DOI: 10.7860/JCDR/2023/61459.17744

Review Article

Dentistry Section

# Grapeseed Extract and its Role in Maintaining Oral Health: A Literature Review

PAYAL S WAGHMARE[1], PRIYANKA PAUL MADHU[2], AMIT RECHE[3]




## ABSTRACT

Plant products are becoming a topic of discussion because of their properties and many medicinal benefits. Among these natural products, Grapeseed Extract (GSE) is becoming an essential part of medicine. It possesses antibacterial, antioxidant, anti-inflammatory, and antiviral properties. GSE's antibacterial property makes it effective in controlling various bacterial diseases and aiding in the treatment process. It has also been found to inhibit oral bacteria. GSE has shown considerable results in patients with periodontal diseases and treatment of bone loss. GSE is a potent antioxidant and reduces free radicles and oxidative stress thus inhibiting various adverse effects. GSE contains antioxidant properties which protects body from premature ageing. Its antifungal properties are useful in treating and preventing fungal infections, including oral candidiasis. Phytochemicals present in Grapeseed Extract, such as resveratrol and Proanthocyanidin (PA), have demonstrated benefits in cancer treatment and prevention of recurrence. The protective properties of plant extracts and phytochemicals are also being explored in the prevention of common oral diseases, such as dental caries in both children and adults. Current studies are investigating the remineralisation efficiency of phytochemicals in dentistry. It has been shown to increase the dentine resin bond strength if it is added in the primer and also effectively reduces the polymerisation. Another important consideration is determining the safe doses of GSE, which refers to the quantity or percentage added to products to ensure safe tolerance and maximise its effects. Overall, GSE possesses several beneficial properties and holds great clinical importance.


**Keywords:** Antibacterial, Antioxidants, Antitumour, Antiviral, Periodontal diseases, Proanthocyanidin

## INTRODUCTION

Natural products are used in folk medicine, which is a promising source of new therapeutic agents, especially in the treatment of dental caries [1]. Despite the fact that contemporary preventative interventions such as fluoridation and broad-spectrum antimicrobials, as well as reducing on sugar consumption and practicing proper oral hygiene, show lower caries prevalence, dental caries remains the most common disease in humans [2]. Periodontal diseases are a collection of conditions that include bacterial-induced inflammatory responses of the periodontium, resulting in periodontal tissue degradation, gingival inflammation, and alveolar bone loss [3]. When pathogenic microbial plaque interacts with a vulnerable host, periodontal disorders develop [4]. Many different substances, such as fluorides (amine fluoride, sodium fluoride, etc.), chlorhexidine, and stannous fluoride, are used in modern toothpastes to prevent periodontitis and caries. For successful plaque removal, calcium phosphates such as hydroxyapatite, Amorphous Calcium Phosphates (ACP), surfactants, and different abrasives are used [5]. Reactive Oxygen Species (ROS) have been identified as harmful mediators in many diseases, and periodontal deterioration is connected to oxidative stress generated by host and microbial interaction [6,7]. Enzymes that convert ROS into non-toxic molecules and antioxidant substances like alpha-carotene, beta-carotene, retinol, selenium, and ascorbic acid make up the antioxidant defense system employed by the body to avoid oxidative damage [8]. In the last decade, researchers have focused their attention on the utilisation of organic chemicals as antibacterial elements in toothpaste [9].

Plants produce polyphenolic chemicals (polyphenols) as secondary metabolites. Polyphenol-rich foods and drinks have been shown to have anti-inflammatory, antimicrobial, antiplaque, and anticaries qualities, making them beneficial to oral health [10]. Examples of Proanthocyanidins (PAs) found in Grapeseed Extract (GSE), derived from *Vitis vinifera* seeds, are epicatechin, catechin, and epicatechin3-O-gallate. These compounds are high in polyphenols and free monomeric flavanols, i.e., proanthocyanins [1,2,11]. PAs have been shown to strengthen collagen in tissues by enhancing collagen cross-links. They promote collagen production and accelerate the conversion of soluble collagen into insoluble collagen [11]. GSE has the potential to suppress osteoclast differentiation, decrease osteoclast activity, and accelerate bone production through its favorable effect on osteoblasts [12].

