

Resveratrol and Colorectal Cancer: Focus *In vitro*, *In vivo* and Clinical Assays

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ARTICLE INFO

Received: 📅 January 23, 2021

Published: 📅 February 05, 2021

Citation: Paolo Ruggero Errante, Afonso Caricati Neto. Resveratrol and Colorectal Cancer: Focus *In vitro*, *In vivo* and Clinical Assays. Biomed J Sci & Tech Res 33(4)-2021. BJSTR. MS.ID.005439.

Keywords: Resveratrol; Natural Compound; Cancer; Colorectal Cancer; Cancer Prevention

ABSTRACT

Resveratrol is a natural non-flavonoid polyphenol present in different plants such as grapes, peanuts, soybeans and berries, which has beneficial effects on humans due to its anti-inflammatory, antioxidant, neuroprotective, cardioprotective and cancer prevention action. Since the effects of resveratrol *in vitro* on different tumors are significant, its application in the prevention of colorectal cancer can have a positive impact, since resveratrol can be consumed by eating natural foods. However, its effects in experimental models using chemical carcinogens and in clinical trials with humans in the prevention of colorectal cancer have been shown to be inconsistent, largely due to its low aqueous solubility and bioavailability. To overcome these problems, new formulations containing resveratrol have been used to promote increased solubility, bioavailability and therapeutic effect in cancer prevention.

Abbreviations: NF-kB: Nuclear Factor kappa B; VEGF: Vascular Endothelial Growth Factor; EGFR: Epidermal Growth Factor Receptor; FGF-2: Fibroblast Growth Factor 2; TGF- β : Transforming Growth Factor Beta; EMT: Epithelial Mesenchymal Transition; F344: Fisher 344; IGF 1: Insuline-Like Growth Factor I; IGFBP 3: Insulin-Like Growth Factor-Binding Protein-3

Mini Review

Resveratrol (3,40,5-trihydroxy-trans-stilbene) is a natural stilbene and non-flavonoid polyphenol present in more of 70 plants species, including peanuts (*Arachis hypogaea*), Japanese knotweed (*Fallopia japonica*), grape vine (*Vitis vinifera*) and foods such as wine, soy, Itadori tea, and red fruits. Resveratrol is a natural compound whose use has been described in the treatment and prevention of different diseases such as inflammatory, cardiovascular, neurological disease and cancer [1]. Resveratrol has *in vitro* cytotoxic effects against lymphoid and myeloid tumors, breast, skin, cervix, ovary, stomach, prostate, liver, pancreas, thyroid and colon tumors [2]. Its antitumor effects have been associated with different mechanisms, such as interruption of cell cycle and induced of apoptosis; inhibition of nitric oxide synthase expression; antioxidant effect with inhibition of lipid peroxidation and DNA damage; inhibition of the cyclooxygenase pathway of arachidonic acid metabolism; and procarcinogen bioactivation and carcinogen detoxification [3].

Resveratrol alters the activity of cyclin-dependent kinases and the cell cycle in the G0/G1 phase, and activation of the p53-dependent pathway, limiting the tumor growth [4,5]; and inhibits anti-apoptotic proteins of Bcl-2 family and activates pro-apoptotic proteins like Bad, Bak, Bax, PUMA, Noxa and Bim [6]. Resveratrol promotes inhibition of signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa B (NF-kB), nuclear transcription factors activated by acetylation and/or phosphorylation that's increased proliferative, invasive, angiogenic and metastatic activity [7]; have an inhibitory role on the expression of metalloproteinase-2 and metalloproteinase-9 (MMP-2 and MMP-9) and angiogenic molecules such as vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR) and fibroblast growth factor 2 (FGF-2) [8]; and suppresses signaling associated with transforming growth factor beta (TGF- β)-mediated epithelial mesenchymal transition (EMT) [9].

Colorectal Cancer

Approximately 90 to 95% of cancer cases described in humans are related to lifestyle, diet, pollution and obesity [10], where colorectal cancer corresponds to the third most frequent cancer in men, behind prostate and lung cancer. Colorectal cancer has an important relationship with lifestyle and diet rich in red meat and processed meat, low content of non-absorbable vegetable fibers, high content of refined carbohydrates, alcoholism and smoking [11]. Colorectal cancer has a peak incidence between 60 and 70 years of age, with worldwide distribution and greater incidence in the United States, Canada, Australia, New Zealand, Denmark and Sweden [12,13]. Because determinates plants (for example grape) and their derivatives have been used as complementary therapy in the treatment and prevention of several types of cancer, there is great potential in the use of plants containing resveratrol in the prevention of colorectal cancer.

