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 the topic for discussion because of its properties and many medicinal benefits. Among these natural products, Grapeseed Extract (GSE) is becoming an essential part of medicine. Antibacterial, antioxidants, anti-inflammatory and antiviral are some of the important properties. Due to its antibacterial property it is used to control various bacterial diseases and eased the course of treatment, many oral bacteria are also inhibited by GSE. 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. Antifungal properties are very useful in treatment and prevention of fungal infection. Grapeseed is useful in treating oral candidiasis as well. A number of phytochemicals including resveratrol, Proanthocyanidin (PA) are beneficial in treating cancer and prevents recurrence. The protective properties of plant extracts and phytochemicals are recently been used in prevention of most common oral disease like dental caries in children and adults. Many studies are going on about remineralisation efficiency of phytochemicals in the field of 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 the safety doses of GSE, it refers to the quantity or percentage in which it is added in the concerned products so it is safely tolerated and its effects are maximum. Overall, GSE contains many useful properties and is of 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 cutting back on sugar consumption and practising proper oral hygiene, shows lower caries prevalence, dental caries is most common disease in humans [2]. Periodontal diseases are a collection of conditions which include bacterial-induced inflammatory response of the periodontium that results in, periodontal tissue degradation, gingival inflammation and alveolar bone loss [3]. When a pathogenic microbial plaque interacts with a vulnerable host, periodontal disorders develop [4]. Many different substances, like fluorides (amine fluoride, sodium fluoride, etc.,), chlorhexidine, and stannous fluoride, are utilised in modern toothpastes to prevent periodontitis and caries. For successful plaque removal, calcium phosphates 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 change ROS into non toxic molecules and antioxidant substances like alpha-carotene, beta-carotene, retinol, selenium and ascorbic acid make up the antioxidant defence system employed by body to avoid oxidative damage [8]. Researchers have focused their attention in last decade on the utilisation of organic chemicals as an antibacterial element of toothpaste [9].

Plants produce polyphenolic chemicals (polyphenols) as secondary metabolites. Polyphenol rich foods and drinks have been shown to have antiinflammatory, antimicrobial, antiplaque and anticaries qualities, making them beneficial to oral health [10]. Epicatechin, catechin and epicatechin-3-O-gallate, which are structural building blocks, are examples of Proanthocyanidins (PAs) found in Grapeseed Extract (GSE) , which are derived from *vitis vinifera* seeds, are high in polyphenols and free monomeric flavanol, i.e., proanthocyanins [1,2,11]. By enhancing collagen cross-links, PAs have been shown to strengthen collagen in the tissues. PA promotes collagen production and speeds the conversion of soluble collagen into insoluble collagen [11]. Through its favourable effect on osteoblasts, GSE has the potential to suppress osteoclast differentiation, decrease osteoclast activity and accelerate bone production [12].

Composition of Grapeseed

On a dry weight basis, standardised GSE include 74-78% oligomeric PA and fewer than 6% free flavanol monomers. GSE is abundant in PA, particularly in the monomeric phenolic chemicals, epicatechin, catechin and epicatechin-3-O-gallate. These can interact with gallic acid to produce gallate esters, which in turn can produce glycosides [13]. [Table/Fig-1] gives information about scientific classification of the 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 of GSE's antioxidant properties, which have the capacity to scavenge free radicals as well as possess metal chelating properties. GSE has the capacity to prevent the formation of hydroperoxide, and their influence on gene expression and cell signalling pathways [14]. GSE demonstrate 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 the doses of 25, 50 and 100 mg GSPE/kg to animals for seven days, this significantly decreased TPA induced hepatic DNA fragmentation by 36%, 42% and 47%, respectively compared to controls. DNA fragmentation came down to 32%, 42% and 50% in brain cells in 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: Gram-positive and Gram-negative microbes are among the multitude of microbes that the GSE suppresses. However, it performs better when used against gram-positive organisms, different studies have suggested different minimum inhibitory value of GSE [16]. The expression of stress response pathways is induced by certain environmental factors, including oxidative stress and exposure to antimicrobial drugs, stimulate the development of stress response pathways. The phenolic content and antibacterial impact of GSE may vary depending on the grape types and extraction techniques used. The concentrations of GSE determine whether an action is bacteriostatic or bactericidal. The kind of grapevine used determines the concentration of phenolic compounds in GSE, which is further affected by viticulture and environmental conditions. Plant tissues are stimulated to synthesise both flavonoid and non flavonoid polyphenols after being infected by pathogenic organisms [17,18]. It was investigated how 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), affected the antibacterial impact of GSE. According to the findings, acetone, water and acetic acid (90:9.5:0.5) extract has a stronger antibacterial impact on few gram-positive microbes, but there was no discernible difference between the two extracts' antibacterial effectiveness against gram-negative bacteria [19]. The GSE demonstrated biofilm inhibitory and bacteriostatic effects against certain significant oral infections and microorganisms that cause plaque, including *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Streptococcus mutans* [20,21].