### Composition of Grapeseed

On a dry weight basis, standardised GSE includes 74-78% oligomeric PA and less than 6% free flavanol monomers. GSE is abundant in PA, particularly in the monomeric phenolic compounds epicatechin, catechin, and epicatechin-3-O-gallate. These compounds can interact with gallic acid to produce gallate esters, which in turn can produce glycosides [13]. [Table/Fig-1] provides information about the scientific classification of GSE (*Vitis Vinifera*) [14].

| | |
|---|---|
| Kingdom | Plantae |
| Division | Mangoliophyta |
| Class | Mangoliopsida |
| Order | Vitals |
| Family | Vitaceae |
| Genus | Vitis |
| Species | Vinifera |

**[Table/Fig-1]:** Taxonomy of grapeseed *Vitis vinifera* [14].

### Properties of Grapeseed Extract (GSE)

**Antioxidant properties:** Flavonoids are the crucial contributors to GSE's antioxidant properties, which have the capacity to scavenge free radicals and possess metal-chelating properties. GSE can prevent the formation of hydroperoxide and influence gene expression and cell signalling pathways [14]. GSE demonstrates a dose-dependent protective ability against 12-O-Tetradecanoylphorbol-13-Acetate (TPA)-induced Deoxyribose Nucleic Acid (DNA) fragmentation. Grape

Seed Proanthocyanidin Extract (GSPE) was administered in doses of 25, 50, and 100 mg GSPE/kg to animals for seven days, resulting in a significant decrease in TPA-induced hepatic DNA fragmentation by 36%, 42%, and 47%, respectively, compared to controls. DNA fragmentation was reduced to 32%, 42%, and 50% in brain cells with similar concentrations of GSPE. Combined treatment with Vitamin C plus Vitamin E Succinate (VES) and GSPE further decreased DNA fragmentation in hepatic and brain cells [15].

**Antibacterial properties:** GSE has been found to suppress both Gram-positive and Gram-negative microbes, although it is more effective against Gram-positive organisms. Different studies have suggested different minimum inhibitory values for GSE [16]. Certain environmental factors, such as oxidative stress and exposure to antimicrobial drugs, induce the expression of stress response pathways. The phenolic content and antibacterial impact of GSE may vary depending on the grape types and extraction techniques used. The concentration of GSE determines whether its action is bacteriostatic or bactericidal. The concentration of phenolic compounds in GSE is influenced by the type of grapevine used, as well as viticulture and environmental conditions. Plant tissues are stimulated to synthesise both flavonoid and non-flavonoid polyphenols after being infected by pathogenic organisms [17,18]. The antibacterial impact of GSE was investigated using different solvent extraction methods, such as water:acetone:acetic acid (9.5:90:0.5) and water:methanol:acetic acid (9.5:90:0.5). The findings showed that the acetone, water, and acetic acid (90:9.5:0.5) extract had a stronger antibacterial impact on certain Gram-positive microbes, but there was no discernible difference between the two extracts' antibacterial effectiveness against Gram-negative bacteria [19]. GSE demonstrated biofilm inhibitory and bacteriostatic effects against significant oral infections and microorganisms that cause plaque, including *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Streptococcus mutans* [20,21].

**Antifungal properties:** GSE can prevent the development of yeast cells from Candida species in a dose-dependent manner. GSE polyphenols can also provide immunity against disseminated illness in mice due to their direct interaction with Candida species, in addition to their direct contact with these cells and their antifungal properties. Han Y examined the antifungal effects of GSE alone and in combination with amphotericin B against disseminated candidiasis in female Bagg albino/c mice aged 6-7 weeks. The findings demonstrated the antifungal activity of GSE alone, as well as its synergistic interaction with amphotericin B. The survival duration of mice treated with GSE and amphotericin B was significantly longer than the survival time of mice that received four doses of amphotericin B alone [22]. It has been revealed that GSEs isolated from *Vitis vinifera* and cultivated under hydrostatic pressure are rich in polymeric flavan-3-ols and have a substantial antifungal action against Candida species other than *Candida albicans* [23].

**Antiviral properties:** GSE has been shown to have antiviral effects against various viral infections. The flavonoid components of GSE were found to dose-dependently downregulate the expression of the Human Immunodeficiency Virus-1 (HIV-1) entrance coreceptor. This indicates that flavonoids may inhibit the attachment of the HIV virus to the cell receptor and prevent it from entering a normal lymphocyte by interfering with the virus's ability to connect to the receptor [24]. Su X and D'Souza DH investigated the antiviral properties of GSE against Hepatitis A Virus (HAV; strain mHM175), bacteriophage MS2, and murine norovirus 1. GSE dose-dependently reduced the high titers of these viruses after two hours at 37°C [25]. Resveratrol, a non-flavonoid polyphenolic compound present in grapeseed at high concentrations, has strong bioactivity and cytoprotective action. It also has antiproliferative action at high concentrations. Resveratrol has been shown to be effective against various double-stranded and single-stranded viruses, including influenza virus, Herpes Simplex Virus (HSV), varicella-zoster virus, and polyomavirus [26].

