Tumors

RES can participate in the occurrence and development of common gynecological tumors through various pathways and play an anti-tumor role.

3.1. Inducing Cell Apoptosis

The expansion of tumor cell number depends on two aspects: the proliferation rate and the apoptosis rate of tumor cells. The expression of low-density lipoprotein-related receptor binding protein (LRP5/6) is related to the proliferation of breast cancer cells. Studies have found that after RES treatment of breast cancer cells, it can not only downregulate the expression of low-density lipoprotein-related receptor binding protein (LRP5/6), inhibit the Wnt/β-catenin signaling pathway, but also inhibit cell division and arrest the cell cycle in the S phase, thereby preventing the proliferation of mouse breast cancer 4T1 cells and inducing cell apoptosis. NA polymerase δ catalytic subunit 1 is involved in the replication and repair of DNA and is essential for maintaining the stability of the cell genome. Other experiments have found that RES-treated MDA-MB-231 triple-negative breast cancer cells have a dose-dependent effect on inhibiting the expression of NA polymerase δ catalytic subunit 1 mRNA and protein, down-regulating the expression of anti-apoptotic proteins such as poly (ADP-ribose) polymerase 1 (PARP1), and conversely increasing the expression of cleaved poly (ADP-ribose) polymerase 1, thereby achieving the purpose of cell apoptosis [4].

The caspase family is responsible for the initiation and execution of apoptosis, and Bax plays the role of the initiator of the mitochondrial pathway in apoptosis, promoting changes in mitochondrial membrane permeability, leading to apoptosis. Regarding the apoptotic effect of RES on cervical cancer, a study analyzed that the apoptosis rate of cervical cancer cells in the RES treatment group and the cisplatin group was higher than that in the control group, and the proliferation rate was lower than that in the control group. Further detection of proteins related to cell apoptosis found that the expression of caspase-3, caspase-9, and Bax proteins in the RES treatment group and the cisplatin group was significantly higher than that in the non-treatment group, while the expression of Bcl-2 was lower than that in the non-treatment group. Therefore, the possible mechanism is to increase the expression of caspase-3, caspase-9, and Bax proteins and reduce the expression of Bcl-2 to achieve

the purpose of promoting cell apoptosis. The study also pointed out that RES can block the cell cycle, increasing the proportion of cells in the G1 phase and reducing the proportion of cells in the G2 and S phases in the RES-treated group. This may be related to the decrease in the levels of cyclin-dependent kinase 2 (CDK2) and cyclin D1 (cyclinD1) in cells after treatment and the increase in p21 expression [5].

A randomized in vivo experiment found that RES can upregulate the expression of Bax and Caspase-3 proteins and downregulate the expression of Bcl-2 in ovarian cancer rats, achieving the effect of promoting apoptosis and inhibiting tumor growth. The apoptosis and metabolism of tumor cells often involve galectin (Gal-3). An in vitro study experiment showed that the expression of microRNA-424-3p (miR-424-3p) in ovarian cancer cells treated with RES increased, while the expression of Gal-3 decreased, and the two were negatively correlated. This may be through upregulating miR-424-3p to reduce Gal-3 and interfere with the apoptosis of tumor cells. In addition, increased cleavage of intracellular PARP protein indicates the initiation of programmed cell death, and RES can also increase the cleavage of PARP protein in ovarian cancer cells, causing cell apoptosis, and thereby inhibiting the proliferation of ovarian cancer cells. An in vitro study showed that RES can inactivate the Wnt signaling pathway, inhibit the expression levels of Wnt3a and β-catenin, regulate a series of proliferation genes such as c-myc, and ultimately induce OC cell apoptosis [6].

A study showed that the number of cell colonies of endometrial cancer cells treated with RES was significantly reduced compared with the control group, accompanied by increased expression of Beclin1 and LC3 II/I, decreased expression of LC3 I and p62, and a time-dose-dependent inhibition of proliferation rate. This may be related to the inhibition of Akt/mTOR expression in endometrial cancer cells and the dose-dependent activation of the p38-AMPK signaling pathway in endometrial cancer cells [7].

