PLANT SCIENCE TODAY
ISSN 2348-1900 (online)
Vol x(x): xx–xx
https://doi.org/10.14719/pst.2549

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MINI REVIEW ARTICLE

Exploring the Impact of Resveratrol on Gynecological Cancer: Insights and Perspectives

Revathi Unni K, Amrisa Pavithra E, Aparna G Kumar & Santhy K S*

Department of Zoology, Avinashilingam Institute for Home Science and Higher Education for Women, Deemed to be University, Coimbatore – 641043, Tamil Nadu, India

***Email:** santhyanandan@gmail.com

OPEN ACCESS

ARTICLE HISTORY

Received: 30 March 2023
Accepted: 14 September 2023

Available online
Version 1.0 : 15 October 2023

Check for updates

Additional information

Peer review: Publisher thanks Sectional Editor and the other anonymous reviewers for their contribution to the peer review of this work.

Reprints & permissions information is available at https://horizonepublishing.com/journals/index.php/PST/open_access_policy

Publisher's Note: Horizon e-Publishing Group remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Indexing: Plant Science Today, published by Horizon e-Publishing Group, is covered by Scopus, Web of Science, BIOSIS Previews, Clarivate Analytics, NAAS,UGC Care etc. See https://horizonepublishing.com/journals/index.php/PST/indexing_abstracting

CITE THIS ARTICLE

Revathi U K, Amrisa P E, Kumar A G, Santhy K S. Exploring the Impact of Resveratrol on Gynecological Cancer: Insights and Perspectives. Plant Science Today (Early Access). https://doi.org/10.14719/pst.2549

Abstract

Gynecological cancers, a group of malignancies affecting the female reproductive system, are a significant cause of morbidity and mortality in women. Different types of gynecological cancers differ by distinct attributes, risk determinants, and therapeutic methodologies. So, depending on the type and stage of the cancer, a tailored combination of therapies is required for the treatment. However, it is shocking that the side effects of these therapeutic methods range from mild to severe. Hence, developing innovative therapeutic approaches to improve patient outcomes is imperative. Here's the juncture where the role of plant-derived compounds in curing gynecological cancers becomes evident. Various plant-derived compounds, including phytochemicals, polyphenols, alkaloids, and terpenoids for their cytotoxic, apoptotic, anti-angiogenic, and immunomodulatory properties, have been examined so far. Besides, certain phytocompounds can modulate hormonal-dependent gynecological cancers. Among the widely studied phytocompounds, RSV is the one that is extensively researched *in vitro, in vivo* and *in-silico* studies. In this context, this review article provides insights into the present-day knowledge about how RSV can potentially manage gynecological cancers. However, further research is needed to standardize their mode of action, optimal dosages, and potential interactions with conventional treatments. Rigorous clinical trials must validate their safety and efficacy profiles in different patient populations. As a result, a novel avenue for treating and preventing gynecological cancers could emerge by harnessing the multifaceted properties of phyto compounds, instilling new hope for patients and healthcare providers alike.

Keywords

Cervical cancer; Endometrioid cancer; Gynaecological malignancy; Resveratrol; Ovarian cancer

Introduction

Gynecological cancers encompass diverse malignancies affecting the female reproductive system, presenting a significant global health challenge. Among these, cervical cancer is the fourth most prevalent cancer among women, accounting for many diagnoses and fatalities (1). The alarming statistics from 2018, revealing approximately 570,000 new cases and 311,000 lives lost to cervical cancer, underscore the urgency of effective interventions (2). According to WCRF International's data, endometrial cancer, also referred to as uterine or corpus uteri cancer, ranks as the sixth most frequently occurring cancer in women and the fifteenth most prevalent cancer overall (3). 2020 witnessed a surge in endometrial cancer cases, with over 417,000

