Review Article *Open Access*

Journal of Progressive Medicine and Health Care

ISSN: 3070-2305

DOI: *doi.org/10.63721/25JPMHC0112*

Role of Trans-Resveratrol in Cancer and Pregnancy: A Mini Review

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Citation: Chiga Rikkim K Marak, Shruti Sarma, Arabinda Chandra Nath (2025) Role of Trans-Resveratrol in Cancer and Pregnancy: A Mini Review. J. of Pro Med and Hea Care 1(3), 1-8. WMJ/JPMHC-112

Abstract

Trans-resveratrol chemically known as 3,5,4'-trihydroxy-trans-stilbenes, is a plant-derived polyphenol with pleiotropic biological activities including antioxidant, anti-inflammatory, cardioprotective, vasodilating and putative anticancer effects. The aim of the present study is to investigate the pharmacokinetics, preclinical and clinical evidence about the impact of trans-resveratrol in pregnancy, its role in cancer prevention and therapy, and its applications in women's health. All in vivo or in vitro studies reporting the effects of resveratrol interventions on women's fertility were included. We discuss mechanisms of action, major human trials, safety concerns particularly during pregnancy and provide practical recommendations and research priorities. The current literature, suggests that resveratrol may play an important role in female infertility. Specifically, it may impact the reproductive outcomes, owing to its potential therapeutic effects improving ovarian function. While resveratrol shows promising biological activity and target engagement in multiple tissues, human trials show modest benefits, variable bioavailability, and notable safety signals in some pregnancy models. High-quality randomized trials are needed to define efficacy, optimal dosing, formulation, and safety, especially in pregnant populations.

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Submitted: 18.11.2025 **Accepted:** 22.11.2025 **Published:** 02.12.2025

Keywords: Trans-Resveratrol, Pregnancy, Cancer, Women's Health, Polyphenols, Polycystic Ovary Syndrome, Bioavailability

Introduction

Rresveratrol (t-RES; 3,5,4′-trihydroxystilbene), a naturally occurring polyphenolic stilbene that is found abundantly in grapes, blueberries, raspberries, mulberries, peanuts, and red wine [1]. It has emerged as one of the most extensively studied natural compounds over the past few decades owing to its wide range of biological activities and potential applications in human health [2]. Originally it was identified as a phytoalexin produced by plants in response to ultraviolet radiation, stress and microbial attack [3]. Resveratrol is also called as "French paradox," due to its cardioprotecttive nature, which associated moderate red wine consumption with cardiovascular benefits [4]. Many preclinical and clinical evidence has elucidated its multifaceted bioactivities, including potent antioxidant, anti-inflammatory, cardioprotective, neuroprotective, anti-aging, and anticancer effects, mediated largely through pathways involving sirtuin-1 (SIRT1), AMP-activated protein kinase (AMPK), and nuclear factor-kappa B (NF-κB) [5]. Resveratrol is present in two isomeric form viz. cis resveratrol and trans resveratrol both of which may be glycosylated, however trans-resveratrol is biologically more stable and pharmacologically active, and has therefore been the primary focus of biomedical research. Its biological activities have been shown to depend on its structural determinants including the number and position of carboxyl groups, intramolecular hydrogen bonding, stereoisomery, and the presence of double bond. Trans-stilbene compounds which possess ortho-diphenoxyl or para-diphenoxyl functionalities having a 40 -hydroxyl group and double bond show high chemopreventive activity [6].

In recent years, interest in trans-resveratrol has expanded beyond general metabolic health issues into specific areas of women's health, particularly pregnancy, and reproductive disorders, cancer, where oxidative stress, chronic inflammation, hormonal dysregulation, and epigenetic modifications play pivotal roles [7]. Preclinical studies have demonstrated its ability to ameliorate pregnancy complications such as preeclampsia and gestational diabetes, though cautionary findings regarding fetal safety highlight the need for careful dose-timing considerations [8]. In oncology, resveratrol has shown promising therapeutic and chemopreventive potential against breast, ovarian, and cervical cancers by modulating cell cycle regulators, inducing apoptosis, and sensitizing tumors to conventional therapies [9,10]. Furthermore, in women's health beyond pregnancy and cancer, trans-resveratrol has been investigated for its beneficial effects in polycystic ovary syndrome (PCOS), fertility regulation, and management of menopausal symptoms, making it a versatile bioactive candidate at the intersection of reproductive medicine and chronic disease prevention [11,12]. However, despite these encouraging findings, clinical translation remains limited due to poor oral bioavailability, rapid metabolism, and heterogeneity in trial outcomes, underscoring the need for novel delivery systems and rigorously designed studies to define its safety and efficacy in female populations.

