Meta-Analysis of the Antioxidant and Antitumor Effects of Resveratrol in Animal Models of Breast Cancer: Integrative Review for Clinical Study Design

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Article

Meta-Analysis of the Antioxidant and Antitumor Effects of Resveratrol in Animal Models of Breast Cancer: Integrative Review for Clinical Study Design

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Abstract: Natural compounds are promising adjuvants in various treatments, with lowest rate of harmful effects to the organism, greater tolerance and convenience for patients, especially those undergoing longer treatments of chronic diseases. Breast cancer is the type of cancer that most affects women in the world, being the most frequent cause of cancer death between women. Several chemotherapeutic drugs already standardized for cancer treatment originate from components predominantly extracted from plants. The resveratrol, the main grapes polyphenol, has its antioxidant activity well established in the literature, highlighting its potential antitumor effect. The aim of this work was to synthesize, in a quantitative and qualitative means, data on the effect of resveratrol on breast tumorigenesis, based on in vivo and clinical studies. The results obtained in our meta-analysis in animal models showed that resveratrol has an antineoplastic effect in 85% of studies in female rodents with breast cancer, reaching its highest percentage of antitumor effect with a dosage of 25 mg/kg of resveratrol (reduction tumor rate of 97.8%). Associated with other antioxidants, resveratrol had a synergistic effect on tumor reduction (86.01%), as well as when associated with hormonal modulators (58.33%) and antineoplastic drugs (91%), in addition to having its action potentiated when used together with radiation therapy (89% tumor reduction). Data from clinical studies have shown a reduction in breast tumorigenesis through its already known mechanisms of action, such as selective apoptosis, inhibitors of cell proliferation and inflammatory mediators, in addition to hormonal regulation. Therefore, our statistical and qualitative results showed resveratrol as a potential agent in the prevention or adjuvant treatment of female breast cancer, generally amplifying the antitumor effects when combined with standard treatment.

Keywords: resveratrol; apoptosis; breast cancer; meta-analysis; oxidative stress

1. Introduction

The occurrence of cancer is of multifactorial origin and encompasses the combination of different genetic and environmental factors such as eating habits, weight, smoking, physical inactivity, alcohol, exposure to contaminating factors, random genetic mutations, among others. The synergism between these characteristics increases the risk of both cancer and other diseases, with primary prevention, with behavioral habits from the early stages of life, being the most effective way to significantly reduce harmful patterns to the body in general [11,24,25,61].

Biological capabilities acquired during the multiple steps of tumor development include mutation and genomic instability, self-sufficiency in growth factors associated with cell proliferation, resistance to inhibitory growth control mechanisms, and resistance to apoptosis (programmed cell death). Furthermore, tumor cells are characterized by unlimited potential for proliferation and replication, angiogenesis, cell migration with tissue invasion and metastasis, inflammation induced

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by neoplasms, cellular energetic dysregulation and persistence in the face of immunological reaction [22,25,36,39,43].

The characterization and analysis of the described tumor cells and tissues indicate that factors that directly interfere both in some of these properties and in the phases of tumor development, are potential candidates for the production of drugs and treatments for cancer [22,25,36,39].

Breast cancer is the type of cancer that most affects women in the world, and is also the most frequent cause of death from cancer in women (15.5% of cancer deaths in women in 2020, which corresponds to approximately 684,996 deaths, according to the International Agency for Research on Cancer (IARC) GLOBOCAN cancer statistics). In Brazil, breast cancer is the leading cause of cancer death in women, with a tendency for a higher incidence and mortality to progressively increase from the age of 40 [15,27].

Oxidative stress, an imbalance between the production and elimination of oxidants such as reactive oxygen species (ROS), is a metabolic condition well characterized by medicine and its pro-oxidant imbalance is correlated with the development of degenerative and/or chronic diseases, including cancer [5,20,22,56]. ROS are pro-tumorigenic and tumor cell proliferation is accompanied by high ROS production [23]. Elevated levels of ROS have been identified in several types of human tumors [51].