new diagnoses (4). Notably, Poland exhibited the highest incidence rate of endometrial cancer among women in 2020, closely followed by Lithuania (5). Regarding endometrial cancer mortality, the Bahamas held the highest rate in 2020, trailed by Jamaica (6). With its intricate pathogenesis and insidious progression, ovarian cancer stands as the eighth most prevalent cancer in women (7) and holds the eighteenth position among the most commonly diagnosed cancers overall (8). The year 2020 witnessed an excess of 313,000 new instances of ovarian cancer and registered the highest incidence rate of ovarian cancer, with Samoa following closely behind (9). During 2020, Samoa experienced the highest ovarian cancer mortality rate, with Fiji ranking next in line (10). The origin of high-grade serous ovarian cancers (HGSC) is within the fallopian tube. When considering ovarian, fallopian tube, and peritoneal cancers together, they rank as the fifth leading contributor to cancer-related fatalities among women in the United States (11). 3,479 cases involving the fallopian tube were detected using data from 24 population-based registries in the United States from 1995 to 2004 (12). Vaginal cancer is a rare condition, with approximately 75% of cases being attributed to the human papillomavirus (HPV) (13). The likelihood of developing vaginal cancer rises with age, typically becoming evident around the age of 67 (14). Those without convenient access to cervical cancer screening are more susceptible to vaginal cancer (15). In 2020, there were roughly 17,908 reported instances of vaginal cancer across the globe, and it is projected that 1,740 fatalities resulting from this disease will occur in the United States during 2023 (16). Moreover, 2020 witnessed an estimated 7,995 worldwide fatalities due to vaginal cancer (17).

In the quest for innovative treatments, plant-derived phytocompounds have gained significant focus due to their potential in addressing cancer (18). Among these, Resveratrol (RSV) stands out for its multifaceted pharmacological properties, including antioxidant, anti-inflammatory, and anticancer effects (19). As the data unfolds, RSV has consistently demonstrated its most promising outcomes in cervical (20), endometrial (21), vaginal (22), and ovarian cancer (23), suggesting its potential effectiveness across various gynecological ailments, thereby forming the focal point of our discussion in this research article.

This study delves into the potential of RSV as a therapeutic agent for gynecological cancers, shedding light on its mechanisms of action and potential benefits. By elucidating the intricate interactions between RSV and specific cancer types, we aim to contribute to a deeper understanding of its role in inhibiting proliferation, inducing apoptosis, and impeding invasion and migration. Additionally, we will explore its potential to modulate critical signaling pathways implicated in cancer progression.

Materials and Methods

To comprehensively review the role of RSV in gynecological cancer, a rigorous search strategy was implemented across multiple scholarly databases. The following methodology outlines the specific search platforms, criteria, and keywords employed in this study.

Search Platforms:

The search was conducted on prominent academic databases, including Web of Science, Scopus, PubMed, and Google Scholar. These platforms were selected for their extensive coverage of scientific literature across various disciplines.

Search Criteria:

The search criteria were designed to capture relevant articles focusing on the relationship between RSV and gynecological cancer. The criteria included a combination of keywords related to "Resveratrol", "gynecological cancer," and specific cancer types (e.g., cervical, endometrial, ovarian, vaginal, fallopian tube). The search was restricted to articles published within the last decade to ensure the inclusion of recent research findings.

Inclusion Criteria:

To ensure the inclusion of high-quality and relevant studies, the following criteria were applied: Articles discussing the impact of RSV on gynecological cancer at the cellular, molecular, or clinical levels. Studies published in peer-reviewed journals. Research conducted on human subjects or cell lines. Articles available in the English language.

Exclusion Criteria:

Articles failing to meet the following criteria were omitted from the review: Studies unrelated to the effects of RSV on gynecological cancer. Non-peer-reviewed publications, such as conference abstracts or editorials. Studies lacking relevant outcome measures or appropriate experimental design.

Keywords for Searching:

The search queries encompassed a combination of keywords but were not limited to RSV, Gynecological cancer, Cervical cancer, Endometrial cancer, Ovarian cancer, Vaginal cancer, fallopian tube cancer, and Anticancer effects.