Antifungal properties: In a dose-dependent way, GSE can prevent the development of yeast cells from candida species. The GSE polyphenols may also produce immunity against the disseminated illness in mice because of their direct engagement with candida species, in addition to GSE's direct contact with these cells and its antifungal properties. Han Y examined the antifungal effects of GSE both alone and in combination with amphotericin B against disseminated candidiasis in bagg albino/c female mice at the age of 6-7 weeks. The findings of this investigation 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 have a substantial antifungal action against candida species other than *candida albicans* [23].

Antiviral properties: The GSE has been shown to have antiviral effects against a variety of viral infections. The flavonoid components of GSE were characterised as considerably dose-dependently down regulating the expression of the Human Immunodeficiency Virus-1 (HIV-1) entrance coreceptor. This indicates that flavonoid may inhibit HIV virus from attaching to the cell receptor and 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 the Hepatitis A Virus (HAV; strainmHM175), bacteriophage MS2 and murine norovirus 1. After two hours at 37°C, these viruses' high titers were dose-dependently reduced by the GSE [25]. Resveratrol is a non flavonoid polyphenolic compound present at high concentration in grapeseed. It is known to have strong bioactivity and cytoprotective action and at high concentration it has antiproliferative action. Resveratrol has been shown to be effective against a variety of double stranded and single stranded viruses. Resveratrol's antiviral properties make it a viable alternative for inhibiting viral pathogen proliferation. It has been claimed that resveratrol works well as an antiviral agent against a variety of viruses, including influenza virus, Herpes Simplex Virus (HSV), varicella zoster virus and polyomavirus [26].

Antitumour property: In order to determine whether resveratrol prevents cancer, Aluyen JK et al., conducted a study in which resveratrol has shown to demonstrate different mechanisms to induce its chemoprotective effects. One of them is to make malignant cells undergo apoptosis. Caspase facilitates planned cell death by activating apoptotic pathways. A decreased level of caspase is often directly associated to the prevention of apoptosis in carcinogenesis. Researchers examined that resveratrol is effective in stopping or reducing cellular growth by triggering apoptosis in an in-vivo study that examined colorectal cancer in rats. Proapoptotic, antiproliferative, and antiinflammatory pathways are the three main mechanisms of resveratrol. Therefore, it appears that resveratrol has anticancer properties [27]. In-vitro as well as in-vivo studies by Zhang XY et al., examined the anticancer effects by combining PA and doxorubicin. In-vitro, 12.5-100 mg/L PA reduced proliferation of A549 CNE and K562 cells in a concentration and time dependent manner. These findings suggest that PA increases 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 cell cycle and have anticancer properties [29]. Cytotoxic properties against tumour cells while being safe for healthy cells [30]. Flavan-3-ol polymers called PA have an impact on cancer cells that prevents their proliferation [31]. Biomedical research could be revolutionised by the advancement of phytochemicals in nanodosage forms, which is why grapeseed oil has been studied as a nanocarrier for treatment of cancer. Two tumour cell lines, the Henrietta Lacks (HeLa) and M.D. Anderson-Metastatic Breast 231 (MDA-MB 231) cell lines, and two healthy cell lines, the B16 and L929 cell lines, were used to compare the efficiency of lipid nanocarriers derived from natural oils (laurel leaf oil and grapeseed oil) in scavenging free radicals and thwarting specific tumour cells. The ability of scavenging around 98% of O2 free radicals was demonstrated in this experiment using nanocarriers made from a mixture of laurel leaf and grapeseed oils with a dosage of 5 mg/mL, tumour cell growth was significantly reduced even in the absence of an anticancer drug. A 20% mortality rate was seen for normal B16 cells as compared to a 40% death rate for tumour HeLa cells and MDA-MB 231 when the survival profiles of healthy and tumour cells treated to a dosage of 2.5 mg/mL lipid nanocarriers were compared. Consequently, lipid nanocarriers made from laurel leaf oil and grapeseed oil may be used to reduce the toxicity and increase the therapeutic efficacy of anticancer medicines in clinical applications [32]. The anticancer activity displayed by nanocarriers, which is the result of complex cellular events and processes, may, in the opinion of some scientists, 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 etc.,) [32,33].