Resveratrol (RSV), the main grape polyphenol, is also found in red fruits and red wine. Studies in rats have pointed to RSV as an important reducer of the harmful consequences of a high-fat diet, correlating it with longevity and quality of life [8,12]. This compound has attracted attention for its diverse pharmacological properties. RSV is a potent anti-inflammatory and antioxidant capable of combating the accumulation of reactive oxidizing species and can act beneficially in metabolic conditions such as cancer, cardiovascular diseases and aging [44] and other studies point to RSV as an agent of antioxidant activity preventive [33,46,50].

Therefore, we carried out a meta-analysis to better understand the anti-proliferative and anti-tumorigenic effects of RSV in the phases of breast tumorigenesis.

2. Methods

2.1. Search Strategy

We performed a computerized search out in the PubMed, ClinicalTrials.gov, Cochrane and Google Scholar databases, using the keywords “resveratrol in vivo”, “resveratrol in vivo breast cancer”, “resveratrol in breast cancer”, “clinical studies with resveratrol”, “resveratrol and cancer”, “resveratrol and cell proliferation”, “resveratrol and anti-tumor action”, “antitumor mechanism of resveratrol” and “antineoplastic resveratrol”, in english, with no cut-off limit for date to date .The search strategies were previously discussed and reviewed by the thesis author and the supervisor responsible for the research.

2.2. Study Selection

The two reviewers (Trettel, G.D and Bertoncini, C.R.A) independently screened the titles, abstracts, and full texts that were sequentially selected as eligible. Disagreements were resolved by joint review and consensus. The selection criteria for publications for preclinical studies were given in vivo in female rats and mice, comparative experiments of tumor mass before and after treatment with resveratrol, described in the forms of trans-resveratrol, resveratrol and synthetic analogues of resveratrol: HS -1793 and piceatanol, in addition to resveratrol as an adjuvant in synergy with other compounds known in the literature for their antioxidant and/or anti-tumor action. Duplicate publications not consistent with the theme were screened and excluded using the Rayyan tool, altough, a manual search of references was performed from the beginning of the research.

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2.3. Data Synthesis

Data collected from preclinical studies were structured in spreadsheets and classified according to the substances used, which were distributed into four groups: RSV, RSV + hormone modulators, RSV + antioxidants and RSV + antineoplasics. The equation below was used to calculate the percentages of tumor that remained after the treatment proposed by the study (residual tumor).

$$\frac{Mean\ treated}{Mean\ control} \times 100 = \%\ of\ residual\ tumor$$

The results were displayed in a forest graph in the RStudio software (version 1.4.1717), with the help of the readxl (Wickham and Bryan, 2022) and ggplot2 (Wickham, 2016) libraries.

3. Results

Figure 1. Flowchart of pre-clinical studies selected for systematic review and meta-analysis based on literature research.

Table 1. Data from preclinical studies on the use of resveratrol applied in the treatment of rodent mammary cancer. Significant difference P<0.05.

Table 2. Data from preclinical studies on the use of resveratrol associated with antioxidant compounds in the treatment of rodent mammary cancer. NI: Not informed by the author. Significant difference P<0.05.

Table 3. Data from preclinical studies on the use of resveratrol associated with hormones in the treatment of rodent mammary cancer. NI: Not informed by the author. Significant difference P<0.05.

Table 4. Data from preclinical studies on the use of resveratrol associated with antineoplastic drugs in the treatment of mammary cancer in rodents. NI: Not informed by the author. Significant difference P<0.05.

Figure 2. Forest-plot of the percentage of residual mammary tumor in female rodents after treatment with resveratrol, combined or not with other substances.

Table 5. Characteristics of clinical studies with resveratrol or trans-resveratrol in patients diagnosed with breast cancer**. HD:** high-dose T-RSV / **LD:** low-dose T-RSV / **PE:** physical exercise / **HER2:** human epidermal growth factor receptor type 2 / **Metastasis:** MX - M0 / **NI:** Not informed by the author **/ PgR:** progesterone receptor / **ER:** estrogen receptor / **Nodal status:** N0-N1 / **TNM:** Size of solid tumors in cm (T1-T4) / **T-RSV:** Trans-resveratrol / **#:** median / ***:** tumor type.

