

## Impact of Grape Seed Extract on the Oral Cancer: A Systematic Review

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### Abstract

**Introduction:** The oral cancer includes various kinds of malignant neoplasms developed in the mouth. The present study aims at applying the grape seed extract in dentistry (systematic review study).

**Materials and methods:** In this systematic review study, the articles of databases of Google Scholar, PubMed and SCOPUS were searched within 2000-2020. All information was classified in a table.

**Results:** In searching the mentioned databases for conducted preclinical systematic review study and concerning the intended time interval, 101 articles were found connected to the searched words through the abstracts. Once the repetitive titles and articles were deleted, 101 articles were selected, and then reduced to 22 by the assessment team. The full texts of these 22 articles were reviewed. For final selection, out of the articles, 10 ones had the inclusion criteria which contained the study objectives.

**Conclusion:** The grape seed extract contains active compounds such as anthocyanin, proanthocyanidins and procyanidins leading to the induction of apoptosis in the malignant cells. The experimental and animal studies

animal studies confirm the impact of grape seed extract on treatment of oral cancer cells. Therefore, it is necessary to conduct the clinical trial studies in the field of use of the grape seed extract as the therapeutic supplement in treating the oral cancer.

### Keywords

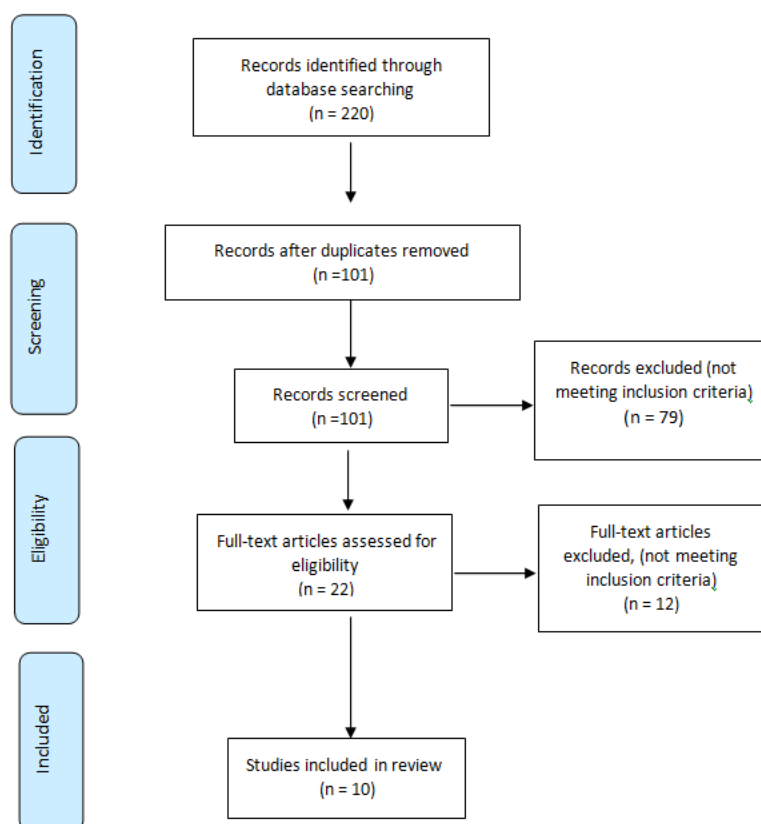
Oral cancer; Grape seed extract; Oral squamous cell carcinoma

## Introduction

After the cardiovascular diseases, cancer is known as the most common cause for death among the societies. Cancer depends on factors such as age, gender and genetic background [1]. Oral cancer accounts for less than 3% of all cancer, but it is the 11th common cancer around the world [2]. The oral cancer includes various types of malignant neoplasms developing inside the mouth [1, 3]. These cancers include the tumors of lip, tongue, gum, mouth floor, hard and soft palates, tonsils, salivary glands, oropharynx, nasopharynx and hypopharynx [1-4]. Over 90% of oral cancer cases are of type Squamous Cell Carcinoma and about 9% of cancers include the carcinomas of salivary glands, sarcoma and lymphomas [1].

