# Resveratrol against Oral Squamous Cell Carcinoma

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Contributor: Giuseppe Angellotti , Giulia Di Prima , Elena Belfiore , Giuseppina Campisi , Viviana De Caro

Oral squamous cell carcinoma (OSCC) is one of the most prevailing and aggressive head and neck cancers, featuring high morbidity and mortality. The available conventional treatments suffer from several adverse effects and are often inefficient in terms of their survival rates. Thus, seeking novel therapeutic agents and adjuvants is of the utmost importance for modern society. Natural polyphenolic compounds have recently emerged as promising chemopreventive and anticancer agents. Specifically, the natural compound resveratrol (RSV) has recently gained momentum for this purpose. RSV is useful for treating OSCC due to its antiproliferative, antimetastatic, and proapoptotic effects. Additionally, RSV acts against tumor cells while synergically cooperating with chemotherapeutics, overcoming drug resistance phenomena.

resveratrol polydatin oral squamous cell carcinoma polyphenols anticancer

## 1. Introduction

Oral cancers represent the most common head and neck cancers, and about 90% of their cases are histologically defined as squamous cell carcinomas. The onset of this kind of tumor is multifactorial, starting from changes in the normal mucosa and evolving into cancer lesions and then metastasis [1]. Among the risk factors, the abuse of alcohol and tobacco consumption are considered the main leading causes since they are proinflammatory, and it is well-known that the development of oral cancer is closely related to several inflammation pathways [2]. Despite the available therapeutic strategies (e.g., chemotherapy, radiotherapy, and surgery) having been greatly improved over the past few decades, the actual main shortcomings concern the improvement in patients' survival rates, since they are still below 50% in clinical cases [3]. For this reason, the identification of novel therapeutic agents as well as the development of new therapeutic approaches, aimed at both treatment and chemoprevention, are mandatory. In recent years, the scientific community has extensively focused its attention on the effectiveness of several natural plant-derived compounds that have demonstrated interesting chemopreventive and therapeutic properties against pancreatic and hepatic cancers (e.g., curcuminoids), tumors affecting the gastrointestinal tract (e.g., catechins), breast and prostatic cancers (e.g., indole compounds), melanoma (e.g., apigenin and β-carotene), and oral cancers [4][5][6]. Specifically, several naturally occurring compounds have been shown to possess promising efficacy against oral cancer cells by interfering with the cell cycle, inducing early apoptosis and affecting invasion into other tissues and organs, thus interfering with the metastasis process [7]. Furthermore, these natural actives were generally characterized by low costs, the absence of systemic toxicity, fewer side effects when compared to standard therapies, and a certain capability of enhancing conventional anticancer drugs' effects. The latter aspect

makes these phytocompounds excellent candidates for the treatment of aggressive tumors, such as oral cancers [8]. Among the various investigated natural biomolecules, polyphenols have recently gained considerable interest due to their wide-spectrum properties being potentially useful in the treatment of cancers (e.g., antitumor, antioxidant, antiproliferative, anti-inflammatory, and immunomodulatory) [9]. However, their unfavorable physicochemical properties (e.g., lipophilicity leading to low water solubility) and susceptibility to oxidation and chemical degradation due to pH, light exposure, and high temperature compromise their bioavailability, administrability, and handling, thus limiting their clinical use [10]. Among polyphenols, resveratrol (RSV) has recently emerged as an effective molecule against oral squamous cell carcinoma (OSCC). It should be highlighted that the literature fully reports on the use of RSV as an anticancer agent against various cancer types [11], while its specific employment in the treatment of OSCC is still a little-traveled road. Indeed, although in vitro studies corroborate the potentiality of RSV against OSCC, few in vivo studies report on the treatment of OSCC with RSV using different routes of administration and vehicles.