Table 6. Data on the effects of resveratrol and trans-resveratrol in clinical studies conducted between 2005 and 2019. **CG:** Control group / **Ext:** Extract / **Glucuronide:** RSV metabolite / **IG:** Treated group (Ixor®)/ **OR**: Chance ratios / **PGE2:** Prostaglandin E2 / **PTV:** Margin of variations and errors associated with treatment / **RASSF1a:** Tumor suppressor gene / **SULT1A2:** Sulfotransferase / **Th17**: Pro-inflammatory helper T cells.

4. Discussion

According to the data presented in Tables 1 to 4, the results indicated that the use of RSV as the main treatment in rodents with breast cancer reduced tumors in at least 85% of the cases analyzed, with 34 studies showing positive and beneficial effects of the RSV as an antitumor agent, among the 40 studies that fit into our methodological analysis.

The data presented in Table 1 show that RSV delayed the appearance of breast tumors induced by nitroso-methyl-urea (NMU) and suppressed their incidence in the first days of treatment, an effect that suggests greater efficacy in early stages, when there are possibly hyperplastic lesions. and smaller pre-malignants in the mammary gland and with a more pronounced response on the ERs. RSV also inhibited the formation of atypical ductal hyperplasia induced by 7-12,dimethylbenzanthracene (DMBA) promoted by 17β-estradiol (E2), data that, in association with

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previous works reported in the literature, suggest RSV as a new selective modulator of the receptor. estrogen (SERM) [6,10,31,32,54,55,57].

It was observed that NFkB activation induced by tumor necrosis factor-type pro-inflammatory cytokines (TNFs) was suppressed in the majority of animals treated with RSV through the increase in recombinant NFkB inhibitory protein (IK-Bα). Therefore, the downregulation of NFkB suggests that RSV may attenuate the initial steps of tumor development including dysregulation of proliferation control and protection against apoptosis of healthy cells [3,9].

Analyzes of RSV and its analog piceatanol in Welchs Concord grape juice, in vivo, demonstrate significant inhibition of tumor multiplicity and mass in rat breasts, indicating possible inhibition of the promotion phase of tumorigenesis. There was a significant reduction in DNA synthesis of the adenocarcinoma cell line isolated from rat breast induced by DMBA and inhibition of tyrosine kinase signaling cascades [23,25,26,28,58,60].

RSV supplementation showed antitumor effects by delaying the development and metastatic capacity of tumors in HER-2/neu transgenic mice, an effect associated with downregulation of HER-2/neu expression and consequent apoptosis of mammary tumor cells [35,51].

The results obtained by Garvin (2006) [20] corroborate other studies that point to the chemotherapeutic potential of RSV. The data obtained indicate that the anti-tumor effects of RSV may be due to the synergism between the induction and significant increase in apoptosis in tumors treated with the antioxidant, in addition to the inhibition of angiogenesis through vascular endothelial growth factor (VEGF) at extracellular levels. It is well established that RSV is a potent sirtuin 1 (SIRT1) agonist, responsible for regulating transcriptional activation and apoptosis associated with the tumor suppressor gene p53 [16,63,64,67].

Another consolidated effect of RSV and shown in the results of our meta-analysis is its action as a potent competitive inhibitor of 5-LOX activity [10,44,45,53]. RSV is certainly capable of inhibiting the proliferation of cancer stem cells in vivo. Experiments demonstrated that RSV treatment suppressed the expression of fatty acid synthase (FAS) and strongly increased pro-apoptotic genes cell death-associated protein kinase 2 (DAPK2) and Bcl-2-interacting protein 3 (BNIP3) [44].

The high expression of metalloproteinase-9 (MMP-9), an enzyme that degrades components of the extracellular matrix, is strongly associated with the worsening of the invasive potential of breast cancer cells. Studies showed that RSV suppressed tumor progression by inhibiting the expression of MMP-9 and pro-inflammatory mediators such as TNF-α, interlekin 1 beta (IL-1β), cyclooxygenase 2 (COX-2), and induced nitric oxide synthase (iNOS) [30,54,59].

Data from Lee et al (2012) [37] showed this inhibition of MMP-9 mRNA in 4T1 cell lines by RSV, in addition to the fact that its oral administration inhibited cancerous cell growth and/or prevented its lung metastasis.