The mandibular and oral cavity cancer is basically treated by surgery and radiotherapy [5]. During the recent year, regarding the low side effects and low costs as well as the promising impacts, use of the natural compounds to cope with the cancer has been taken into account. Nowadays, numerous plant compounds with different biological impacts are separated and entered the novel pharmaceutical science [6,7]. Grape seed extract (GSE) is such compound. The grape seed extract has a wide range of medical and pharmaceutical effects such as anti-oxidative, anti-inflammatory and antimicrobial activities [8]. Using GSE locally speeds up and facilitates the skin lesions [9]. Due to having antioxidants, GSE acts as a factor to protect from the free radicals [10]. Grape contains active compounds such as flavonoids, polyphenols, anthocyanin, proanthocyanidins and procyanidins [11]. In biological terms, these active compounds have cellular toxicity, anticancer and antimicrobial effects by the intervention made in different biological pathways.

Tong et al. [12] showed that the compounds found in grape seed are able to improve the activation of immune system functioning and antitumor impacts through stimulating the immune system. In a systemic study, Olaku et al. [13] investigated the role of grape seed extract in treating the toxicity by radiotherapy and suggested that both types of extract (grape seed extract (GSE) and grape peel extract (GPE)) reduce the impacts of chemotherapy cytotoxicity or radiotherapy on the natural cells. In view of the various impacts of grape seed extract on dentistry, we investigated the impact of grape seed extract on the oral cancer in this systematic review study (Figure 1).



**Figure 1:** PRISMA flow.

## Materials and Methods

Regarding the main approach of this study in line with the comprehensive review and study, the evidence and studies conducted in connection to use of grape seed extract in oral cancer were reviewed. The figure 1 shows the process of PRISMA selection. The articles of databases of Google Scholar, PubMed and SCOPUS were searched within 2000-2020. The articles were selected by reviewing the titles and their abstracts and from the bibliographies of the selected articles.

The keywords used to search for the articles were selected by PICO (P: "Oral Cancer", I: "Grape Seed Extract", C: "Standard Treatment" and O: "The Effect of Treatment"). The keywords used for searching the articles were mouth cancer, grape seed, oral tumor, oral cancer, extract.

The inclusion criteria for all articles entered this review are:

- 1) Paying attention to years of 2000 to 2020;
- 2) Selecting the original articles with given methodology connected to the topic;
- 3) Selecting the article related to the treatment by grape seed extract among the patients with oral cancer.

The exclusion criteria for the articles deleted from the review are:

- 1) Review studies, reports of case and letters and questionnaires;

## 2) Articles with insufficient quality.

Once the articles were selected in accordance with the inclusion and exclusion criteria, different sections of article including the primary information of article (journal, year of publication and authors), title and objective of article, methodology and results were separated so that the reviewer has the single blind conditions to the article information while reading the articles and has no role in extracting the results over a special factor or well-known researcher and accordingly, he does not enter the review of articles of reviewers' bias type.

## Results

In the review search of the aforementioned databases and concerning the intended time interval, 220 articles were found connected to the searched words through the abstracts. Once their titles and abstracts were studies, 101 articles were selected, and then reduced to 22 by the assessment team. For final selection, out of the articles, 10 ones had the inclusion criteria with the study objectives (Table 1).

Outcome Criteria	Type of Study	Population of Study	Title	Year
KB Cancer Cell Apoptosis	<i>In vitro</i>	Oral squamous cell carcinoma KB cell line	Evaluation of the cytotoxic activity of hydromethanolic grape seed extract in oral squamous cell carcinoma (KB cell line)	2014
Decreased gene expression Bcl-2, p53	<i>In vitro</i>	Oral keratinocytes under the oxidative stress of chewing tobacco	Protective effects of antioxidants against smokeless tobacco-induced oxidative stress and modulation of Bcl-2 and p53 genes in human oral keratinocytes	2001
Inducing properties of apoptosis on CAL27 cells	<i>In vitro</i>	oral squamous cell carcinomas	Cranberry and grape seed extracts inhibit the proliferative phenotype of oral squamous cell carcinomas	2011
Increasment of apoptotic molecules such as caspase-2 and caspase-8	<i>In vitro</i>	oral squamous cell carcinomas	Inhibition of oral cancer growth in vitro is modulated through differential signaling pathways by over-the-counter proanthocyanidin supplements	2011