Resveratrol in Cancer

Cancer is one of the most destructive diseases worldwide. In the year 2000, cancer was suggested to be responsible for 12% of the nearly 56 million deaths worldwide and it was reported to further increase by 50% to 15 million in the year 2020, mainly due to steadily aging populations in both developed and developing countries [13]. Medical literature is full of different studies showing the role of polyphenolic compounds in cancer. Resveratrol was especially shown to have chemopreventive and chemotherapeutic effects on different cancer types. Jang et al. first demonstrated the chemopreventive effects of resveratrol in multi-stage carcinogenesis (e.g., initiation, promotion, and progression also angiogenesis and metastasis) [14]. Kundu et al have reported that resveratrol can block carcinogen activation and increase detoxification via inhibition of phase I and induction of phase II enzymes [15]. Resveratrol has been shown to suppress proliferation of a wide variety of human tumor cells in vitro which have led to numerous pre-clinical animal studies to evaluate the cancer chemopreventive and chemotherapeutic potential of resveratrol [16]. There is growing in vitro evidence demonstrating the inhibitory effects of resveratrol on liver cancer. Delmas et al showed that the proliferation of rat hepatoma and human hepatoblastoma HepG2 cells were negatively impacted by the addition of resveratrol to the culture medium and ethanol potentiated the effects of resveratrol in both cell lines [17]. These results were attributed to the ability of resveratrol to prevent or delay the cells from entering mitosis and increasing the number of cells arrested in the S and

G2/M phase. Another study has revealed the anti-proliferative effects of resveratrol in two human liver cancer cell lines, namely HepG2 and Hep3B. The results showed that resveratrol inhibited cell growth only in p53-positive HepG2 cells, which was a result of cellular apoptotic death via p53-dependent pathway [18]. It was also shown that resveratrol-treated cells were arrested in G1 phase and were associated with an increase in p21 and Bax expression. Michels et al. observed cytotoxic effect of resveratrol on rat hepatoma cells due to induction of apoptosis via caspase activation [19]. Resveratrol treatment of human glioblastoma cells was shown to induce a delay in cell-cycle progression during S phase associated with an increase in histone H2AX phosphorylation. Furthermore, it was able to inhibit the ability of recombinant human TOPO II alpha to decatenate kDNA, so that it could be considered a TOPO II poison.[20]. Several studies have demonstrated the remarkable anti-inflammatory potential of resveratrol, primarily attributed to its role as an aryl hydrocarbon receptor antagonist and an inducible COX-2 inhibitor. In an experimental model of carrageenan-induced hyperalgesia in rats, pretreatment with resveratrol did not prevent swelling or edema, yet it effectively reversed the heightened pain sensitivity associated with local tissue injury [21,22].

Resveratrol has been widely investigated for potential use in breast cancer. In MCF-7 breast cancer cells, resveratrol inhibited cell proliferation in both a dose- and time-dependent manner. Remarkably, even at a concentration of 100 μM, significant cytotoxic effects were observed within 24 hours, reducing cell viability to nearly 57.5% compared to untreated controls, with a calculated half-maximal inhibitory concentration (IC_{50}) of 51.18 μM. Beyond its cytotoxicity, resveratrol also induced apoptosis in MCF-7 cells, as evidenced by increased expression of apoptotic markers [23]. Supporting these findings, another study reported that resveratrol moderately decreased MCF-7 cell viability while markedly elevating the proportion of early apoptotic cells. Further mechanistic insights were provided by Kim et al., who demonstrated that resveratrol suppresses breast cancer cell invasion through the downregulation of YAP target genes [24]. This effect is mediated via the activation of Lats1, leading to YAP inactivation. In addition, resveratrol was shown to inactivate RhoA, which further enhances Lats1 activity and promotes YAP phosphorylation, thereby strengthening its anti-invasive effects.