## 2. Oral Squamous Cell Carcinoma (OSCC)

OSCC is a neoplasm that originates from oral keratinocytes mutating in malignant cells, and it is one of the most common oral cancers in terms of morbidity and mortality worldwide [12][13]. Various sites of the oral cavity can be affected by this tumor, such as the lips, the tongue, and the floor of the mouth [14]. The most common risk factors leading to OSCC development seem to be related to the abuse of alcohol and cigarette consumption. In particular, the chemical substances produced when smoking tobacco (benzopyrenes and nitrosamines) diminish the immune responsiveness of the oral environment as well as compromise the DNA of cells, promoting carcinogenesis [15]. Consequently, at the beginning of the carcinogenesis process, some lesions appear in the epithelium. Lesions could be histologically classified in terms of observed changes in the affected tissue, such as keratinocyte aspect modifications or hyperplasia. These alterations characterize the stage of cancer before the metastasis process [16]. Unfortunately, OSCC is mainly diagnosed at a very late stage [17] thus badly compromising the probability of survival and reducing patients' quality of life. Consequently, the success of OSCC treatment depends on an appropriate and quick intervention at the first stage of the tumor [18]. The conventional therapeutic approaches are based on surgery, radiotherapy, systemic chemotherapy, or combinations thereof [19]; however, these strategies are often aggressive, thus negatively affecting patients' quality of life, while likewise being often unsatisfactory in terms of survival rate. Considering the high incidence of OSCC, it is still necessary to identify novel bioactive compounds as well as to design new drug delivery systems aimed at increasing the efficacy of conventional treatments, minimizing their adverse effects and thus allowing their drawbacks to be overcome. A winning strategy with which to reduce the chemo- and radiotherapy-related side effects, whilst also improving and empowering their efficacy, could consist of the administration of natural molecules as chemopreventive and adjuvant agents. Cancer chemoprevention is based on the use of nutraceuticals or phytochemicals to reverse carcinogenesis before the metastasis phase occurs. This can be achieved thanks to their ability to block key events of tumor initiation and/or inhibit the ability of cancer cells to migrate to other tissues, thus reversing the premalignant stage.

Chemoprevention is a promising strategy, since it has been demonstrated that adequate treatment during the early stage of cancer could positively affect the carcinogenesis pathways [20][21]. Numerous chemicals are used as chemopreventive agents, such as antiestrogens, antiandrogens, anti-inflammatories, and vitamins. Among them, phytochemicals have been demonstrated to be efficacious and characterized by low side effects and costs [20][22]. In particular, polyphenols have recently been under the spotlight due to their wide-spectrum therapeutic properties, among which the chemopreventive and anticancer activities should be pointed out. Indeed, recent findings evidenced polyphenols as chemopreventive agents and effective adjuvants with which to treat oral cancerous or precancerous lesions, in order to suppress or reverse tumor progression [23].

## 3. Resveratrol (RSV) and Polydatin (PD)

RSV is a polyphenol-based compound belonging to the phytoalexin group. It is widely found in red grapes, berries, and peanuts, and it is naturally synthesized by plants in response to external stimuli, such as microbiological infections [24]. Chemically, it exists in two isomeric forms (*cis* and *trans*, **Figure 1**), but only *trans*-RSV is biologically active. The isomerization to the *cis* form is the result of various instability phenomena (e.g., UV irradiation; exposure to alkaline pH) which might occur, for example, during grape juice fermentation.

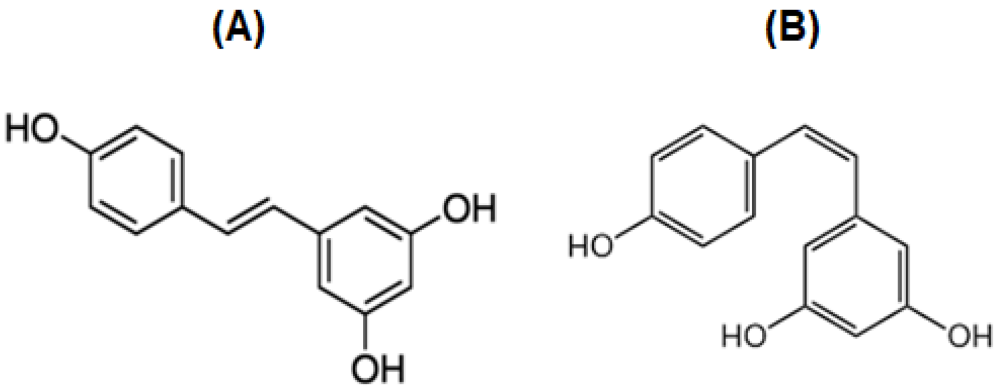


**Figure 1.** Chemical structure of *trans* (**A**) and *cis* (**B**) RSV.

Furthermore, RSV also exists as dimers, trimers, and glucosides. In this case, the most representative derivative is PD (**Figure 2**).