P53-associated cell death	<i>In vitro</i>	oral squamous cell carcinomas	The chemoadjuvant potential of grape seed procyanidins on p53-related cell death in oral cancer cells. Journal of Oral Pathology and Medicine	2012
Production of sodium ascorbate radical	Comparative Grape skin and kernels	Oral tumor cells	Selective cytotoxic activity of grape peel and seed extracts against oral tumor cell lines	2000
Suppression of protein kinase B and nuclear factor $\kappa$ B signaling pathway	<i>In vitro</i>	Squamous cell carcinoma of the tongue	Grape seed proanthocyanidins inhibit the proliferation, migration and invasion of tongue squamous cell carcinoma cells through suppressing the protein kinase B/nuclear factor- $\kappa$ B signaling pathway	2017
Apoptosis, reactive oxygen species (ROS), mitochondrial function and DNA damage	<i>In vitro</i>	Oral cancer	Concentration effects of grape seed extracts in anti-oral cancer cells involving differential apoptosis, oxidative stress	2015
Pernoplastic and neoplastic lesions	<i>In vivo</i> Case-Control	Oral tumorigenesis	Grape seed extract and resveratrol prevent 4-nitroquinoline 1-oxide induced oral tumorigenesis in mice by modulating AMPK activation and associated biological responses	2015
MDA, GSH Serum and tissue	<i>In vivo</i> Case-Control	Oral cancer	Natural chemopreventive alternatives in oral cancer chemoprevention	2016

**Table 1:** Qualitative information from reviewing the articles [1-31].

Seven studies were experimental, one study in comparative-experimental and two studies as the animal research. In connection to the research objective, no clinical trial and systematic review studies were conducted. Hence, the present study is a preclinical systematic review study (Table 2).

Results	
1	Hydromethanolic extract of black grape seed is able to control the growth and property of cellular toxicity on KB cancer cells and causes the induction of apoptosis in this KB cellular line.
2	Using the GSPE has significantly expressed the p53 gene. The expression of anti-apoptotic Bcl-2 gene increases considerably after the incubation by GSPE.
3	The grape seed corn extract not only harnesses the proliferation of oral cancer, but also the mechanism of such harness likely acts through creating the main regulators of apoptosis in this line.
4	50-70 mg concentration of proanthocyanidins (PAC) for 24 hours increases the expression of caspase-2 and caspase-8 and consequently leads to apoptosis.
5	Anti-proliferative impact of GSP is connected to the status of p53 gene in OSCC cells. GSP shows the chemical potential through the occlusion of cellular cycle and induction of apoptosis. GSP may play a role as a chemical and new preventive material for OSCC.
6	The grape seed extract had more cytotoxic activity against the cancer cells than the grape peel extract. GSP removes selectively two lines of human oral tumor and has higher efficiency in fibroblasts of human gum. These extracts produce the radical in alkaline conditions and increase the intensity of sodium ascorbate radical in higher concentrations. On the other hand, lower concentration of these extracts reduces the intensity of sodium ascorbate radical a bit and destroys the superoxide anion. These properties of grape seed extract show their possible application to prevent the cancer.
7	Through suppression of signaling pathways of Akt/NF- $\kappa$ B, GSP prevents the proliferation, immigration and attack of Tca8113 cells. This indicates that GSP may act as a possibly new preventive chemical against the tongue squamous cell carcinoma (TSCC).
8	High concentrations of GSE prevents the proliferation of oral cancer Ca9-22 cells. In high concentration of GSE, ROS production and mitochondria depolarization increased. High concentrations of GSE damages the DNA based on $\gamma$ H2AX. Differential concentrations of GSE may have different anti-proliferative performance against the oral cancer cells in terms of apoptosis, oxidative stress and DNA damage.
9	Upon beginning and after the emergence of oral cancer, the grape seed extract decreases the local and general oxidative stress and dysplasia intensity. Once the cancer began, the grape seed extract and curcumin showed the same effects.
10	These findings show that the grape seed extract and resveratrol can prevent the oral tumor through activating the AMPK and as a result, avoiding the proliferation and development of apoptosis and autophagy.

**Table 2:** Results of the study in the tabular form.

To evaluate the risk of bias, JBI (Joanna Briggs Institute) checklist for quasi-experimental studies was used. In the under-study researches, except two animal studies, other studies were experimental without any control group. In JBI checklist, except two items, i.e., 4 and 6, others were established. In animal studies, all items of checklist were established. Generally speaking, this study had a high risk of bias.

## Discussion

Studies have shown that the grape seed extract has preventive and inhibitory properties against the cancer [14,15]. Results of this study revealed that despite the impact of grape seed extract on cancer, no clinical study is registered in databases and studies are only experimental and animal researches. Therefore, the results of this systematic study is a preclinical review. Results indicated that numerous experimental studies imply the apoptotic property of grape seed extract in oral cancer cells. In this line, Chatelain et al. [16] showed that the grape seed extract creates the main regulators of apoptosis of oral cancer cells. Aghbali et al. [17] also argued that the hydromethanolic extract of black grape seed is able to inhibit the growth and property of cellular toxicity on KB cancer cells and leads to the induction of apoptosis in this KB cell line.