By searching for and reviewing the literature systematically and thoroughly, this method makes sure to include relevant and reliable studies that add to a full understanding of RSV's potential role in gynecological cancer. The selected articles underwent critical analysis, and interpretation, forming the basis of the insights presented in this review article.

Results

Endometrioid cancer

The most typical gynecological cancer, endometrioid cancer is a type of uterine cancer that develops in the lining of the endometrium as a consequence of abnormal

cell growth and division and also has the potential to invade or spread to other areas of the body (24). Primary hysterectomy (laparoscopic) (25), bilateral salpingo-oophorectomy (26), and lymphadenectomy (27) are the usual treatments for uterine cancer (28). Chemotherapy or adjuvant therapy depends on the particular histology, tumor stage, etc. (29).

A naturally occurring polyphenolic phytoalexin, RSV produced by plants and found in abundance in grape skins, wine, berries, nuts, etc., (30) has demonstrated a broad range of therapeutic potential for treating various diseases. It functions as a chemopreventative agent because of its anti-carcinogenic action. It was found that 11 target proteins of this particular cancer showed an affinity with RSV, among which Mitogen-activated protein kinase 3 (MAPK3), Tumor necrosis factor (TNF), and Mitogen-activated protein kinase 8 (MAPK8) were validated with the highest affinity (31).

Although RSV exhibits anticancer properties in various human cancers, the precise process underlying endometrial cancer is still unclear. It has been demonstrated that MTA1 (metastasis-associated protein 1) supports the development of tumors and the spread of malignancies, including endometrial cancer (32). During the initial phases of cancer, the epithelial-mesenchymal transition (EMT) plays a crucial role in facilitating the invasion and movement of tumor cells (33). RSV's exact anti-invasion mechanism about endometrial cancer and its effect on MTA1-induced EMT are still not well understood, so more research is needed to figure them out. Research has indicated that RSV decreased MTA1 expression while inhibiting endometrial cancer cell proliferation, migration, and invasion (34). It is intriguing to note that overexpression of MTA1 may be partially reversed by the effects of RSV on cell activity. Through RNA -sequencing analysis, it was then demonstrated that ZEB2 was downregulated first, followed by MTA1 (35). ZEB2 (Zinc finger E-box binding homeobox 2) knockdown inhibited endometrial cancer cell migration and invasion, but this effect could be reversed by MTA1 overexpression (36). RSV has the potential to counteract the outcomes of MTA1 over-expression, leading to elevated levels of ZEB2 and vimentin expression while decreasing the expression of E-cadherin. In addition, MTA1 and ZEB2 had a physical interaction that revealed an association between them. Without significantly altering body weight, RSV inhibited tumor growth and the expression of MTA1 and ZEB2 in vivo. According to these findings, RSV prevented MTA1-ZEB2-induced EMT from causing tumor growth and cancer progression in endometrial tissue (37).

Ovarian cancer

Ovarian cancer, a complex and multifaceted disease, represents a significant challenge in women's health and oncology. The ovaries, essential components of the female reproductive system, produce eggs and hormones (38). Ovarian cancer, however, disrupts this delicate equilibrium, giving rise to malignant growths that can emanate from various cell types within the ovaries. Its diverse histological subtypes, including epithelial, germ cell, and stromal tumors, present a varied clinical landscape that necessitates tailored therapeutic strategies.

