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In vivo and Invitro Studies on Chemo protective Efficacy of Resveratrol in Breast Cancer

Srisudha M[1]*, Urjaben Patel[2]

1 Department of Human Genetics, Sri Ramachandra University, Porur, Chennai

2 MSN, APRN, FNP-C, Mount Carmel College of Nursing, Columbus, Ohio

***Corresponding author:**
Srisudha M

machavaramsrisudha@gmail.com

Tel: +919963179596

Department of Human Genetics, Sri Ramachandra University, Porur, Chennai

Abstract

The review was aimed to evaluate the effects of Doxorubicin, Rapamycin, Tamoxifen, Pacilitaxel and herceptin and didox with chemo protective effect by resveratrol. The treatment with the antioxidant resveratrol in combination with the anti-cancer drugs, showed Resveratrol is one of the proven antioxidant which can be given with the anticancer drugs during chemotherapy to prevent damage to the normal cells. The beneficial effects when administered in different concentrations with anticancer drugs to breast cancer cells were well studied.

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Introduction

Breast Cancer

Breast cancer is the most commonly diagnosed cancer and it is the leading cause of cancer deaths in women all over the world. Epidemiologic data supports that diet and nutrition play a key role in carcinogenesis process, as reflected in the global differences in breast cancer incidence worldwide. High fat, meat-based and low fibre diets are associated to high breast cancer incidence, whereas the lowest incidence rates are observed in populations taking mainly plant-based diets. The high content of phytoestrogens in plants has been proposed as the underlying factor responsible for the low breast cancer incidence in populations but the mechanisms are poorly understood [1-4].

Resveratrol

Resveratrol (trans-3, 4', 5-trihydroxystilbene), a naturally-occurring polyphenolic compound, is highly enriched in a variety of food sources, such as grapes, peanuts, and red wine. Previous studies showed unique beneficial effects, such as lifespan prolongation, cardiovascular protection, and anti-inflammation action. Few studies have shown that resveratrol has a chemo-preventive effect against the development of cancers of the skin, breast, prostate, and lung cancers. Cancer chemo-preventive effect of resveratrol was shown to prevent cancer progression in a number of animal models. In addition to these studies, it has also been reported that resveratrol can inhibit the growth of human cancer cells in vitro when it was present alone at rather high concentrations (usually >50 μM) or when it was used in combination with the other anticancer drugs.

Paclitaxel

Paclitaxel, which is the most commonly-used chemotherapeutic agents and was shown to have efficacy in a number of human cancers types like ovarian, breast cancer etc. Mechanism of action of Paclitaxel disrupts the formation of normal spindles at the metaphase of cell division, resulting in G2/M or G1 cell cycle arrest and it will subsequently lead to apoptotic cell death. It was reported that resveratrol could sensitize a number of cancer cell lines to the anticancer actions of several other cancer drugs, including paclitaxel. It was suggested that since resveratrol and paclitaxel can modify different regulatory proteins involved in apoptosis and cell cycle regulation processes when used in combinations.

Doxorubicin

Doxorubicin (DOX), an anthracyclines antibiotic is among the most effective anticancer agents used to treat breast cancer. In previous studies, it was shown that doxorubicin exerts its cytotoxic effect by DNA base pairs on the double helix and by inhibiting the enzyme called topoisomerase II (TOPO-II), the enzyme was responsible for DNA helix conformation and stability. It was observed that chronic cardio-toxicity including development of a cardiomyopathy is a major limitation factor of the chemotherapeutic use of doxorubicin. To minimize DOX effective chemotherapeutic dose and thereby its side effects, a variety of approaches have been investigated in previous studies. One of them is the search for natural compounds using chemo-protective or anticancer properties that can be used in combination with doxorubicin to reduce the side effects.

Tamoxifen

Tamoxifen is a selective estrogen receptor (ER) modifier that competitively inhibits the interaction between estrogen and ER. Tamoxifen is predominantly administered as first-line treatment for both early and advanced ER-positive breast cancer patients. Previous preclinical studies have shown that the anticancer drug Tamoxifen treatment can induce breast cancer cell growth both arrest and death, which are consistent with the clinical efficacy of Tamoxifen, which can elicit a cessation of tumor growth and increase overall survival. Nonetheless, approximately 50% of breast cancer patients who initially respond well ultimately developed unresponsiveness and relapse in the clinical settings of continuous Tamoxifen exposure, thus highlighting the dire need to probe the underlying molecular mechanisms and to identify corresponding novel therapeutics to overcome acquired Tamoxifen resistance.