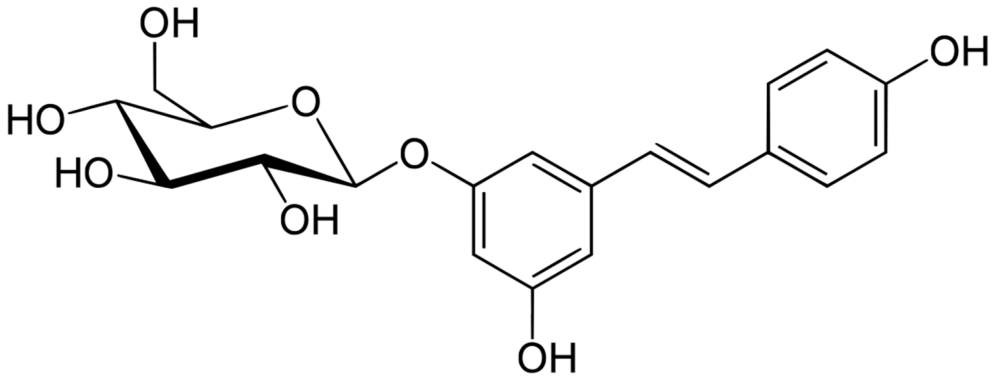

**Figure 2.** Chemical structure of PD.

The presence of β-d-glucosyl residue at position 3 confers favorable physiochemical characteristics (e.g., enhanced water solubility) while preserving and maintaining RSV's beneficial properties [25]. Among the various polyphenols in nature, RSV has recently been the most studied due to its antioxidant [26], anti-inflammatory [27], antiaging [28], cardioprotective [29], and bone-regenerative [30] properties. For these reasons, it is widely used as an active ingredient or adjuvant in cosmetic and pharmaceutical products [31]. In recent years, the scientific community has focused on the antitumor, antiproliferative, and chemopreventive effects of RSV that allow its application in the treatment of various types of cancers. Although the real process of RSV-mediated chemoprevention has not been fully and clearly understood yet, several mechanisms have been proposed to describe its antitumor activity. Briefly, it acts by inducing cancer cell apoptosis through the activation of multiple pathways, and in particular by modulating the activity of the mitogen-activated protein kinase (MAPK) and p53 protein pathways [32]. Furthermore, RSV has been shown to reduce the aptitude of cancer to metastasis in two ways: i) the inhibition of the gene expression of extracellular matrix metalloproteinases (e.g., MMP-2 and MMP-9) involved in tumor invasiveness; ii) the suppression of vascular endothelial grow factor (VEGF) expression, leading to the reduced formation of new tumor-specific blood vessels [33]. Therefore, it is evident that RSV could be a key molecule in the treatment of neck and head cancers, such as OSCC.

## 4. Innovative RSV-Loaded Formulations to Treat OSCC

Despite several papers confirming RSV and PD as anticancer and chemopreventive agents against OSCC, only one article has been published in recent years reporting the development and in vitro/in vivo evaluation of RSV-loaded drug delivery systems.

Zheng et al. recently (2019) proposed RSV-loaded liposomes for the treatment of head and neck squamous cell carcinomas. Liposomes were also formulated by adding a specific targeting dodecapeptide (named GE11) which is able to bind to EGFR, a receptor commonly overexpressed in head and neck squamous cancer cells. Liposome characterization revealed the homogeneity and nanometric sizes of vesicles, high RSV encapsulation efficiency, and sustained drug release behavior. The effectiveness of the proposed formulations (with or without the GE11 peptide) was assessed in vitro by a cytotoxicity assay against the SCC HN cancer cell line (SCC-VII). Cells were treated with free RSV or RSV-loaded liposomes (at an RSV concentration of 50 μg/mL) for 24 h and compared to untreated control cells. As a result, the RSV-loaded liposomes were shown to be more cytotoxic than free RSV, and the GE11-linked liposomes in particular displayed a stronger effect. Based on these promising in vitro results, the researchers further performed in vivo studies on SCC-xenografted nude mice that were divided into four groups: subjected to no treatment (control group; group I), systemic treatment with RSV (10 mg/kg three times every three days; group II), or systemic treatment with RSV-loaded liposomes with or without the GE11 peptide (doses corresponding to 10 mg/kg three times every three days; group III and group IV, respectively). While the control group was characterized by uncontrolled tumor growth, the group treated with free RSV depicted a limited reduction in tumor growth. In contrast, the treatment with RSV-loaded liposomes produced significant antitumor effects and, in particular, liposomes containing the GE11 peptide were the most effective ones, causing a two-fold

decrease in terms of tumor volume compared with the free RSV group and a three-fold decrease compared to the control group. This effect could be ascribable to the strong affinity of the GE11 peptide toward the EGFR receptor overexpressed in head and neck squamous cell tumors [34]. These results are greatly relevant and confirm the usefulness of innovative drug delivery systems loaded with natural compounds, such as RSV, in establishing advanced therapeutic approaches with which to efficiently treat OSCC.

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