In summary, multiple studies have shown that RES can promote apoptosis of common gynecological tumors. For breast cancer, it downregulates LRP5/6 expression, inhibits the Wnt/β-catenin signaling pathway, and induces cell apoptosis; for cervical cancer and ovarian cancer, it can increase the expression of caspase-3, caspase-9, and Bax proteins, and reduce the expression of Bcl-2, promote apoptosis; for endometrial cancer, it can inhibit cancer cell proliferation and induce apoptosis by affecting the Akt/mTOR and p38-AMPK signaling pathways. These results suggest that RES has great promise in the treatment of common gynecological tumors.

3.2. Regulating Cell Autophagy

Autophagy is a lysosome-dependent catabolic process. Autophagy can remove damaged or aged organelles and cope with environmental stress, but in some cancer cells, such as disseminated dormant breast cancer cells, cancer cells can decompose and utilize their cellular components to provide nutrients and energy, and extend their survival time with autophagy. However, RES can not only increase the expression of corresponding proteins such as phosphorylated AMP-activated protein kinase (p-AMPK) and silent information regulatory protein 3 (SIRT3), but also increase the levels of autophagy-related genes and proteins, promote the formation of autophagosomes, and self-degrade cancer cells. It can also inhibit the autophagy pathway in dormant breast cancer cells that obtain nutrients through autophagy, such as downregulating the expression of the p62 protein, preventing these cancer cells from using autophagy to provide themselves with energy for survival, and causing the accumulation of damaged organelles and ROS inside the cells, leading to apoptosis [4].

A study on the regulation of autophagy in cervical cancer cells by RES in vitro showed that, first, the RES treatment group starting from 40 μM can significantly promote the expression of the autophagy gene VMP1, and can also significantly inhibit the expression of p62, which is statistically significant compared with the control group. It can also promote the formation of autophagic flow, and the formation of autophagosomes is increased compared with the control group. In addition, mitochondrial membrane potential ($\Delta\Psi m$) is a key factor in maintaining the normal function of

mitochondria. It is closely related to mitochondrial energy production, material transport, and cell apoptosis. Under normal circumstances, the mitochondrial membrane potential is maintained at a certain level to ensure that the mitochondria can perform aerobic respiration and produce ATP and other functions. An increase in its decrease rate indicates an increase in the proportion of early cell apoptosis. The study also investigated the effect of RES on ΔΨm and found that the proportion of ΔΨm decrease increased, suggesting an increase in the proportion of early cell apoptosis, which may be related to endogenous induction of cell apoptosis [8].

ARH-I plays a role in the regulation of cellular autophagy, participating in regulating the activity of autophagy-related proteins or the fusion of autophagosomes and lysosomes, and affecting the level of cellular autophagy. A related study used a 3D spheroid culture model to investigate the effect of RES on ovarian cancer cells and confirmed that IL-6 can downregulate ARH-I to inhibit autophagy in breast cancer cells. However, p62 expression in tumor spheroids treated with RES decreased, while LC3-II expression was upregulated, activating autophagic flux. Moreover, after treating ovarian cancer cells with RES at a concentration of 25 μ mol/L for 24 hours, the content of autophagic proteins such as LC3 and Beclin-1 in the cells increased, indicating that RES can induce autophagy and affect the growth and proliferation of ovarian cancer cells. RES can also simulate the enhanced autophagic flux and LC3II/β-tubulin expression in a glucose-deficient environment, thereby stimulating cellular autophagy [6].

About endometrial cancer, experimental studies have shown that RES can not only upregulate the mRNA levels of autophagy-related proteins Beclin1 and LC3m, thereby upregulating the expression levels of Beclin1 and LC3 proteins to cause cell autophagy, but also downregulate the levels of P-PI3K and P-AKT proteins. This result confirms that RES can inhibit the activation of the PI3K/AKT signaling pathway to promote autophagy in endometrial cancer cells, thereby inhibiting the proliferation of endometrial cancer cells [9].