Rapamycin

Rapamycin (mTOR) is a serine/threonine kinase that belongs to the phosphatidylinositol 3-kinase-related kinase (PIKK) family and it was discovered as a target of a naturally occurring molecule called rapamycin. Studies have shown that mTOR regulates proliferation, cellular metabolism, protein and lipid synthesis and autophagy with the response to extracellular signals such as nutrient availability and growth factors. There are two different forms of mTOR which has two distinct complex features: mTOR Complex 1 (mTORC1) and Mtor Complex 2 (mTORC2). It is shown that the two complexes differ in their protein composition, downstream targets and sensitivity to the drug rapamycin. MTORC 1 shown acutely rapamycin-sensitive and mTORC2 was shown rapamycin- insensitive. The PI3K/mTORC1 signalling pathway was shown hyper-activated in breast cancer, and it is also important for tumour progression and resistance to endocrine therapy [5]. This pathway is the most frequently inappropriately activated pathway in breast cancer and several alterations of the genes within the PI3K/Akt/mTOR pathway are often found in ERα+ breast cancers. The Prominent way by which mTORC1 signalling pathway promotes endocrine resistance is by direct phosphorylation of ERα on Ser167 by the 40S Ribosomal S6 kinase 1 (S6K1), which is a major downstream effector of mTORC1, leading to ligand-independent activation of ERα [Yamnik et al., 2009, Yamnik and Holz, 2010]. ERα transcriptionally upregulates S6K1 expression, leading to its own activation in a feed-forward loop [6]. Since it is thought that hyper-activation of PI3K/Akt/mTOR signaling was responsible for de novo and acquired drug resistance, mTOR inhibitors have proved as a highly promising strategy for use in combination with endocrine therapy to prevent emergence or reverse drug resistance.

Herceptin

Trastuzumab, also called as Herceptin is a monoclonal antibody that interferes with the HER2/neuroeceptor. Its main use is to treat certain breast cancers. The HER receptors are proteins that are embedded in the cell membrane and communicate molecular signals from outside the cell (molecules called EGFs) to inside the cell, and turn genes on and off. The HER protein, Human Epidermal Growth Factor Receptor, binds to Human Epidermal Growth Factor, and stimulates cell proliferation. In some cancers, notably certain types of breast cancer, HER2 is over-expressed, and causes cancer cells to reproduce uncontrollably.

Body of the Paper

Effect of Resveratrol with Doxorubicin

Resveratrol treatment has shown to sensitize MCF-7 cells to Doxorubicin therapy. The potential chemo-sensitizing effect of resveratrol, were analyzed in increasing concentrations of the polyphenol in combination with doxorubicin cytotoxic therapy. While treatments with resveratrol (100 and 250 mM) alone significantly alters breast cancer cells viability (31 and 70%, respectively), a combination of resveratrol (50, 100, 150 and 250 mM) with doxorubicin (5 mM) resulted in a markedly increase in cytotoxicity. These data indicates that resveratrol efficiently sensitizes MCF-7 cells to doxorubicin therapy, at least in part by cell death induction [7].

Effect of Resveratrol with Tamoxifen

The Preliminary dose response experiments determined that the 50% inhibitory concentration of resveratrol on parental MCF-7 and resistant MCF-7/TR cells was approximately 146.3 µM, with less than 20% inhibition at concentrations of 50 µM [8]. This 50 µM dose is very close to the plasma levels achieved with daily dietary intake of resveratrol. Thus, all subsequent experiments will be conducted at this concentration (0~50 µM) to investigate the effects of resveratrol on Tamoxifen sensitivity in MCF-7/TR cells [9-10].