**Antitumour property:** Aluyen JK et al., conducted a study to determine whether resveratrol prevents cancer and found that it demonstrates different mechanisms to induce its chemoprotective effects. One of these mechanisms is inducing apoptosis in malignant cells. Caspase facilitates planned cell death by activating apoptotic pathways. A decreased level of caspase is often directly associated with the prevention of apoptosis in carcinogenesis. Researchers found that resveratrol is effective in stopping or reducing cellular growth by triggering apoptosis in an in-vivo study that examined colorectal cancer in rats. Resveratrol acts through proapoptotic, antiproliferative, and anti-inflammatory pathways, suggesting its anticancer properties [27]. In-vitro and in-vivo studies by Zhang XY et al., examined the anticancer effects of combining PA and doxorubicin. In-vitro, 12.5-100 mg/L PA reduced the proliferation of A549 CNE and K562 cells in a concentration-and time-dependent manner. These findings suggest that PA enhances the antitumour effects of doxorubicin, and the mechanism by which it does so is attributed to the promotion of doxorubicin-induced apoptosis through elevations in intracellular doxorubicin [28].

**Advancements in phytochemicals:** In grapeseed oil, several phenolic chemicals operate to modulate the cell cycle and have anticancer properties [29]. They exhibit cytotoxic properties against tumour cells while being safe for healthy cells [30]. Flavan-3-ol polymers called PA have an impact on cancer cells, preventing their proliferation [31]. The advancement of phytochemicals in nanodosage forms could revolutionise biomedical research, which is why grapeseed oil has been studied as a nanocarrier for cancer treatment. In this study, lipid nanocarriers derived from natural oils (laurel leaf oil and grapeseed oil) were compared in terms of their efficiency in scavenging free radicals and inhibiting specific tumour cells. Using nanocarriers made from a mixture of laurel leaf and grapeseed oils at a dosage of 5 mg/mL, it was demonstrated that they could scavenge around 98% of O2 free radicals. Tumour cell growth was significantly reduced even in the absence of an anticancer drug. When comparing the survival profiles of healthy and tumour cells treated with a dosage of 2.5 mg/mL lipid nanocarriers, a 20% mortality rate was observed for normal B16 cells, while the death rate for tumour HeLa cells and MDA-MB 231 was 40%. Therefore, lipid nanocarriers made from laurel leaf oil and grapeseed oil may be used to reduce toxicity and increase the therapeutic efficacy of anticancer medicines in clinical applications [32]. The anticancer activity displayed by nanocarriers, resulting from complex cellular events and processes, may be attributed to the range of bioactive chemicals present in grapeseed and laurel oils, such as antioxidant activity, modulation of antioxidant enzymes, induction of cell cycle arrest, and apoptosis [32,33].

## Role of Grapeseed Extract (GSE) in Oral Health

**Antibiofilm properties:** A study conducted by Ooshima T et al., examined the effects of grape extract on acid production. They cultured 1 cc of *S. mutans* in 100 mL of red phenol broth enriched with the extract and 1% glucose. pH measurements were taken at regular intervals using a pH meter. The results showed a decrease in pH from 6.5 to 3.0 (highly acidic) due to bacterial growth and acid production. However, when treated with epicatechin, the pH value was maintained at 4.8, indicating a suppression of acid production [20]. GSE has also been found to reduce the formation of *S. mutans* biofilms and inhibit planktonic development at a concentration of 4 mg/mL. Furthermore, GSE demonstrated a dose-dependent antibiofilm effect against *S. mutans* in the treatment of simulated enamel lesions at subminimal inhibitory concentration levels [21]. The inhibitory impact of GSE on biofilm production is dose-dependent. GSE showed the strongest antibiofilm action against multispecies biofilm producers, including *F.nucleatum, P.gingivalis*,

Streptococcus sobrinus, Actinomyces viscosus, and Lactobacillus rhamnosus, at a concentration of 2000 mg/mL (sub-MBC values). However, higher concentrations of the extract reduced its efficacy, mainly due to its poor solubility in water [34].

