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Grape- A Potent Oral Health Beneficial Agent Oral Health Care

Dr. Keerthi Narayan. V
Senior lecturer
Oral and Maxillofacial Pathology and Microbiology
Thai Moogambigai dental college and hospital
Chennai- 600107

Dr. Vidhyadharan
Bachelor of dental surgery
Thai Moogambigai dental college and hospital
Chennai-600107

Abstract:- In dental scenario natural products have been in practice for management of oral or tooth infections for more than thousands of years. Pathogenic bacteria's found along with the normal microflora commensals are the primary etiologic agents for oral diseases such as dental caries, periodontal disease, tooth mobility or even tooth loss. It is well known that Oral infections are prevalent in majority of the population that can directly alter individuals' general health status. Fruits of Vitis vinifera contain higher quantity of polysaccharides, proanthocyanins, organic and inorganic acids, salts and vitamins. Because of its nutritional and medicinal benefits especially in the oral cavity many experiments have been carried out over the years. Today, most grapes are consumed as dried form popularly known as raisins that contain polyphenols, flavonoids, potassium, magnesium, iron and vitamins B complexes. It is postulated that raisins comprise antibacterial phytochemicals effectively in suppressing pathogenic oral microbes associated with caries or gingival diseases than the normal flora microbes thereby promoting gingival and periodontal health. Polyphenolics, a chief component of grape seed retain innumerable effective biological properties such as anticancerous, antimicrobial, inhibitory effects against viruses, enzymes and also reduces inflammation. However, their advantages in improving the oral health are understood. The present review article focuses on various chemical compositions, its mechanism of beneficiary effects on human body and its prevention or therapeutic role on oral diseases.

Keywords:- *Vitis Vinifera; Grape Seeds; Flavanol Monomers; Proanthocyanidins; Flavonols; Hydroxyl Benzoic Acid Derivatives; Dental Plaque.*

I. INTRODUCTION

Vitis vinifera L belonging to class Vitaceae popularly known as Grape, grows in pools of twenty to two hundred in numbers of varying colours such as black, cherry, green, dusky blue. Grapes skin, specifically of the red and black species, a derived of stilben is rich in resveratrol. Today, most grapes are used as dried form popularly known as raisins that are made from seedless grapes contains polyphenols, flavonoids, minerals, inorganic salts such as iron, potassium, calcium, magnesium along with vitamin B complexes every so often benefit general as well as oral health of an individual. These are ideal source of fiber consisting of more than 60% monosaccharide than polysaccharide by concentration and their sugary sensation is mainly by glucose and fructose.

Extract of grape seed (GSE) is made of nearly two-thirds about 70- 90% of procyanidins, a potent antioxidant and scavenger for free radicals. Phenols, the third richest constituent present 5 to 8 % by weight followed by monosaccharide and acidic elements. The total refinable phenolics in grapes exist only about 10 % or less in the pulp, 40–70 % in the seeds and 25–35 % in the skin. About 90 – 95% of phenolic compounds from homogenous grape seed extracts are oligomeric proanthocyanidins. Proanthocyanidin structures vary based on the derivatives of flavanols building single compound or monomeric units, the degree of oligomerization and the occurrence of methylations, esterification of the 3-hydroxyl group whereas anthocyanins are usually either mono or diglycerides [1, 2].

Other phenolic compounds such as flavanols, flavonols, stilbenes and phenolic acids are also seen in grape seed extract. These phenolics, largely dispersed in varying distribution in seeds, skin are antioxidant and free radical scavenging showing anticariogenic, antibacterial, Immunomodulatory, Antitumoral property and also show hypoglycemic and hepatoprotective activity. Cholesterol and fat-free high in antioxidants are also detected in grapes. [2, 3]

Epicatechin, Catechin and taxifolin are the principal flavanols found in grape seeds and encompass the wide-ranging of the residual phenols in grape seed extracts. The Oligomeric proanthocyanidins under heat and acidic conditions releases anthocyanins, in turn produces flavanols. The extraction techniques vastly influence the chain of oligomeric proanthocyanidins and the concentration of flavanols in grape seed extracts. A small volume of residual sulphur dioxide may be present following aqueous method of grape seed extraction. [3, 4]

Melatonin (N-acetyl-5-methoxytryptamine) present in grapes ranged from 0.005-1.2 nanogram per gram. The phase of growth, variety and location plays a vital role in determining levels of melatonin in grape skin. Recent studies have also shown that presence of melatonin in the grape flesh and seeds.