Role of Grapeseed Extract (GSE) in Oral Health

Antibiofilm properties: Using the method outlined by Ooshima T et al., it was possible to ascertain how the grape extract affected acid production. A 1 cc of *S. mutans* was planted in 100 mL of red phenol broth enriched with the extract and 1% glucose. At regular intervals, a sample (4 mL) of the culture was taken and its pH was recorded with a pH metre. This was incubated at 37°C in a microaerophilic environment. Result demonstrated the drop of pH value from 6.5 to 3.0 (highly acidic) due to the bacterial growth and acid production

has been seized in the presence of epicatechin treatment to the pH value 4.8 [20]. *S.mutans'* biofilm formation and planktonic development were both reduced by the GSE at a concentration of 4 mg/mL. Additionally, a dose-dependent antibiofilm action of grapeseed opposed to *S. mutans* was discovered in alleviation of simulated enamel lesions at subminimal inhibitory concentration levels [21]. GSE has a dose-dependent inhibitory impact on the production of biofilm. The strongest antibiofilm action in opposed to multispecies biofilm producers, including *F.nucleatum, P.gingivalis*, Streptococcus sobrinus, Actinomyces viscosus, and Lactobacillus rhamnosus was demonstrated by GSE at a concentration of 2000 mg/ml (sub-MBC values). Higher quantities in this extract reduced its efficacy, mostly 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. Reactive Nitrogen Species (RNS) and ROS, which are necessary for effective defence against invading pathogens, are produced when macrophages are stimulated by bacteria or their components. Oxidative stress, which is brought on by elevated ROS/RNS levels, destroys bone and tissue. To investigate the effect of PAs on production and accumulation of NO2-, the stable metabolite of NO, in the culture media of Lipopolysaccharide (LPS) stimulated macrophages using the Griess colorimetric assay was measured. The basal level of NO released from unstimulated RAW 264.7 macrophages was estimated at 4 µM. Stimulation of macrophages with LPS of *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 blocked the induction of NO2– generation. At non toxic concentrations, the capacity of GSE to inhibit NO production by macrophages stimulated with LPS of *A.actinomycetemcomitans* and *F.nucleatum* was, respectively, 62% and 50% of the LPS-stimulated but untreated cells [35].

Grapeseed Extract (GSE) on shear bond strength: The use of primers, which are bifunctional molecules, is one method used to increase the longevity of the resin-dentin bonded contact. An essential component of contemporary bonding agents is primer [36]. Collagen crosslinkers have been found to be effective at strengthening collagen based biomaterials because they help to form new cross links both within and between the intricate collagen mesh. Additionally, they have been discovered to strengthen the contact between dentin and composite resin [37]. PA establishes hydrogen, covalent, or ionic bonds with proteins. In solitary settings, collagen would not be able to retain its triple helix shape without the association between dentin collagen and PA [38]. At the resin-dentin contact, PA has been discovered to be resistant to enzymatic degradation [39]. According to the experiment performed by Khan SA et al., study was done to determine the effect of experimental primer containing collagen cross linker in improving the shear bond strength of tooth coloured resin restorations. Shear bond strength was determined with universal testing machine. The specimens were positioned one by one in a custom made metal jig. The results showed that, after application of 6.5% PA primer for one minute the shear bond strength of group B (10.37MPa) was higher than shear bond strength of group A (7.78MPa). The mode of fracture was assessed with electronic zoom microscope for every specimen [40]. PA can be cross-linked in a variety of ways, including as ionic, covalent, hydrogen and hydrophobic interactions [41].