The antitumor effect of resveratrol has been described *in vitro* in different colorectal cancer cell lines, such as HT-29 [14], LoVo [15], oxaliplatin-resistant colorectal cancer cells (HCT116/L-OHP) [16], human colorectal cancer stem cells [17], parental CRC cell lines (HCT116, SW480) and their isogenic 5-FU-chemoresistant clones (HCT116R, SW480R) [18] and cisplatin-resistant colorectal cancer cells HCT-116 [19]. In the process of colorectal carcinogenesis, there are two distinct pathways, the APC/ β -catenin pathway (adenoma-carcinoma sequence) and the mismatch repair pathway (microsatellite instability). In the first pathway, localized epithelial proliferation occurs and the formation of adenomas that become dysplastic and later turn into cancer. In the second pathway, genetic lesions occur in the DNA genes of mismatched repair (*MSH2*, *MSH6*, *MLH1*, *PMS1* and *PMS2*) causing hereditary nonpolyposis colorectal carcinoma [20,21]. To study the role of resveratrol in different mechanisms of colorectal carcinogenesis, Fisher 344 (F344) rats previously treated with resveratrol demonstrated a minor number of aberrant cryptic foci in colon mucosa after chemical carcinogenesis, with increase in the expression of Bax protein [22].

Using Wistar rats was observed the influence of resveratrol in the inhibition on cyclooxygenase-2 synthesis, important to cellular proliferation, inhibition of apoptosis and angiogenesis in colorectal genesis. The preventive use of resveratrol demonstrated a low expression of aberrant crypt foci, lower activity of cyclooxygenase-2 and increased expression of cleaved caspase-3 [23,24]. The diminish of aberrant crypt foci and depletion of mucin foci (a risk factor to development of colon carcinoma) was observed in Sprague-Dawley rats treated with resveratrol [25]. The prophylactic use of resveratrol in C57BL/6]-*Ap^{c^{min}/C}* mice (heterozygotes mice susceptible to spontaneous intestinal adenoma formation) demonstrated a reduction in the expression of D1 and D2 cyclins and dysplastic cells in intestinal mucosa [26] or prostaglandin E_2 levels in intestinal cells [27]. Epidemiological studies in humans demonstrated that consumption of grape was associated with

lower risk development of different kinds of cancer [28], including breast [29] and head and neck carcinoma [30].

In patients with colorectal cancer, the oral use of resveratrol was demonstrated a lower diminish on proliferative cancer cell activity [31]; moderate decrease in the Wnt/ β -catenin pathway in the intestinal crypt floor, critical pathway to maintenance of stem cells, and involvement in development of colorectal cancer [32]; relative increase of apoptosis on metastatic cells [33]; and reduction of plasma levels of insulin-like growth factor I (IGF1) and binding to insulin-like growth factor-binding protein-3 (IGFBP3), that regulate cancer progression and metastasis [34]. These limited and unsatisfactory results, in addition to the publication of a study that did not describe any beneficial effect of resveratrol on mortality associated with cancer [35], raised doubts about its real benefits in the face of cancer. These results may be associated with different types of study, tumor models and dose of resveratrol. Resveratrol is an extremely photosensitive compound with low chemical stability, low aqueous solubility and bioavailability, leading to a plasma half-life of 8 to 14 minutes, where the primary molecule is metabolized and converted into other secondary compounds with a half-life of 9.2 hours, such as sulfate conjugate, leading to a low therapeutic potency [36].

New Formulations of Resveratrol

Because the low therapeutic power, new formulations of resveratrol were produced with objective to obtained greater bioavailability, aqueous solubility, pharmacokinetic profile, antioxidant activity and antitumor activity [37], such in the production solid lipid nanoparticles [38], mitochondrial targeting resveratrol liposomes [39], resveratrol conjugated gold nanoparticles [40], resveratrol with methylated- β -cyclodextrin [41], colloidal mesoporous silica nanoparticles [42], resveratrol loaded into PEGylated liposomes (RES-L) with the liposome surface modified with transferrin moieties (Tf-RES-L) [43] and folate-conjugate human serum albumin-encapsulated resveratrol nanoparticles (FA-HSA-RESNPs) [44].

Discussion

Resveratrol has significant antitumor activity *in vitro* due to its ability to promote decreased prostaglandin E_2 synthesis; diminish of oxidative stress; bioactivation of procarcinogens and detoxification of carcinogens; and control of proliferation, invasion, angiogenesis and tumor metastasis. However, the results obtained through the use of experimental models induced by chemical carcinogens and the clinical trials in humans used in the prevention of colorectal cancer are limited and low significant in function of different factors, including low chemical stability, solubility and bioavailability of resveratrol. For increased bioavailability and modulation of resveratrol metabolism, new formulations and bioavailable analogs have been produced in search of new therapeutic agents for cancer prevention.

Conclusion

Optimizing the chemical stability and solubility of resveratrol can make it have great potential in preventing colorectal cancer.

Conflict of Interest

The authors declare that there is no conflict of interest.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2021.33.005439

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