II. BENEFICIAL EFFECTS

Naturopathic medicine or alternative medicine of ampelotherapy known as grape therapy comprises of heavy ingesting of grapes, including seeds, skin and parts of the flesh, including leaves. It has been well-known that free radicals play an important role in pathogenesis of cancer, diabetes, cardiovascular diseases, autoimmune disorders, neurodegenerative diseases. Grape seeds show potential reducing activity 50 times more than vitamins C and E. These are efficient and effective antioxidants that prevent damage of vital substances like lipids, proteins, enzymes, and carbohydrates by binding with free radicals. They are also effective against nephrotoxicity caused due to over dosage or long term consumption of antibiotics. [4, 5, 6, 7]

III. GRAPES- AS A IMMUNOMODULATORS

Grape seed extracts principally due to its proanthocyanidin (PA), a naturally occurring polyphenol compound obtained from Vitis vinifera seeds have been suggested as a favourable immunomodulator agent shows extensive range of biological activities such as antioxidation. Seed extract intensely inhibit osteoclast differentiation, decreased osteoclast activity, and stimulate bone formation through its synergistic action on osteoblast in treatment of inflammation associated with bone destruction or bone damage caused due to bacterial or immune suppressing agents, influence by modifying the balance between osteoblasts and osteoclasts through regulating their release and gene expression. [7, 8]

Various immunopathological conditions are associated with inflammation. Several finding proposes that Resveratrol is one of the resilient known natural antioxidants presenting at a maximum quantity in black grape juice, skin, and seed. Resveratrol, reserved phorbol myristate acetate is associated with ester-mediated induction of COX-2 in human secretary mammary glands cells. It shows anti-inflammatory and immuno-modulatory action. It also inhibited phorbol myristate acetate-mediated activation of protein kinase C [9]

Effect on the immune system by resveratrol can be mediated by various mechanisms such as Induction of CD95 signaling-dependent apoptosis, inhibition of COX, modulatory activation of nuclear factor kB (NF-kB) or by direct effects on cell cycle specifically on G1 phase. Resveratrol along with quercetin have been known for its anti-inflammatory action. They inhibit the release of interleukin (IL)-8 and granulocyte-macrophage colony stimulating factors (GMC-SF) by acting on A549 cells thereby aiding in the treatment of systemic inflammatory disease involving skin and mucosa such as lupus erythematous. Resveratrol also inhibits cytokine-stimulated nitric oxide (NO) synthase production, expressed in human primary respiratory epithelial cells. On combination of resveratrol and quercetin a significant increase in the phagocytosis rate on the human promonocytic cell line was observed whereas other polyphenols demonstrated the pro-intraphagocytic effect, cytostatic activity on U937 cell growth [5, 9, 10]

Pro-inflammatory cytokines play a vital role in malnutrition and cardiovascular disease (CVD). In patients with chronic or end stage kidney diseases there is a significant increase in C-reactive protein (CRP), interleukin 6 (IL-6), interleukin β (ILβ) and tumor necrosis factor (TNF-α). The level of CRP and pro-inflammatory cytokines like ILβ, IL8, IL1, and TNF-α are predictive factors for mortality in the End stage renal disease population. The proanthocyanidin in the grape seed induce production of endothelial growth factor VEGF in human keratinocytes [11, 12]

Many studies proved that procyanidins and other polyphenolics from grape seed act as reducing agents by various mechanisms. The phenolic compounds acts directly on the cells by free radicals tracking, by chelating or by donating hydrogen, and by rapid or slow quenching singlet oxygen responsible for various antioxidant effects on human health.

Studies also have shown that proanthocyanidins have pro-active effects against tumor/cancer, cardiac disease, and aging by inhibiting malignant cell growth or proliferation, delaying cardiac cell death, and maintaining membrane integrity as cells proceed to senescence. The health-promoting properties of anthocyanins includes antinflammatory action on the blood vessels and reduction of platelet coagulability or clotting formation, which may reduce risks of developing atherosclerosis, an initial step in cardiovascular disease. Mutations in two controlling genes of white grapes decreases or hinders the production of anthocyanins and other pigment chemicals of polyphenols, the causative agents for the color of dusky purple grapes and grape seeds [12, 13].

Similarly grape seed extract or skin extract contains Flavonoids or proanthocyanidins, proven antioxidants also demonstrated to have antiulcer activity. They decreased the volume of gastric total or free acid content volume by anti-secretory mechanism thereby reducing the number of ulcers and ulcer index. A higher dosage of 180-200mg/kg extract of seed showed maximum activity and efficacy as an antiulcer drug [14].

IV. ROLE IN ORAL DISEASES

The efficacy and related mechanism of grape seed extract in both cell culture and nude mice xenografts were studied. The mechanistic insights were found and identified that GSE ability to act selectively by translational potential against Head and neck squamous cell carcinoma (HNSCC) both in cell culture and mouse xenograft. The above study supports black grape has anticancer effects specifically against HNSCC by targeting both specific DNA destruction/loss or damage and repair. Several studies illustrated grape and its seed have shown optimum controlling effect on malignant proliferative cell formation and development. The efficacy of GSE to counteract the

redox and bioenergetic alterations in HNSCC cells was also investigated. Surprisingly it was found that GSE targets Electronic transfer chain complex (ETC- III) and induces oxidative and metabolic stress, thereby, causing auto cell lysis and programmed cell death in HNSCC cells.