RSV is a natural polyphenol that can be found in many plants. It has been shown to have many different effects on cancer cells, including stopping them from growing, making them commit suicide (apoptosis), stopping them from making new blood vessels (angiogenesis), and interfering with signaling pathways that are important for the growth of tumors. When RSV was added to two human ovarian cancer cell lines, OVCAR-3 and CAOV-3, the number of cells in the G1 phase increased and the number of apoptotic cells went up (39). This effect was linked to the blocking of STAT3 signaling, which led to changes in gene expression related to the progression of cancer. The findings from this study suggest that RSV holds potential as a promising candidate for the management of ovarian cancer, given its observed impact on the behavior of ovarian cancer cells (40). In a mouse model of ovarian cancer, RSV showed that it could slow the growth of tumors by increasing the number of cytotoxic T lymphocytes (CTLs) and antigen-presenting cells in the tumor tissues. Significantly, the levels of transforming growth factor- (TGF-) went down a lot, and at the same time, the release of interferon-gamma (IFN-) went up (41). RSV stops mTOR complex 1 from working by turning off AKT and turning on AMP-activated protein kinase. This starts a process called autophagy that stops cancer cells from dividing (42). RSV induces apoptosis in ovarian cancer cells by eliciting endoplasmic reticulum stress which is achieved by inhibiting the hexosamine biosynthesis pathway and disrupting protein glycosylation. This interference is achieved by activating GSK3β, facilitated by suppressing the inhibitory S9-phosphorylation of GSK3β (43). The concurrent administration of curcumin and RSV exhibits a notable capability to enhance the sensitivity of epithelial ovarian cancer cells to cisplatin treatment. When curcumin and RSV are used together, they effectively stop ovarian cancer cells from being resistant to chemotherapy by blocking the PI3K/AKT/mTOR signaling pathway (44). Lysophosphatidic acid (LPA) stimulated ovarian cancer cell migration and inhibited autophagy, while RSV had the opposite effect. The study also identified the involvement of the PI3K-AKT, JAK-STAT, and Hedgehog (Hh) pathways in this process. By inhibiting the Hh pathway and restoring autophagy, RSV was found to counteract LPA-induced malignancy, supporting its inclusion in the therapy of ovarian cancer for limiting metastasis and chemoresistance (45). RSV exerts a repressive influence on the proliferation, triggers apoptosis, and hampers the invasion and migration of ovarian cancer cells. The research further revealed that the tumor suppressor gene miR-34a intensifies RSV's inhibitory impact on ovarian cancer cells by targeting the anti-apoptotic gene Bcl-2 (46).

Cervical Cancer

It is a malignant growth of the cervix and is predominantly caused by persistent human papillomavirus (HPV) (47). It is the 4th most common

cancer in women and the 2nd most common gynecological malignancy (48). About 500,000 women are diagnosed worldwide. Most cervical cancers are of epithelial origin (49). Usually, sexual activity results in HPV infection, and other risk factors are an immunosuppressed state, tobacco smoking, limited access to health care and screening, continuous consumption of oral contraceptive pills for more than five years, and family history (50). Recent advances in screening and vaccination against the papillomavirus (HPV) have increased protection against cervical cancer (51).

Like every other cancer, surgery (52), chemotherapy (53), and radiotherapy (54) are the treatment methods available for cervical cancer depending on the staging (55). The treatment measures are essential for combating the disease, but they often entail a variety of side effects including nausea, fatigue, gastrointestinal disturbances, immune system suppression, etc. Moreover, these side effects hinder treatment adherence, limit therapy efficacy, and compromise overall well-being. So here, phytotherapy garnered attention as a complementary approach with fewer side effects. By experimental analysis, many studies state that radiation reduced the number of human cervical cancer cells such as HeLa and SiHa by 20%, whereas RSV decreased the number by 25 percent (56). Some studies state that RSV has the added benefit of reducing the growth of new cancer cells at the same time (57). By observing the effect of RSV, researchers found that RSV significantly improved the effectiveness of radiation therapy on cancer cells. This conclusion was obtained when they reduced the radiation dosage; the killing effect of cancer was not reduced, and it was even enhanced. RSV acts as a radiosensitizer to human cervical cancer cells, such as HeLa and SiHa, which makes the cancer cells more sensitive to treatment (58). With less radiation, RSV reduces the side effects on healthy cells. A research paper highlighted that the treatment with RSV reduced the level of ERK (59) and FOXO3a (60), which was obtained in western blot analysis. Another flow cytometry-based investigation observed that upon treatment with RSV, there was an elevation in mRNA and protein levels of BAX, along with increased mRNA expressions of p16, p21, and p27. In contrast, CDK4, E2F1, and p-pRb1 protein levels displayed a reduction (61).