Remineralisation: PAs may be found in large amounts in GSE, it has been demonstrated to improve collagen by promoting collagen cross-links [42]. Furthermore, studies have shown PAs expedited the process by which soluble collagen turns into insoluble during development. Collagen matrices treated with PA were shown in, in-vitro and in-vivo studies to be safe and resistant to enzyme degradation [43]. Xie Q et al., used an in-vitro pH cycling model to evaluate the effect of GSE on the remineralisation of artificial root caries. After pH cycling mineral precipitation band was observed on superficial surface of both the groups. Advance demineralisation band was seen on the surface due to acid challenge during pH cycling. The results showed that a significantly wider mineral precipitation band was observed in the GSE treated group when compared to those of fluoride and control groups [2].

Grapeseed Compounds and Bioactivity

The three most prevalent ROS are hydrogen peroxide, superoxide and hydroxyl radicals. The purpose of the physiological production of these ROS is to serve as signalling molecules for the immune system and homeostasis management. Oxidative stress, which is linked to oxidative stress-related disorders including type 2 diabetes mellitus, cancer, cardiovascular and pulmonary diseases and degenerative illnesses, is caused by an imbalance between antioxidants and ROS that is caused by excessive ROS production. Antioxidant enzymes including, superoxide dismutase, glutathione peroxidase and catalase, are responsible for controlling this process [44-46]. As a result, grape and its by-products include a variety of phenolic compounds, including resveratrol, quercetin, procyanidins, and others, that have antioxidant and antiinflammatory properties [47]. Polyphenolic contents of grapeseed has been illustrated in [Table/Fig-2] [46,48-50]. Various studies about grapeseed have been tabulated in [Table/Fig-3] [14,17,18,51,52].

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

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

Safety Doses

The GSE is available commercially as a dietary supplement and is included 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 usual dosage of GSE utilised in food applications ranged from 0.01-1%, and the No-Observed-Adverse Effect Level (NOAEL) of grapeseed extracts in the rats was 1.78 g/kg body weight/day [53]. According to Sano A et al., participants' physiological and clinical laboratory tests did not show any unexpected changes on taking tablets containing 200 mg and 400 mg GSE. The fact that none of these people's urine sedimentation tests returned any unfavourable results is another proof that consuming GSE tablets in dosages of 200 mg and 400 mg is safe [54]. GSE has a lethal dose of greater than 4000-5000 mg/kg in rats. In contrast to the modest concentrations (0.01-10%) used in the food industry, GSE may be helpful at therapeutic doses of 150-300 mg/day [55]. The cytotoxicity of the epicatechin derivatives in the two cell lines was equivalent 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 considerably increased in mouse spleen cells. For instance, 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 all over the world. It is also very popular because of its cost-effectivity. It contains variety of useful contents and useful polyphenols. These polyphenols are very useful in medicinal purposes and has wide

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

range of uses in healthcare sector. Grapeseed has antibacterial, antifungal, anticariogenic and has remineralising properties. Grapeseed has proved to be effective in maintaining overall general health. Hence, it can be concluded that grapeseed can be included in oral hygiene maintenance and treatment due to its properties.