Resveratrol exerts diverse effects on growth regulation, cell cycle arrest, and apoptosis induction in human prostate cancer cell lines such as PC-3 and C42B [25,26]. Compelling evidence suggests that its anti-prostate cancer activity is largely mediated through modulation of the androgen receptor (AR) and its downstream target genes [27-29]. In a study by Farhan et al, resveratrol was shown to suppress cell proliferation and trigger apoptosis-like cell death in PC-3 and C42B cells. Interestingly, these effects were markedly attenuated in the presence of copper chelators and reactive oxygen species (ROS) scavengers, indicating that intracellular copper interacts with resveratrol to generate ROS, which subsequently induce DNA damage and contribute to its cytotoxic action [30].

Resveratrol and Pregnancy

Resveratrol has emerged as a compound of considerable interest in pregnancy research due to its antioxidant, anti-inflammatory, and metabolic regulatory activities. In the context of pregnancy, some studies have raised concerns regarding potential adverse effects, such as alterations in fetal development or placental function. However, some research highlighted its beneficial role in supporting maternal and fetal health. Some studies have reported that Resveratrol can improve placental function, reduce oxidative stress, and enhance uteroplacental blood flow, thereby contributing to better fetal growth and development [31]. Paul et al reported that the polyphenol is used in mitigating pregnancy-related complications such as gestational diabetes, preeclampsia, and intrauterine growth restriction through its ability to modulate inflammatory pathways and improve insulin sensitivity [32]. In this review, the focus is placed on the health-promoting effects of resveratrol during pregnancy, particularly its positive implications for fetal development and maternal well-being, while acknowledging the need for further studies to establish safe and effective therapeutic use. In a comprehensive systematic review, Roberts et al. emphasized that across diverse animal models of pregnancy-related complications including preeclampsia, obesity, diabetes, and fetal growth restriction resveratrol supplementation exerted significant protective effects. It was shown to lower maternal

blood pressure, enhance insulin sensitivity, improve lipid metabolism, and alleviate placental oxidative stress and inflammation, collectively underscoring its potential as a therapeutic agent for improving maternal and fetal outcomes. However, despite these promising maternal benefits, the review underscores important concerns regarding fetal safety. When blood glucose is poorly controlled during gestational diabetes, it can lead to fetal hyperglycemia and macrosomia, increasing risks such as respiratory distress, shoulder dystocia, and long-term metabolic disorders in offspring. Resveratrol has shown promise in this context by improving insulin sensitivity, lowering triglyceride levels, and enhancing glucose and lipid profiles in various animal models of gestational diabetes and maternal obesity. These findings highlight its potential to reduce maternal insulin resistance and improve overall pregnancy outcomes [33,34]. Thus, while resveratrol demonstrates strong biological plausibility for managing pregnancy complications, current evidence remains insufficient to justify clinical use in pregnant women. Before translation to human trials, rigorous preclinical studies with standardized dosing, clear pharmacokinetic profiling, timing-specific analyses, and long-term offspring follow-up are essential to establish a robust safety and efficacy profile. Based on a comprehensive survey of the available literature and various clinical studies, we evaluated the effects of resveratrol on reproductive health and related conditions, which have been systematically compiled and presented in tabular form for clarity and comparison.

Table 1: Clinical Studies Evaluating the Effects of Resveratrol in Reproductive Health and Related Conditions.