During pregnancy in rodents, exposure to aryl hydrocarbon receptor (AhRR) antagonists, such as RSV may exert protective effects against the development of breast tumors in the newborn. Pretreatment with RSV antagonizes the effects of the carcinogenesis inducer tetrachlorodibenzene (TCDD) on the expression of BRCA-1, cytochrome p450 family 1 (CYP1A1) and cyclin-dependent kinase 4 (CDK4) protein, in addition to increasing the occupancy of sites of BRCA-1 by AhRR [13,47].

HS-1793, a synthetic analogue of RSV, significantly inhibited breast tumor growth, proliferation and formation of tumor vessels, in a dose-dependent manner, with greater efficacy than RSV [30].

RSV stimulates autophagy in breast cancer stem cells (CSCs) by suppressing the Wnt/b-catenin pathway in vitro and in vivo [18].

Data from animals treated with RSV in association with antioxidants suggest modulatory effects of EGCG on the structure of the mammary gland, induction of selective apoptosis, reduction of tumor cell disorder, increase in the quantity and activity of CD4+ and CD8+ T cells in the spleen and tumor atmosphere of mice carriers of 4T1 breast tumor [7,66].

RSV associated with vitamin C triggers a significant increase in phagocytosis in addition to reducing the growth of cancer cells, possibly by stimulating the activity of NK cells, reducing the levels of C-reactive protein and pro-inflammatory cytokines, delaying the metastatic process and

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tumor growth, increased tumor encapsulation and cellular protection against lipid peroxidation [40,62]. Thymoquinone (active compound from Nigella sativa L) in combination therapy with RSV reduced tumor measurements by approximately 60%, inducing necrosis of the tumor area, apoptosis and inhibition of angiogenesis by decreasing VEGF expression, without liver or kidney toxicity [1].

Curcumin (Cur), an active compound from the Curcuma longa root, is studied for its antiproliferative, pro-apoptotic, antioxidant and inhibitory effects on tyrosine kinase activity. In vivo and in vitro studies point to curcumin as a possible inhibitor of tyrosine kinase (RTK) receptors, in addition to the ability to consistently reduce the diameter of tumor vessels in mice xenotransplanted with TNBC cells, when in synergy with calcitriol and RSV. Other analyzes suggest that one of the most relevant antitumorigenic effects of curcumin was the inhibition of neoangiogenesis and reduction of the expression of the β3 subunit integrin (Itgb3) [19].

Data using the flavonone naringenin, easily found in citrus fruits (mainly orange peel), showed blockade of (TGF)-β1 in breast cancer cells and suppression of lung metastasis by inhibition of PKC protein activation [70] in addition to regulation of mitochondrial apoptosis [48,49] and p53. Associated with RSV, selective action on alpha and beta estrogen receptors (ERα and ERβ) was noted [48,49,71].

The combination of polyphenols such as RSV and quercetin decreased cell proliferation and arrested the G2/M phase selectively in breast cancer cells, suggesting such compounds as potent inhibitors of cell proliferation [23,49,55]. In addition to quercetin, the antioxidant catechin, both when associated with RSV, demonstrated a reduction in the expression of the AKT1 pathway and can increase the levels of forkhead proteins (FOXO1), which has shown an important association with the anticancer activities of RSV [9,49,55].

The association of the hormonal modulator glucan with RSV showed a potent synergistic action on the antitumor action mechanisms of these compounds, as well as strong stimulation of immune reactions [62,65].

Calcitriol (Cal), an active metabolite of vitamin D, is considered a multi-target anticancer hormone and explored in pharmacological doses as an oncological drug. The data indicate a broad reduction in volume and microvascular density in animals treated with Cal+Curcumin and Cal+RSV, in addition to a reduction in the activation of the tumor endothelium due to a decrease in the tumor absorption of integrin-directed biosensors in vivo, suggesting a notable biological effect of inhibition. of tumor neoangiogenesis [19].

Melatonin acts as a SERM modulator, just like RSV, preventing the proliferation of cancer cells and negatively regulating estrogen-synthesizing enzymes such as aromatase [33]. Prolonged administration of RSV associated with melatonin significantly reduces the number of invasive carcinomas and tumor incidence. These data suggest that at pharmacological doses the antioxidant effects of melatonin, when associated with RSV, can suppress breast tumors by inhibiting growth factors [33,34].