Vaginal cancer

Only 1 to 2 percent of all female genital tract tumors and 10% of all vaginal malignant neoplasms are primary vaginal cancers, making them highly uncommon (62). Most lesions in the vagina will be those that have spread from cervical or vulvar cancer or other cancers to the vagina (e.g., breast, endometrium, trophoblast, ovary, lymphoma) (63). These malignancies historically affect older and postmenopausal women more frequently. Younger women who develop vaginal malignancy are at increased risk of developing cervical cancer due to the prevalence of high-risk HPV infections (64). There are numerous forms of vaginal cancer, but squamous cell carcinoma is the most prevalent. It begins in the vaginal tissue. Although uncommon, vaginal cancers are becoming more common in younger women due to the rise in enduring high-risk HPV infections, particularly in areas with a high HIV incidence (65).

There have not been many studies to determine which chemotherapy drug is most effective because vaginal cancer is less common (66). Therefore, there has not yet been a "best" or "standard" chemotherapy treatment regimen (67). Depending on what each woman requires, different treatments are chosen. Doctors typically prescribe the same medications that are used to treat ovarian cancer. Cisplatin (68), Carboplatin (69), Fluorouracil (5-FU) (70), Paclitaxel (Taxol®) (71), Docetaxel (Taxotere®) (72) and Irinotecan (Umemiya et al., 2022) are some of the medications that have been used.

In a research, it was found that 60% of patients had HPV16 cleared after receiving a polyherbal vaginal pessary named Praneem (combination of purified extracts of neem, saponins, and mentha-citrate oil) (73,74) intravaginally for 30 days while suffering from low-grade squamous intraepithelial lesions.

In 50% of the patients who had not been able to completely eradicate HPV after the initial therapy, a second round of administration was successful in inducing HPV clearance (75). It was hypothesized that Praneem's ability to neutralize infections thought to be a co-factor in HPV carcinogenesis and its microbicidal activity in the reproductive system might be the cause of its effects (76). Biomarkers like (glutathione S-transferase P1 (GSTP1), inducible nitric oxide synthetase (iNOS), the transcription factor nuclear factor kappa B (NF-κB), the oncogene c-MYC, vascular endothelial growth factor (VEGF) and the proliferation marker Ki-67) that are relevant for a particular patient's small-cell vaginal carcinoma were identified in anticancer studies (77).

Liposomal RSV has greater anti-oxidative and anti-inflammatory properties than RSV solution in a topical formulation based on nanomedicine that is intended to treat vaginal inflammation and infection (78). The combination of curcumin, epicatechin gallate, and RSV (4:1:12.5), known as TriCurin, was found to have synergistic effects (79). TriCurin was more effective at killing TC-1 and HeLa cells and reduced tumor development by 80–90% (80). In addition to simultaneously activating the tumor suppressor protein p53 in HeLa cells, it quickly reduced the expression of NF-kB and HPV18 E6. Additionally, it has been said to be a potential therapeutic agent for diseases linked to HPV (81).

Fallopian Tube Cancer

It is a rare type of cancer, but the incidence is still 1% of reproductive cancers (82). Fallopian tubes are tube-like structures connecting the uterus and ovaries, an essential part of reproduction (83). When the sperms come through the vagina into the uterus, it will move to the fallopian tubes, and the egg from the ovary enters the tubes through the other end; there is the formation of pregnancy in the tube, and the pregnancy that forms inside the tube comes back and implants into the uterus (84).