Previous studies have documented that activation of the PI3K/Akt and ERK1/2 signaling pathways plays a critical role in cancer cell survival and resistance, and therefore, targeting these pathways may serve as potential therapeutic strategies. Resveratrol at non-cytotoxic concentrations (less than 50 µM) regulates these pathways and synergizes with Tamoxifen in resistant breast cancer cells. MCF-7/TR cells were treated with 50 µM Tamoxifen without (0 µM) or with various doses of resveratrol (5, 10, 20, 40 and 50 µM, respectively). After the treatment of 48 h, Western blot analysis showed that p-Akt and p-ERK1/2 in MCF-7/TR cells were evident, though in the presence of Tamoxifen (50 µM). However, treatment of Tamoxifen in combination with resveratrol resulted in a remarkable inhibition of Akt and ERK1/2 phosphorylation, especially in the 40 µM and 50 µM resveratrol groups. Moreover, co-treatment with two agents also promoted cleavage of caspase-3 and polyADP-ribosepolymerase (PARP) in a dose-dependent manner, suggesting the induction of apoptosis [11].

Effect of Resveratrol with Rapamycin

The effect of rapamycin and resveratrol, alone or in combination on the activity of the mTORC1/Akt signalling pathway in MCF7 cells, human breast adenocarcinoma cell line, and MCF10a cells, immortalized non-transformed mammary epithelial cells [12, 13]. MCF7 cells have high levels of mTORC1 signalling which was evidenced by increased phosphorylation of S6K1, and its substrates S6 and eIF4B, relative to MCF10a cells, and low levels of PDCD4, a negative regulator of cap-dependent protein translation

initiation that is degraded by activated S6K1 signalling [Dorrello et al., 2006]. As expected, rapamycin blocked phosphorylation of S6K1 and its downstream targets. Resveratrol alone was not as efficient in blocking signalling downstream of S6K1, however, the combination of the two drugs completely inhibited the mTORC1 signalling pathway, strikingly reducing S6 and eIF4B phosphorylation, and increasing PDCD4 levels [14, 15]. A consequence of mTORC1 inhibition is reactivation of Akt signalling due to suppression of the mTORC1-mediated negative feedback loop to Akt, which over time re-activates mTORC1 signalling and is thought to contribute to drug resistance in patients. While treatment with rapamycin increased phosphorylation of Akt, the combination treatment of rapamycin and resveratrol was able to block activation of Akt and its downstream target PRAS40 to levels below those of untreated control. The combination of rapamycin and resveratrol is able to block up regulation of autophagy and induce apoptosis in breast cancer cells [16, 17].

Effect of Resveratrol with Herceptin and Didox

Herceptin with resveratrol and didox, quantitative gene expression analysis for some apoptosis key elements was assessed using real time PCR technique. In T47D cell line, the apoptotic gene, Bax expression was not significantly changed in single treatments compared to the untreated cells [18]. Similarly, no marked change in the Bax expression was observed in all combination treatments compared to single treatment with herceptin. Reciprocally, Bcl-2 anti-apoptotic gene was not significantly over expressed in single herceptin treatment compared to the untreated cells, while a significant decrease in the Bcl-2 expression was observed following herceptin/ didox combination compared to single herceptin treatment [19, 20]. However, Bcl-2 expression was not markedly decreased following herceptin/resveratrol combination compared to herceptin single treatment. The anti-apoptotic gene, Bcl-xl was not significantly over expressed with all single treatments, however, a marked decrease in the expression of Bcl-xl was observed after combinations, compared to single herceptin treatment. In MCF-7 cell line, Bax was markedly over expressed in all single treatments compared to untreated cells, and combination treatments compared to single treatment with herceptin. Bcl-2 expression was significantly decreased in all single treatments compared to untreated cells, and combination treatments compared to single treatment with herceptin. On the other hand, Bcl-xl expression was not significantly changed in the combination treatments compared to the single treatment with herceptin. However, Bcl-xl expression was apparently decreased in all single treatments compared to untreated cells [21].