Author & Year	Aim	Study Type / Population	Intervention	Outcome Measures	Findings
Ding, 2017 [35]	To evaluate oral nifedipine + resveratrol in preeclampsia	RCT, 400 women with preeclampsia	Nifedipine ± resveratrol	BP control time, recurrence of crisis, maternal/neonatal adverse effects	Resveratrol significantly reduced treatment time and drug requirement, while prolonging time to next hypertensive crisis.
Malvasi, 2017 [36]	Effect of trans-resveratrol during spontaneous pregnancy in overweight women	RCT, 110 women, 24–28 weeks, BMI 25–30	Resveratrol vs. placebo/DC+MI	BP, lipid profile, glucose	Improved lipid and glucose parameters at 30–60 days compared with placebo; superior to DC/MI group.
Mendes da Silva, 2017 [37]	To assess resveratrol for reducing endometriosis pain	RCT, 44 women (20–50 yrs) with laparoscopic endometriosis	Resveratrol vs. placebo	Pain (VAS scale)	Resveratrol not superior to placebo for pain management.
Ma, 2018 [38]	To investigate effects of resveratrol in women with a scarred uterus	Cohort, 78 patients (mean age 30.4 yrs)	Resveratrol (n=46) vs. placebo (n=32)	Uterus remodeling, fertility	Resveratrol promoted uterine remodeling, endometrial/muscle regeneration, vascularization, and increased pregnancy rate.
Bahramrezaie, 2019 [39]	Effect of resveratrol on angiogenesis in PCOS	RCT, 62 ICSI candidates with PCOS	Resveratrol vs. control	VEGF/HIF1 expression, oocyte/embryo quality, fertilization rate	Reduced VEGF/HIF1 expression; improved oocyte and embryo quality in resveratrol group.
Ochiai, 2019 [40]	Resveratrol's impact on IVF–embryo transfer	Cohort, 8686 embryo transfers	Dietary resveratrol	Pregnancy outcomes	Associated with decreased clinical pregnancy rate and higher miscarriage risk.
Gerli, 2021 [41]	Impact of resveratrol on ICSI outcomes	RCT, 101 infertile women (18–42 yrs)	Resveratrol vs. control	Follicle/oocyte number, fertilization, embryo/blastocyst rate, pregnancy outcomes	Resveratrol improved oocyte yield, fertilization rate, embryo quality, cryopreservation, and live birth rate.
Battaglia, 2022 [42]	Follicular fluid miRNome modification in poor ovarian reserve	Cohort, 12 women (35–42 yrs, AMH <1.2, AFC <5)	Resveratrol-based supplement (3 mo)	miRNome, oocyte quality	Improved fertilized oocyte quality; miR-125 expression anticorrelated with biochemical pregnancy.

Table 2: In Vitro Studies on the Effects of Resveratrol in Reproductive Biology.

Author & Year	Aim	Sample / Design	Intervention	Outcome Measures	Findings
Schube, 2010 [43]	To assess resveratrol protection against oxLDL damage in granulosa cells	Human granulosa cells from IVF patients	150 µg/mL ox-LDL ± 30 µM resveratrol, 36 h	Oxidative stress, cell vitality, autophagy, steroidogenesis	Resveratrol reduced oxidative stress, cell death, LOX-1/TLR4/CD36 expression; enhanced mitosis, protective autophagy, and steroid biosynthesis.
Novaković, 2015 [44]	In vitro effect of resveratrol on oxytocin-induced myometrial contractions	Myometrium samples, 42 women (third-trimester C-section)	Resveratrol (diluted ethanol solution)	Myometrium contraction, K^+ channel activity	Dose-dependent relaxation of contractions; low-dose effect via K^+ channels, high-dose via additional mechanisms.
Savchuk, 2016 [45]	To study resveratrol's effect on fetal adrenal steroidogenesis	Primary human fetal adrenocortical cells (GW 10–12)	ACTH (10 ng/mL) ± resveratrol (10 µM), 24 h	Steroid levels (DHEA, androstenedione, 11-deoxicortisol), cytochrome activity	Resveratrol suppressed steroid synthesis and inhibited cytochrome 17α-hydroxylase/17,20 lyase and 21-hydroxylase activity.

Conclusion

Trans-resveratrol retains substantial translational appeal given its multi-targeted biology,favorable safety at moderate doses, and evidence of tissue exposure in humans. However, enthusiasm must be tempered by limited clinical efficacy data, bioavailability challenges, and potential safety concerns in pregnancy. In summary, current evidence indicates that trans-resveratrol holds significant potential in supporting women's reproductive health due to its antioxidant, anti-inflammatory, and ovarian-protective properties. Findings from preclinical and limited clinical studies suggest that trans resveratrol may enhance ovarian function and improve certain fertility outcomes; however, its inconsistent bioavailability, variable efficacy across studies, and emerging safety concerns particularly during pregnancy underscore the need for caution. Although its chemopreventive and therapeutic roles in cancer and broader women's health remain promising, the absence of robust, well-controlled human trials limits definitive conclusions. Future research must prioritize high-quality randomized studies to establish clear therapeutic windows, optimal formulations, long-term safety profiles, and evidence-based clinical guidelines, especially for pregnant and fertility-seeking populations.

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