In summary, multiple studies have shown that RES has a regulatory effect on autophagy in common gynecological tumor cells. For breast cancer, RES can increase the expression of related proteins to promote autophagosome formation or inhibit the autophagy pathway of dormant cancer cells; For cervical cancer, it can promote the expression of autophagy gene VMP1, thereby regulating autophagy; For ovarian cancer, autophagic flux can be activated; For endometrial cancer, it can upregulate the expression of autophagy-related proteins and inhibit the PI3K/AKT signaling pathway to promote autophagy. These studies suggest that RES may become a new force in the treatment of common gynecological tumors.

3.3. Affecting Cell Migration and Invasion

RES can increase the expression of E-cadherin and inhibit the expression of vimentin, thereby reducing the invasion and metastasis of breast cancer cells by inhibiting the epithelial-mesenchymal transition pathway. Matrix metalloproteinases (MMPs) can degrade the extracellular matrix and help tumor invasion and metastasis, while RES can regulate the expression levels of related proteins in breast cancer cells, such as inhibiting MMP-2, MMP-9, etc., thereby reducing the invasiveness of breast cancer cells and inhibiting the invasion of tumor cells [4].

ADAM9 is a metalloproteinase that participates in the degradation of the extracellular matrix, intercellular signal transduction, and cell migration and has a regulatory effect on cell proliferation, migration, and invasion. In the research on exploring the effect and mechanism of RES on the migration of cervical cancer cells, it was found that the migration ability of cervical cancer cells treated with RES was significantly reduced, accompanied by a decrease in the expression of ADMA9 protein. Further exploration using gene knockout technology revealed that the knockdown of ADMA9 plasmid enhanced the ability of RES to inhibit the proliferation and migration of cervical cancer cells, while the overexpression of ADAM9 plasmid weakened the inhibition of RES on the proliferation and migration of cervical cancer cells. This suggests that RES can inhibit the

proliferation and migration of cervical cancer cells by inhibiting the expression level of the ADAM9 gene and reducing the content of ADAM9 in cervical cancer cells [10].

Previous studies have found that the stromal cell-derived factor 1 (CXCL12)/chemokine receptor 4 (CXCR4) axis can activate a series of related signaling pathways that promote tumor cell growth, spread, and metastasis, including the AKT signaling pathway, PI3K signaling pathway, Ras, etc. In a study on the effect of RES on breast cancer cells, a report pointed out that RES can act on the CXCR4/CXCL12 signaling axis, thereby inhibiting the proliferation, migration, and invasion of tumor cells [6].

In summary, RES can affect the migration and invasion ability of common gynecological tumor cells, leading to a decrease in the ability of cancer to spread. For breast cancer, RES can inhibit the epithelial-mesenchymal transition pathway and reduce the ability of invasion and metastasis by regulating the expression of related proteins; for cervical cancer, it can inhibit ADAM9 gene expression and reduce related protein content, inhibiting cell proliferation and migration; for breast cancer, it can also act on the CXCR4/CXCL12 signaling axis to inhibit the migration and invasion of tumor cells. This further demonstrates that RES has multi-directional and multi-action effects against common gynecological tumors and has great research value.

3.4. Reversing Treatment Resistance

First, RES can target miR-122-5p to regulate the expression level of cell cycle-dependent kinases and increase the level of miR-519c, thereby enhancing the resistance of breast cancer cells to doxorubicin. In addition, RES can reduce the activity of antioxidant enzymes in breast cancer cells, increase ROS accumulation, and enhance the effect of ionizing radiation therapy [4]. Then, RES can downregulate the expression of MDR1 and Beclin-2 mRNA in cisplatin-resistant ovarian cancer cells, inhibit the expression of P-gp protein, reduce the efflux of cisplatin by cells, stabilize the intracellular cisplatin concentration, and reverse the drug resistance [6]. Finally, RES can also reduce the resistance of cervical cancer cells to cisplatin [5], but there is currently no relevant research progress on the specific mechanism, and the number is relatively small.

In summary, RES can reverse the therapeutic tolerance of common gynecological tumor cells to a certain extent and improve the therapeutic effect. For breast cancer, RES can enhance resistance to doxorubicin by regulating miR-122-5p and miR-519c levels and enhance the therapeutic effect of ionizing radiation by affecting antioxidant enzyme activity and ROS accumulation; for ovarian cancer, it can downregulate the expression of MDR1 and Beclin-2 mRNA, inhibit the expression of P-gp protein and reverse cisplatin resistance; for cervical cancer, it can reduce resistance to cisplatin. Therefore, in the future, the combined effect of RES and anticancer drugs may bring new hope for anti-tumor treatment.