REFERENCES

[1] Mirkarimi M, Eskandarion S, Bargrizan M, Delazar A, Kharazifard MJ. Remineralisation of artificial caries in primary teeth by grape seed extract: An in-vitro study. J Dent Res Dent Clin Dent Prospects. 2013;7(4):206.
[2] Xie Q, Bedran-Russo AK, Wu CD. In-vitro remineralisation effects of grape seed extract on artificial root caries. J Dent. 2008;36(11):900-06.
[3] Haffajee AD, Socransky SS. Microbiology and immunology of periodontal disease. Periodontol 2000. 1994;5(78):111.
[4] Van Dyke TE, Lester MA, Shapira L. The role of the host response in periodontal disease progression: implications for future treatment strategies. J Periodontol.1993;64:792-806.
[5] Epple M, Meyer F, Enax J. A critical review of modern concepts for teeth whitening. Dent J (Basel). 2019;7(3):79.
[6] Slater TF, Cheeseman KH, Davies MJ, Proudfoot K, Xin W. Free radical mechanisms in relation to tissue injury. Proc Nutr Soc. 1987;46(1):01-02.
[7] Pendyala G, Thomas B, Kumari S. The challenge of antioxidants to free radicals in periodontitis. J Indian Soc Periodontol. 2008;12(3):79.
[8] Åsman B, Wijkander P, Hjerpe A. Reduction of collagen degradation in experimental granulation tissue by vitamin E and selenium. J Clin Periodontol. 1994;21(1):45-47.
[9] Hotwani K, Baliga S, Sharma K. Phytodentistry: Use of medicinal plants. J Complement Integr Med. 2014;11(4):233-51.
[10] Giraudi M, Romano F, Aimetti M. An update on herbal antiinflammatory agents in periodontal therapy. Clinical Anti-Inflammatory & Anti-Allergy Drugs (Discontinued). 2015;2(1):27-37.
[11] Cheng L, Li J, Hao Y, Zhou X. Effect of compounds of Galla chinensis on remineralisation of enamel surface in-vitro. Arch Oral Biol. 2010;55(6):435-40.
[12] Park JS, Park MK, Oh HJ, Woo YJ, Lim MA, Lee JH, et al., Grape-seed proanthocyanidin extract as suppressors of bone destruction in inflammatory autoimmune arthritis. PLoS One. 2012;7(12):e51377.
[13] Gunjima M, Tofani I, Kojima Y, Maki K, Kimura M. Mechanical evaluation of effect of grape seed proanthocyanidins extract on debilitated mandibles in rats. Dent Mater J. 2004;23(2):67-74.
[14] Jain S, Mohan R, Singh Y, Rai R, Sharma V, Mehrotra S. Medicinal value of grape seed extracts: A review. World J Pharm Res. 2014;3(2):3036-43.
[15] Bagchi D, Garg A, Krohn RL, Bagchi M, Bagchi DJ, Balmoori J, et al. Protective effects of grape seed proanthocyanidins and selected antioxidants against TPA-induced hepatic and brain lipid peroxidation and DNA fragmentation, and peritoneal macrophage activation in mice. Gen Pharmacol. 1998;30(5):771-76.
[16] Baydar NG, Sagdic O, Ozkan G, Cetin S. Determination of antibacterial effects and total phenolic contents of grape (Vitis vinifera L.) seed extracts. Int J Food Sci. 2006;41(7):799-804.
[17] Montealegre RR, Peces RR, Vozmediano JC, Gascueña JM, Romero EG. Phenolic compounds in skins and seeds of ten grape Vitis vinifera varieties grown in a warm climate. J Food Compos Anal. 2006;19(6-7):687-93.
[18] Katalinić V, Možina SS, Skroza D, Generalić I, Abramović H, Miloš M, et al. Polyphenolic profile, antioxidant properties and antimicrobial activity of grape skin extracts of 14 Vitis vinifera varieties grown in Dalmatia (Croatia). Food Chem. 2010;119(2):715-23.
[19] Jayaprakasha GK, Selvi T, Sakariah KK. Antibacterial and antioxidant activities of grape (Vitis vinifera) seed extracts. Int Food Res J. 2003;36(2):117-22.
[20] Ooshima T, Osaka Y, Sasaki H, Osawa K, Yasuda H, Matsumura M, et al. Caries inhibitory activity of cacao bean husk extract in in-vitro and animal experiments. Arch Oral Biol. 2000;45(8):639-45.
[21] Zhao W, Xie Q, Bedran-Russo AK, Pan S, Ling J, Wu CD. The preventive effect of grape seed extract on artificial enamel caries progression in a microbial biofilm-induced caries model. J Dent. 2014;42(8):1010-18.