**Grapeseed in periodontal disease:** PA is a useful agent in preventing periodontal diseases, which is found in grapeseeds and may have antioxidant effects. When macrophages are stimulated by bacteria or their components, reactive nitrogen species (RNS) and reactive oxygen species (ROS) are produced, which are essential for effective defense against invading pathogens. However, elevated levels of ROS/RNS can lead to oxidative stress, causing damage to bone and tissue. To investigate the effect of PAs on the production and accumulation of NO2-, a stable metabolite of Nitric Oxide (NO), in the culture media of LPS-stimulated macrophages, the Griess colorimetric assay was used. The basal level of NO released from unstimulated RAW 264.7 macrophages was estimated at 4 μM. Stimulation of macrophages with LPS from *A. actinomycetemcomitans* and *F. nucleatum* increased NO2- production by 10-fold compared to the basal level (45 and 42 μM, respectively). Pretreatment of macrophages with non-toxic concentrations of phenolic compounds before LPS stimulation strongly inhibited the induction of NO2-generation. At non-toxic concentrations, GSE was able to inhibit NO production by macrophages stimulated with LPS from *A. actinomycetemcomitans* and *F. nucleatum* by 62% and 50%, respectively, compared to LPS-stimulated but untreated cells [35].

**Grapeseed Extract (GSE) on shear bond strength:** Primers, which are bifunctional molecules, are used to enhance the longevity of resin-dentin bonded contacts [36]. Collagen crosslinkers have shown effectiveness in strengthening collagen-based biomaterials and improving the bond between dentin and composite resin [37]. PAs form various types of bonds with proteins, including hydrogen, covalent, or ionic bonds. The interaction between dentin collagen and PA helps maintain the triple helix shape of collagen [38]. PA at the resin-dentin contact has been found to be resistant to enzymatic degradation [39]. In an experiment conducted by Khan SA et al., an experimental primer containing a collagen crosslinker was applied to assess its effect on shear bond strength of tooth-coloured resin restorations. The results showed that after one minute of applying a 6.5% PA primer, group B exhibited higher shear bond strength (10.37 MPa) compared to group A (7.78 MPa). The mode of fracture was assessed for each specimen using an electronic zoom microscope [40]. PA can be cross-linked through various interactions, including ionic, covalent, hydrogen, and hydrophobic interactions [41].

**Remineralisation:** PAs, present in significant amounts in GSE, have been shown to improve collagen by promoting collagen cross-links [42]. Studies have demonstrated that PAs expedite the process of converting soluble collagen into insoluble collagen during development. Collagen matrices treated with PA have been proven to be safe and resistant to enzyme degradation in both in-vitro and in-vivo studies [43]. Xie Q et al., used an in-vitro pH cycling model to evaluate the effect of GSE on remineralisation of artificial root caries. After pH cycling, a mineral precipitation band was observed on the superficial surface in both groups. The GSE-treated group showed a significantly wider mineral precipitation band compared to the fluoride and control groups, indicating enhanced remineralisation [2].

## Grapeseed Compounds and Bioactivity

The three most prevalent Reactive Oxygen Species (ROS) are hydrogen peroxide, superoxide, and hydroxyl radicals. Physiological production of these ROS serves as signalling molecules for the immune system and homeostasis management. However, an imbalance between antioxidants and ROS, caused by excessive ROS production, leads to oxidative stress. Oxidative stress is associated with various disorders such as type 2 diabetes mellitus, cancer, cardiovascular and pulmonary diseases, and degenerative illnesses. Antioxidant enzymes, including superoxide dismutase, glutathione peroxidase, and catalase, play a role in controlling this process [44-46]. Grapeseed and its by-products contain a variety of phenolic compounds, including resveratrol, quercetin, procyanidins, and others, which possess antioxidant and anti-inflammatory properties [47]. The polyphenolic contents of grapeseed are illustrated in [Table/Fig-2] [46,48-50]. Various studies on grapeseed are summarised in [Table/Fig-3] [14,17,18,51,52].

| Source | Resource | Phenolic compounds |
|---|---|---|
| Hernández-Jiménez A et al., [46].<br>Pastrana-Bonilla E et al., [48].<br>Bell JR et al., [49].<br>Huang D et al., [50]. | Seed | Proanthocyanidins (PA)<br>Gallic acid,<br>Catechin,<br>Epicatechin,<br>Dimeric procyanidin |
| Hernández-Jiménez A et al., [46].<br>Pastrana-Bonilla E et al., [48]. | Skin | Proanthocyanidins (PA),<br>Trans-resveratrol<br>ellagic acid,<br>myricetin,<br>Quercetin,<br>kaempferol |