Apoptosis is a natural cellular incident and includes a special kind of cellular death occurring in absence of inflammation. Removal of unexpected cells in many multicellular and even unicellular creatures is organized by this process. Expression of p53 gene is among the main regulators of apoptosis [18]. In an experimental study, Bagchi et al. [14] showed that using GSPE significantly results in the expression in p53 gene in oral Keratinocyte cells. Lin et al. [19] stated that the GSP anti-proliferative impact is connected to the status of p53 gene in OSCC cells. P53 is a phosphor-protein transcription which regulates the expression of over 2500 target gene and it is involved in various cellular processes like genome stability, life span, metabolism and most importantly, tumor suppressor [20].

The gene is located on the short arm of chromosome 17 (17P31.1) and has 11 exon and 20 kb in length [21]. This protein was initially seen as an oncogene due to high expression in tumor cells. New findings show that the transforming clones already used in previous studies were mutant and in contrast to the various mutants, the natural p53 protects the cells from oncogenes [22]. Findings revealing the changes in natural p53 gene in cellular cells indicated the tumor suppressing property of p53 [20]. Previous studies have shown that the grape seed extract has preventive and inhibitory properties against the cancers of breast, lung, skin, prostate, gastric and colon. On the other hand, the grape seed increases the growth and survival of macrophage, heart and skin cells. The proanthocyanidins existing in grape seed extract is also responsible for the antioxidant, anti-inflammatory, antifungal, antibacterial and ant-allergic activities [23].

In accordance with the studies, the antioxidant power of proanthocyanidins is 20 times higher than vitamin E and 50 times more than vitamin C [44]. However, most studies conducted in recent years as the human and animal researches indicate the vigorous biological and antioxidant impacts of this supplest on increasing the antioxidant capacity, decreasing the amount of malondialdehyde and oxidative pressure [25]. Investigating the inhibition of development of oral squamous cell carcinoma in vitro by the proanthocyanidins supplements, Kingsley et al. [26] showed that 50-70  $\mu\text{g}$  concentration of proanthocyanidins (PAC) for 24 hours increases the expression of caspase-2 and caspase-8 (among the molecules regulating the apoptosis) and consequently leads to apoptosis.

Proanthocyanidins is a kind of bioflavonoid and a very strong antioxidant which can prevent the cellular destructions because of free radicals and repair and empower the connective tissues and help the activity of enzymes [12]. Proanthocyanidins relieves the allergic responses and body immune system by reducing

the histamine production. This substance decreases the inflammatory [67]. In this line, Chung et al., (2012) showed that proanthocyanidins are able to inhibit the cellular proliferation and invasion by controlling the cellular cycle as well as the induction of apoptosis [15]. Another part of experimental studies indicated the anticancer impacts of grape seed extract in different ways. Study by Yang et al. showed that GSPs are likely a possible preventive chemical against the tongue squamous cell carcinoma (TSCC) [28]. Yen et al. [29] observed that the differential GSE concentrations can have a different anti-proliferative performance against the oral cancer cell in terms of apoptosis, oxidative stress and DNA damage. While expressing the properties of grape seed extract in preventing the cancer, Shirataki et al. [68] observed that the grape seed extract has more cytotoxic activity against the cancer cell than the grape peel extract.

The present study showed that only two animal studies have been conducted on the impact of grape seed extract on the oral cancer. To investigate the impact of GSE and resveratrol (Res) on the oral tumors resulting from 4NQO on the rats, Shrotriya et al., showed that the GSE and resveratrol can prevent the oral tumor through mediating the AMPK activation, and as a result, restraining the proliferation and development of apoptosis and autophagy [30]. Scrobota et al. [31] compared the curcumin and grape extract and found out that both materials have the same impact on reduction of dysplasia intensity in the oral cancer of rats after the carcinogenesis. Their study had both positive and negative control samples [31]. Although the animal studies are so limited, concerning the positive results of all animal and experimental studies, it is possible to start and implement the clinical trial studies in using the supplements of grape seed extract to treat the oral cancers.

## Conclusion

The conducted experimental and animal studies show that the grape seed extract is able to treat the apoptosis of oral cancer cells. In this preclinical review study, the experimental and animal studies confirm the impact of grape seed extract on treatment of oral cancer cells. Therefore, it seems necessary to conduct the clinical trial studies on using the grape seed extract as the medical supplement to treat the oral cancer.

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