The antineoplastic drug doxorubicin (Dox), despite stimulating the production of ROS, is widely used in the treatment of metastatic breast cancer and is an important clinical problem that causes treatment failure and abandonment [21].

Dox and RSV showed a synergistic effect in inhibiting the proliferation of breast tumor cells, significantly reducing tumor volume by approximately 50%. Given this result, the researchers indicated that RSV possibly exerts this effect in relation to drug transport through several pathways, such as mediating the expression of ATP-binding cassette (ABC), NF-Kβ, COX2, CYP3A4 and ROS transporters and by inhibition of MDR1 and MRP1. These data suggested that RSV may increase the efficacy of dox and be beneficial for overcoming drug resistance [32].

Decitabine (AZA) activates tumor suppression genes and cellular senescence followed by apoptosis. Studies with AZA and RSV showed that 82% of rats treated with RSV and AZA did not develop mammary tumors, while in animals treated with AZA alone, only 67% did not develop tumors [52]. RSV and AZA upregulated tumor suppressor miRNAs (miR21) in breast tumor tissue

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but not in physiological breast tissue, which may be an additional mechanism by which RSV suppresses tumor development and progression [52].

Researchers constantly aim to develop strategies to alleviate drug resistance during cancer treatment. RSV and PTX were co-encapsulated in a liposome in order to reverse PTX resistance of MCF-7/Adr tumors and amplify the efficacy of both components in vivo. These results demonstrate more potent synergistic tumor inhibition action and a direction that a nanocarrier may have potentially essential applications for the treatment of drug-resistant neoplasms [41].

Cisplatin has antitumor activity attributed to covalent binding to DNA, inducing structural changes, inhibiting cell growth, transcription and replication, resulting in apoptosis. In vitro and in vivo studies on MDA231 xenografts with RSV and cisplatin show increased tumor growth inhibition, in addition to reduced body weight loss and impaired renal function caused by cisplatin. These data indicate that RSV sensitizes the effects of cisplatin by inhibiting cell migration and invasion, reducing the expression of vimentin, fibronectin and increasing the expression of E-cadherin, indicating efficacy in reversing EMT [68,69].

The drug talazoparib is an inhibitor of PARP, a DNA repair protein that, when silenced, results in tumor cell death. Recent studies have explored a dual action of RSV, which consists of inhibition of phosphorylation of the AKT pathway and induction of autophagy and death of breast cancer cells, in vitro and in vivo, which is attributed to its effect on PARP mediated by talazoparib (BMN673) [4].

The combined oral administration of RSV + talazoparib significantly reduced the growth of mammary tumors in mice [4]. These data also indicate a therapeutic approach for other potential PARP inhibitors in oncological treatments.

In clinical studies, qualitative data have shown that resveratrol from grapes and wine is inversely related to breast cancer risk, although the presence of alcohol in the same model may affect collinearity (Pearson's correlation coefficient between total alcohol intake and resveratrol, $r = 0.85$). The positive data found for the response of resveratrol to breast tumorigenesis were directed to its already known mechanisms of action, such as apoptosis, cellular control, anti-inflammatory and hormonal effects [38].

In human breast cancer cells (MDAMB-231 and ZR-75-1), RSV is metabolized to resveratrol-3-O-sulfate by the expression of SULT1A1 and, in smaller quantities, by SULT1A2, SULT1A3, and SULT1E1. This metabolization is significantly greater in tumor tissue than in adjacent non-malignant samples from the same patients [42].

The experiments performed showed that in control tissue samples there was expression of steroid sulfatases (STS), responsible for increased tumor cell proliferation, while the same was not observed in samples treated with RSV [42]. Therefore, the use of RSV may be a targeted therapy in the inhibition of this enzyme, a promising strategy in the treatment of breast cancer and/or with combined therapies.

One of the adverse effects of radiotherapy is skin toxicity, especially in high doses, so research is seeking treatments to alleviate this discomfort. The radioprotective effect of resveratrol was evaluated together with the antioxidants lycopene, vitamin C and anthocyanins (Ixor® supplement) in reducing skin toxicity in patients with breast cancer who underwent chemotherapy with anthracyclines and taxanes. Data showed that RSV acts by inhibiting the production of IL-8, interrupting the phosphorylation of MAPK and NFkB, preventing damage caused by UVB radiation and thus improving the radiosensitivity of tumor cells. Other studies also associate the anticancer effects of RSV with the induction of apoptosis and activation of pro-apoptosis genes: FAS, p-53 and p21 [14].