[22] Han Y. Synergic effect of grape seed extract with amphotericin B against disseminated candidiasis due to Candida albicans. Phytomedicine. 2007;14(11):733-38.
[23] Simonetti G, D'Auria FD, Mulinacci N, Milella RA, Antonacci D, Innocenti M, et al. Phenolic content and in-vitro antifungal activity of unripe grape extracts from agro-industrial wastes. Nat Prod Res. 2019;33(6):803-07.
[24] Nair MP, Kandaswami C, Mahajan S, Nair HN, Chawda RA, Shanahan T, et al. Grape seed extract proanthocyanidins downregulate HIV-1 entry coreceptors, CCR2b, CCR3 and CCR5 gene expression by normal peripheral blood mononuclear cells. Biol Res. 2002;35(3-4):421-31.
[25] Su X, D'Souza DH. Grape seed extract for control of human enteric viruses. Appl Environ Microbiol. 2011;77(12):3982-87.
[26] Berardi V, Ricci F, Castelli M, Galati G, Risuleo G. Resveratrol exhibits a strong cytotoxic activity in cultured cells and has an antiviral action against polyomavirus: potential clinical use. J Exp Clin Cancer Res. 2009;28(1):01-07.
[27] Aluyen JK, Ton QN, Tran T, Yang AE, Gottlieb HB, Bellanger RA. Resveratrol: Potential as anticancer agent. J Diet Suppl. 2012;9(1):45-56.
[28] Zhang XY, Bai DC, Wu YJ, Li WG, Liu NF. Proanthocyanidin from grape seeds enhances anti-tumour effect of doxorubicin both in-vitro and in-vivo. Die Pharmazie- Int J Pharm Res. 2005;60(7):533-38.
[29] Huang S, Yang N, Liu Y, Gao J, Huang T, Hu L, et al. Grape seed proanthocyanidins inhibit colon cancer-induced angiogenesis through suppressing the expression of VEGF and Ang1. Int J Mol Med. 2012;30(6):1410-16.
[30] Engelbrecht AM, Mattheyse M, Ellis B, Loos B, Thomas M, Smith R, et al. Proanthocyanidin from grape seeds inactivates the PI3-kinase/PKB pathway and induces apoptosis in a colon cancer cell line. Cancer lett. 2007;258(1):144-53.
[31] Li AN, Li S, Zhang YJ, Xu XR, Chen YM, Li HB. Resources and biological activities of natural polyphenols. Nutrients. 2014;6(12):6020-47.
[32] Liu RH. Potential synergy of phytochemicals in cancer prevention: Mechanism of action. J Nutr. 2004;134(12):3479S-85S.
[33] Husein AI, Ali-Shtayeh MS, Jondi WJ, Zatar NA, Abu-Reidah IM, Jamous RM. In-vitro antioxidant and antitumor activities of six selected plants used in the Traditional Arabic Palestinian herbal medicine. Pharm Biol. 2014;52(10):1249-55.
[34] Gottaslo R, Salahi B. Effects of oxygen on in-vitro biofilm formation and antimicrobial resistance of Pseudomonas aeruginosae. Pharm Sci. 2013;19(3):96-99.
[35] Houde V, Grenier D, Chandad F. Protective effects of grape seed proanthocyanidins against oxidative stress induced by lipopolysaccharides of periodontopathogens. J Periodontol. 2006;77(8):1371-79.
[36] Nezu T, Nishiyama N, Nemoto K, Terada Y. The effect of hydrophilic adhesive monomers on the stability of type I collagen. Biomaterials. 2005;26(18):3801-08.
[37] Bedran-Russo AK, Pauli GF, Chen SN, McAlpine J, Castellan CS, Phansalkar RS, et al. Dentin biomodification: Strategies, renewable resources and clinical applications. Dent Mater. 2014;30(1):62-76.
[38] He L, Mu C, Shi J, Zhang Q, Shi B, Lin W. Modification of collagen with a natural cross-linker, procyanidin. Int J Biol Macromol. 2011;48(2):354-59.
[39] Liu Y, Wang Y. Proanthocyanidins' efficacy in stabilizing dentin collagen against enzymatic degradation: MALDI-TOF and FTIR analyses. J Dent. 2013;41(6):535-42.
[40] Khan SA, Khalid S, Rafique A, Khalid H. Effect of grape seed extract on shear bond strength at resin-dentin interface. J Pak Dent Assoc. 2017;37(1):152-57.
[41] Al-Ammar A, Drummond JL, Bedran-Russo AK. The use of collagen cross-linking agents to enhance dentin bond strength. J Biomed Mater Res B Appl Biomater Part B: Applied Biomaterials. 2009;91(1):419-24.