**[Table/Fig-2]:** Polyphenolic contents of grapeseed.

| Authors | Study type | Outcome | Intervention | Study duration | Sample population | Result | Analysis |
|---|---|---|---|---|---|---|---|
| Jain S et al., [14] | Review article | NA | NA | NA | NA | Effective in preventing diseases. | Acts as a potent antioxidant. |
| Montealegre RR et al., [17] | Original article | Varieties of grapeseed varies in their phenolic composition. | NA | NA | NA | Composition and amount of polyphenols in red and white grape varies according to the climate. | Polyphenols find its way in various medical purposes and can be used differently according to the climatic conditions. |
| Katalinić V et al., [18] | Original article | White cultivars has highest level of phenolic compounds. | NA | NA | NA | Higher the mixture of different polyphenols higher is the antioxidant property. | This antioxidant property is to reduce free radicles and oxidative stress in patients. |
| Guo L et al., [51] | Animal study | Procynidin fractions can reduce DNA damage. | 20% (v/v) ethanol at 2.5 and 5.0 g kg-1 every day for 30 consecutive days. | 30 days | Male Swiss mice | Procynidin fractions prevents DNA damage induced due to ethanol in brain. | Procynidin can be used in treating various neurologicals diseases. |
| Vinson JA et al., [52] | Animal study | Triglyceride levels can be managed by GSE. | Hypercholesterolemic Diet (HCD) of 0.2% cholesterol and 10% coconut oil. | 10 weeks | Male, weanling, Syrian golden hamsters | Total cholesterol levels were reduced by 25% and 23% following supplementation of 50 mg/kg and 100 mg/kg GSPE. | GSE containing proanthocynidin can cure atherosclerotic disorders. |

**[Table/Fig-3]:** Various studies about grapeseed [14,17,18,51,52].
DNA: Deoxyribose nucleic acid; GSE: Grapeseed extract; GSPE: Grape seed proanthocyanidin extract

### Safety Doses

Grapeseed Extract (GSE) is commercially available as a dietary supplement and is listed in the Everything Added to Food in the United States (EAFUS) database as Generally Recognised As Safe (GRAS) by the Food and Drug Administration (FDA) [51]. According to Bentivegna SS and Whitney KM, the typical dosage of GSE used in food applications ranges from 0.01% to 1%, and the No-Observed-Adverse Effect Level (NOAEL) of grapeseed extracts in rats is 1.78 g/kg body weight/day [53]. Sano A et al., reported that taking tablets containing 200 mg and 400 mg GSE did not cause any unexpected changes in participants' physiological and clinical laboratory tests. Furthermore, urine sedimentation tests did not reveal any unfavourable results, providing further evidence of the safety of consuming GSE tablets at doses of 200 mg and 400 mg [54]. GSE has a lethal dose of greater than 4000-5000 mg/kg in rats. While modest concentrations (0.01% to 10%) are used in the food industry, GSE may be beneficial at therapeutic doses of 150-300 mg/day [55]. The cytotoxicity of the epicatechin derivatives in the two cell lines was similar after exposure for 24-72 hours at concentrations three times higher than the antioxidant dose. DNA damage caused by the phenolic phytochemicals in GSE was significantly increased in mouse spleen cells. For example, 50 mmol/L of H2O2 and 150 mmol/L of catechin both resulted in DNA damage [56].

## CONCLUSION(S)

The GSE and its products are easily and widely available worldwide. They are popular due to their cost-effectiveness and contain a variety of useful contents, including beneficial polyphenols. These polyphenols have medicinal purposes and find wide-ranging uses in the healthcare sector. Grapeseed has antibacterial, antifungal, anticariogenic, and remineralising properties. It has been proven effective in maintaining overall general health. Therefore, it can be concluded that grapeseed can be included in oral hygiene maintenance and treatment due to its properties.

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**PARTICULARS OF CONTRIBUTORS:**
1. Intern, Department of Public Health Dentistry, Sharad Pawar Dental College and Hospital, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi (Meghe), Wardha, Maharashtra, India.
2. Associate Professor, Department of Public Health Dentistry, Sharad Pawar Dental College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi (Meghe), Wardha, Maharashtra, India.
3. Assistant Professor, Department of Public Health Dentistry, Sharad Pawar Dental College and Hospital, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi (Meghe), Wardha, Maharashtra, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**
Dr. Payal S Waghmare,
Intern, Department of Public Health Dentistry, Sharad Pawar Dental College and Hospital, Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi (Meghe), Wardha-442001, Maharashtra, India.
E-mail: payal19waghmare@gmail.com

**PLAGIARISM CHECKING METHODS:** [Jain H et al.]
- Plagiarism X-checker: Nov 18, 2022
- Manual Googling: Dec 19, 2022
- iThenticate Software: Dec 21, 2022 (15%)

**ETYMOLOGY:** Author Origin

**AUTHOR DECLARATION:**
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? NA
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Nov 14, 2022**
Date of Peer Review: **Dec 15, 2022**
Date of Acceptance: **Dec 22, 2022**
Date of Publishing: **May 01, 2023**