There are many reasons why people get fallopian tube cancer. One of the reasons can be genetic (85), i.e., if there is a family history of having fallopian tube cancer, then the person is more likely to have tube cancer. There are BRCA genes, potent markers of the fallopian tube, breast, and ovarian cancers (86). So, these BRCA (Breast cancer genes, BRCA1/2) genes can give an insight into the chance of having tube cancer. Cytogenetic studies show that the disease is associated with overexpression of p53, HER2 (Human Epidermal Growth Factor Receptor)/neu, and c-myc, which are proteins expressed in lymphoid organs, thereby stimulating the development and activation of B-cell malignancies (87). There is also some evidence that BRCA1/ BRCA2 mutations have a role in tumorigenesis (88).

Whenever there is a cancerous cell multiplication in the fallopian tube, the size of the tube increases (89), and symptoms like water retention in the tube, irregular bleeding, intermittent bleeding, and continuous discharge (reddish or pinkish) occur in the patient (90). The patient can have other symptoms like abdominal pain (91), a mass -like feeling in the abdomen (92), discomfort in the abdomen (93), pain during intercourse (94), etc. All these predisposition factors can cause a small origin of cancer inside the fallopian tube. The most common symptom is having a tubal infection (95).

Fallopian tube cancers can happen in any age group, but somebody between 50 and 60 is more vulnerable to fallopian tube cancer. It is mostly seen in women after menopause. In fallopian tube cancer, CA-125 is one of the markers that is usually seen raised. The Carbohydrate Antigen (CA-125) is sometimes increased even in endometriosis, ovarian cancers, or pregnant women (96). So, the elevation of CA-125 doesn't mean having fallopian tube cancer. It is one of the differential diagnoses of fallopian tube cancer. Cancer is always diagnosed with biopsies. The etiology of this cancer is unknown. However, some studies reported that it seems to be associated with chronic tubal inflammation, infertility, tuberculous salpingitis, and tubal endometriosis (97).

NF-kB, activated by TNF- α (tumor necrosis factor α), Interleukin-1β, etc., plays a vital role in developing disease in the inflammatory panel of endometriosis (98). This NF-kB can produce inflammation in the fallopian tubes (99). Researchers demonstrated that RSV effectively inhibits NF-kB activation triggered by various stimuli, including other pro-inflammatory cytokines (such as IL-1β) and LPS, H2O2, okadaic acid, and ceramide (100).

Conclusion

Female reproductive health includes a diverse array of physiological processes like regular menstrual cycles, fertility, pregnancy, contraception, and menopausal transition. But in the present scenario, due to the prevailing sedentary lifestyle, increased consumption of fast food, and the potential impact of genetic predisposition, female reproductive health faces many challenges for maintaining optimal reproductive well-being. Numerous chemical therapies and surgical procedures are available to treat this subset, which includes cancers like cervical, uterine, ovarian, vaginal, and vulvar. However, the problem is that these repercussions exert significant adverse effects and have a detrimental impact on overall reproductive health. By noticing these considerable side effects, pharmaceutical industries more often choose plant-derived molecules to develop alternative or additional therapies. To support this, we have a rich reservoir of plants containing beneficial bioactive compounds that hold promise for targeting specific molecular pathways associated with cancer progression. The convergence of evidence from preclinical studies, in vitro experiments, and clinical trials highlights the consistent and favorable outcomes observed in various gynecological cancer types. The unique ability of RSV to modulate critical signaling pathways, such as PI3K/AKT/mTOR and the tumor suppressor gene miR-34a, offers a promising avenue for targeted and personalized therapeutic approaches.

Shifting towards phytotherapy, we aspire to develop a more holistic and patient-centered approach to gynecological cancer treatment that combines the strengths of conventional methods with the potential of natural compounds to enhance efficacy and overall well-being.

Acknowledgements

This work was supported by the Department of Zoology, Avinashilingam Institute for Homescience and Higher Education for Women, Coimbatore.

Authors' contributions

The authors of this review article contributed equally to all aspects of the research process, including conceptualization, literature review, and manuscript preparation.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interest to declare.

Ethical issues: None

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