[42] Bedran-Russo AK, Pereira PN, Duarte WR, Drummond JL, Yamauchi M. Application of crosslinkers to dentin collagen enhances the ultimate tensile strength. J Biomed Mater Res B Appl Biomater: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials. 2007;80(1):268-72.
[43] Han B, Jaurequi J, Tang BW, Nimni ME. Proanthocyanidin: A natural crosslinking reagent for stabilizing collagen matrices. J Biomed Mater Res A, An Official Journal of the Society for Biomaterials, the Japanese Society for Biomaterials, and the Australian Society for Biomaterials and the Korean Society for Biomaterials. 2003;65(1):118-24.
[44] Alfadda AA, Sallam RM. Reactive oxygen species in health and disease. J Biotechnol Biomed. 2012;2012:936486.
[45] Raaz U, Toh R, Maegdefessel L, Adam M, Nakagami F, Emrich FC, et al. Hemodynamic regulation of reactive oxygen species: implications for vascular diseases. Antioxidants and Redox Signaling. 2014;20(6):914-28.
[46] Hernandez-Jimenez A, Gomez-Plaza E, Martinez-Cutillas A, Kennedy JA. Grape skin and seed proanthocyanidins from Monastrell× Syrah grapes. J Agric Food Chem. 2009;57(22):10798-803.
[47] Xia EQ, Deng GF, Guo YJ, Li HB. Biological activities of polyphenols from grapes. Int J Mol Sci. 2010;11:622-46.
[48] Pastrana-Bonilla E, Akoh CC, Sellappan S, Krewer G. Phenolic content and antioxidant capacity of muscadine grapes. J Agric Food Chem. 2003;51(18):5497-503.
[49] Bell JR, Donovan JL, Wong R, Waterhouse AL, German JB, Walzem RL, et al., (+)-Catechin in human plasma after ingestion of a single serving of reconstituted red wine. Am J Clin Nutr. 2000;71:103-08.
[50] Huang D, Ou B, Prior RL. The chemistry behind antioxidant capacity assays. J Agric Food Chem. 2005;53:1841-56.
[51] Guo L, Wang LH, Sun B, Yang JY, Zhao YQ, Dong YX, et al. Direct in-vivo evidence of protective effects of grape seed procyanidin fractions and other antioxidants against ethanol induced oxidative DNA damage in mouse brain cells. J Agric Food Chem. 2007;55(14):5881-91.
[52] Vinson JA, Mandarano MA, Shuta DL, Bagchi M, Bagchi D. Beneficial effects of a novel IH636 grape seed proanthocyanidin extract and a niacin-bound chromium in a hamster atherosclerosis model. Mol Cell Biochem. 2002;240(1):99-103.
[53] Bentivegna SS, Whitney KM. Subchronic 3-month oral toxicity study of grape seed and grape skin extracts. Food Chem Toxicol. 2002;40(12):1731-43.
[54] Sano A, Uchida R, Saito M, Shioya N, Komori Y, Tho Y, et al. Beneficial effects of grape seed extract on malondialdehyde-modified LDL. J Nutr Sci Vitaminol (Tokyo). 2007;53(2):174-82.
[55] Perumalla AV, Hettiarachchy NS. Green tea and grape seed extracts-Potential applications in food safety and quality. Int Food Res J. 2011;44(4):827-39.
[56] Fan P, Lou H. Effects of polyphenols from grape seeds on oxidative damage to cellular DNA. Molecular and Cellular Biochemistry. 2004;267(1):67-74.

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**