Methylation of the tumor suppressor gene RASSF1a is triggered and stimulated as breast cancer progresses. The dose-dependent effects of resveratrol on DNA methylation in women at risk for breast cancer were evaluated in a double-blind, placebo-controlled study. Despite the limited sample size, the data show that chronic administration of the trans-resveratrol isomer increases its circulating levels, as well as its glucuronide metabolite. Note that this administration also prevented RASSF-1a

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methylation and PGE2 expression in the breast, revealing a novel mechanism for the chemopreventive effect of trans-resveratrol in women at high risk for breast cancer [72].

Methylxanthine alkaloids (MX), central nervous system stimulants, can increase the bioavailability of flavanols and studies seek to elucidate whether polyphenols and MX can act directly on malignant breast tissues (MT), since the in situ conjugation/deconjugation process depends on the tissue microenvironment. The chemopreventive effects of MX were related to the inhibition of the poly nuclear adenosine diphosphate ribose polymerase-1 enzyme and the downregulation of breast cancer resistance proteins (BCRP/ABCG2) [2].

Such evidence may be used to improve the efficacy of antineoplastic drugs that are substrates of breast cancer-resistant proteins (ATP-binding cassette, subfamily G, member 2: ABCG2) and also to sensitize tumor cells to respond to chemotherapeutic drugs, such as tamoxifen, impairing the growth of breast tumors. Normal tissues (NT) and MT from breast cancer patients were applied, investigating whether concentrations and molecular isoforms of metabolites exert antiproliferative, estrogenic and/or antiestrogenic effects in these tissues. Metabolite sulfation was higher in MT due to increased sulfation activity in breast tumor cells. Increased plasma concentration of unconjugated resveratrol was associated with abnormal absorption of RSV V.O by interaction between lipopolysaccharide (LPS) transporters and ATP-binding cassette (ABC) transmembrane proteins. Previous studies have shown that oral resveratrol sulfate in humans could form an intracellular reservoir of resveratrol [2].

A randomized and blinded clinical study conducted at the Hospital das Clínicas of the Federal University of Pernambuco (UFPE) investigated the relationship between home-based physical exercise and resveratrol in relation to the chronic inflammatory process in breast cancer survivors. The combination of exercise + RSV was effective in increasing cardiorespiratory fitness and modulating systemic levels of pro-inflammatory cytokines, reducing the cytokine IL-17A, while RSV alone only showed a modulatory action, reducing the cytokine IL-17A [17]. Therefore, we can consider that resveratrol has important effects for breast cancer therapy, which can be enhanced by several factors, such as the combined action of drugs, physical exercise and synergy with other antioxidants, in addition to a routine of healthy habits.

5. Conclusions

In in vivo studies, RSV delayed the appearance of carcinogen-induced breast tumors, suppressing tumor incidence in the initial days of treatment; It attenuated the activation of pro-inflammatory mediators and the expression of HER-2, inhibited the spectrum of cancer stem cells by stimulating autophagy, and promoted mitochondrial apoptosis so as to consistently reduce tumor ceramics, volume and neoangiogenesis; It showed a synergistic effect with antineoplastic drugs in preventing cellular hormones, positively regulating tumor suppressor miRNAs in breast tumor tissue, preventing tumor progression and resistance to these drugs; It amplified its own effectiveness and that of antineoplastic drugs when co-encapsulated in a liposome.

After a systematic review and meta-analysis, it was possible to significantly advance the understanding of the beneficial role of resveratrol in the tumor microenvironment of breast cancer, showing how resveratrol can act on the stages of the carcinogenesis process, in addition to mapping the possible mechanisms involved in this action, expanding therapeutic targets to be explored as a treatment for breast cancer. The data found in the literature consistently presented the preventive role of resveratrol in several diseases, especially those whose biogenesis is associated with oxidative stress, as well as its importance for maintaining and promoting health as a whole.

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