Effect of Resveratrol with Pacilitaxel

Resveratrol strongly diminishes pacilitaxel's anticancer actions; the experiments which were done previously showed that whether resveratrol could sensitize MDA-MB-435s cells (a human breast cancer cell line) to the anticancer actions of Pacilitaxel in vitro. Resveratrol did not enhance, but rather attenuated, the anticancer efficacy of Pacilitaxel in a concentration-dependent manner in cultured MDA-MB-435s cells. While only 20% of the cancer cells survived after treatment with 20 nM paclitaxel alone for 48 h, co-treatment with resveratrol markedly abrogated paclitaxel-induced reduction in cell viability [22]. Following this observation, we then further determined whether the protective effect of resveratrol against paclitaxel-induced cell death was a general phenomenon for various types of cancer cells or a specific effect for certain types of cancer cells. Resveratrol also exerted a protective effect against paclitaxel-induced cell death in other two human breast cancer cell lines, MDAMB- 231 and SKBR-3. However, when they treated MCF-7 human breast cancer cells, HepG2 human hepatocellular carcinoma cells, DU-145 human prostate carcinoma cells, and MIAPaCa- 2 human pancreas carcinoma cells with paclitaxel with or without resveratrol at varying concentrations for 48 h, resveratrol exerted no protective effect against paclitaxel induced cell death. In addition, resveratrol did not exert a similar protective effect against the cell death induced by 5-fluorouracil or topside in MDA-MB-435s cells, but it slightly suppressed doxorubicin-induced cell death [23, 24].

Future Directions

Anticancer drugs may also damage normal cells during chemotherapy, so Resveratrol is one of the proven antioxidant which can be given with the anticancer drugs during chemotherapy to prevent damage to the normal cells.

Conclusion

Effects of Resveratrol with different anti-cancer drugs have been studied and concluded that resveratrol have beneficial effects when administered in different concentrations with anticancer drugs to breast cancer cells.

References

1 Proteomic Profiling Reveals That Resveratrol Inhibits HSP27 Expression and Sensitizes Breast Cancer Cells to Doxorubicin Therapy.

2 Resveratrol Attenuates the Anticancer Efficacy of Paclitaxel in Human Breast Cancer Cells In Vitro and In Vivo.

3 Abdel Moneim M Osman, Hadeel M Bayoumi1, Sameer E Al-Harthi1, Zoheir A Damanhouri1 Modulation of doxorubicin cytotoxicity by resveratrol in a human breast cancer cell line .

4 Resveratrol Sensitizes Tamoxifen in Antiestrogen-Resistant Breast Cancer Cells with Epithelial-Mesenchymal Transition Features.

5 The Combination of Rapamycin and Resveratrol Blocks Autophagy and Induces Apoptosis in Breast Cancer Cells.

6 mTOR signaling for biological control and cancer.

7 Resveratrol as an adjunct therapy in cyclophosphamide-treated MCF-7 cells and breast tumor explants.

8 Hormonal therapy for postmenopausal breast cancer: The science of sequencing .

9 Resveratrol enhances the treatment effects of tamoxifen.

10 Resveratrol sensitizes tamoxifen in antiestrogen-resistant breast cancer cells with epithelial-mesenchymal transition features

11 Foods to eat and avoid during tamoxifen treatment.

12 Resveratrol potentiates the anti-tumor effects of rapamycin in papillary thyroid cancer: PI3K/AKT/mTOR pathway involved.

13 Resveratrol and rapamycin: are they anti-aging drugs?

14 Resveratrol potentiates the anti-tumor effects of rapamycin in papillary thyroid cancer: PI3K/AKT/mTOR pathway involved.

15 Effects of Combining Rapamycin and Resveratrol on Apoptosis and Growth of TSC2-Deficient Xenograft Tumors.

16 Effects of metformin, rapamycin, and resveratrol on cellular metabolism of canine primary fibroblast cells isolated from large and small breeds as they age.

17 The combination of rapamycin and resveratrol blocks autophagy and induces apoptosis in breast cancer cells.

18 The chemomodulatory effects of resveratrol and didox on herceptin cytotoxicity in breast cancer cell lines.

19 The chemomodulatory effects of resveratrol and didox on herceptin cytotoxicity in breast cancer cell lines.

20 Drug interaction potential of resveratrol.

21 Didox and resveratrol sensitize colorectal cancer cells to doxorubicin via activating apoptosis and ameliorating P-glycoprotein activity.

22 Combined effects of resveratrol and paclitaxel on lung cancer cells.

23 Potentiation of paclitaxel effect by resveratrol in human breast cancer cells by counteracting the 17β-estradiol/estrogen receptor α/neuroglobin pathway.

24 Resveratrol enhances anticancer effects of paclitaxel in HepG2 human liver cancer cells.