4. Conclusion

This article focuses on the anti-tumor effect of RES on common gynecological tumors and emphasizes the relevant mechanism of action of RES in breast cancer, cervical cancer, ovarian cancer, and endometrial cancer, including inducing cell apoptosis, regulating cell autophagy, affecting cell migration and invasion, and reversing treatment tolerance. In addition, the extremely important research value and unlimited application prospects of RES in common gynecological tumors are deeply revealed, providing certain research or application premises for RES for people engaged in related industries, for example, in clinical terms, it provides a new potential direction for the treatment of common gynecological tumors. It can be treated alone or in combination, opening up new ideas for tumor treatment. However, the non-selectivity, photolysis, and chemical instability of resveratrol make it difficult to exert its precise effects, limiting its practical application in clinical practice, moreover, relevant research has mainly focused on cell experiments and animal experiments, and there is a lack of clinical research, resulting in insufficient understanding of its pharmacokinetics and toxicology in humans, and its safety needs further study. Therefore, in the future, in drug research,

we can improve the relevant extraction process or synthesis route, reduce costs and increase efficiency, and also match the carrier to ensure stability; in clinical research, volunteers are recruited and clinical trials are conducted to obtain data on the efficacy and safety of RES. It can also be combined with other treatment methods to explore the best treatment for RES.

References

[1] Mo Miao, Wang Zezhou, Zheng Ying, Zhang Jian, Breast cancer in the world and China in 2022:an analysis on epidemic status[J]. Academic Journal of Naval Medical University, 2025,46(04):497-503

[2] Jiang Danfeng, Zhu Mengxiu, Zhao Qingjuan, etc. Analysis of the incidence and death rate of female reproductive system tumors in China[J]. Journal of Modern Oncology, 2023,31(23):4426-4431.

[3] Kong Tao, Ma Yanbo, Yang ZIjun, etc. Biological function and mechanism of resveratrol [J]. The Chinese Journal of Clinical Pharmacology, 2022,38(06):592-596.

[4] Gao Qingdong, Duan Xufang, Li Yan, etc. Research on the role of resveratrol against breast cancer [J]. China Pharmacy, 2024,35(11):1408-1412.

[5] Yue Xiao-ding, Li Xiu-Juan, Liu Qing, etc. Resveratrol elevates the chemosensitivity of cervical cancer cells by inducing cell cycle arrest and apoptosis [J]. Journal of Xi'an Jiaotong University(Medical Sciences),2019,40(05):736-741.

[6] Zhou Yuan, Liu Fangyuan, Han Fengjuan. [J]. Research Progress on Mechanism of Resveratrol on Ovarian Cancer, Chinese Journal of Integrated Traditional and Western Medicine,2025,45(01):110-116.

[7] Xu Hui, Zhang Jingbo, Wang Qing, etc. Effect of resveratrol on the expression of molecules related to the mTOR signaling pathway in endometrial cancer cells. [J]. Chinese Journal of Birth Health & Heredity,2020,28(05):533-536+577.

[8] Xun Xiaodong, Zhou Zhen, Zeng Lian, etc. Resveratrol induces autophagic death of cervical cancer cells to exert an antitumor effect [J]. Natural Product Research and Development,2021,33(02):208-215.

[9] Fan Yijun, Shi Yuchuan, Li Jun, etc. Resveratrol induces autophagy in endometrial cancer Ishikawa cells by inhibiting the PI3K/AKT pathway [J]. Acta Universitatis Medicinalis Anhui,2022,57(03):361-365+373.

[10] Nan Wenqing, Fan Xuefeng, Song Tao, etc. The effect and mechanism of resveratrol on the inhibition of proliferation and migration of cervical cancer cells by regulation of ADAM9 [J]. Journal of Guangxi Medical University,2021,38(11):2140-2145.