The efficacy of procyanidin present in grape seed (GSP) shows antiproliferative effects related to the tumor suppressor gene p53 functional status or at TP53 of oral squamous cell carcinoma (OSCC) signifying its chemo adjuvant potential. Conclusions suggest that GSP may play a role as a unique chemopreventive or therapeutic agent for OSCC [15, 16].

Oral diseases or conditions can affect a person's general health and are the foremost cause of illness and have harmed economic productivity and learning ability. Orofacial or temporo-mandibular disorders, pulp and periapical lesions, periodontal diseases results in pain and difficulty in speaking, masticatory, loss of tooth and in extreme cases such as cellulitis, ludwig's angina may even lead to death. Recent research has shown that focal infection by bacteria from oral cavity may contribute to increased risk of infective endocarditis, heart attacks, strokes, and lung disease and may be correlated to premature childbirth in certain women population.

Dental plaque plays a crucial role either directly or indirectly in the pathogenesis of dental caries. Plaque is a universal term for the diverse microbial or bacterial community initiated on the tooth surface, rooted in a matrix of polymers of bacterial and salivary source originated in particular at protected and immobile surfaces are well known to be at the greatest risk of disease. A wide range of beneficiary action was observed in grape seed extract when used as a dietary supplement by the presence proanthocyanidin which provides the antibacterial or antimicrobial activity on the tooth surface when used systemically or orally. It has a greater action towards free radical scavenging, on comparison to other antioxidant substances or vitamins. [17].

Acidogenic properties of raisins and bran cereal on in vivo plaque among young children were investigated by Utreja et al. it was observed that in the plaque pH of young children consuming raisins or raisin-containing cereals without added sugar were significantly lower than the cereals without raisins. Terra et al reported that the decrease in plasma C- reactive protein (CRP) is related to a down-regulation of CRP mRNA expression in the hepatic and mesenteric white adipose tissue (WAT) due to procyanidin, a key component in grape seed extract on the inflammatory mediators in rat fed with a high-fat diet. A decline in the expression of the proinflammatory cytokine tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) was also observed [18].

Procyanidin showed increased adiponectin expression and decreased IL-6, reduced expression of epidermal growth factor module-containing mucin-like receptor 1 (EMR1) (a specific marker of macrophage F4/80). IL-6, a stress-induced inflammatory cytokine in association with EMR1 directly implicate in atherogenesis and also play a key role in reduced macrophage infiltration of WAT. Routine intake of food containing procyanidins especially grapes, influence directly on the macrophage accumulation in WAT and abnormal cytokine production hence preventing low-grade inflammatory-related diseases in obese patients [19].

Proanthocyanidins in grape seed extract presenting at a maximum concentration in considerably exaggerated the in vitro demineralization and/or remineralization of root caries lesions by topical application or by oral dietary supplements signifying a favourable natural agent for non-invasive root caries therapy. Xie et al in his studies observed significant effect of GSE on the remineralization and demineralization of highly collagenous dentin and pulp. Several similar studies on PA have also shown its potential role in increased collagen fibre synthesis and conversion of soluble collagen to insoluble collagen during collage extracellular synthesis pathway. Collagen matrices treated with these proanthrocyanins were demonstrated to be innocuous and inactive against enzyme digestion in vitro and in vivo [20].

V. SAFETY DOSAGE FOR CONSUMPTION OR ORAL USE

It was recommended that young adults can consume from 25 to 150 mg of either extract in dry or other forms, twice or thrice daily to boost antioxidant activity. A maximum tolerable dose of 850-900 mg/day has been recommended in the present available usage forms. A high-quality extract that is standardized to 40 to 70% proanthocyanidins or not less than a 90% was found to be adequate in its anti-inflammatory activity and also for treating conditions such as chronic venous insufficiency. No standard oral dosage form has been formulated yet.

VI. CONCLUSION

Grape seeds owing to its high antioxidant, anti-inflammatory, anticancerous, anticarious potential show various prospective health benefits include protection against oxidative damage, diabetes; cholesterol induced cardiovascular diseases or disorder, oral cancer and other related diseases in oral cavity. Bioactivities of polyphenols present in grape seeds are found to play a substantial role in health benefits. Though the outcomes from the present review are fairly encouraging for the use of Grape either as seed or skin/extracts as a therapeutic agent, several limitations currently exist such as dosage form, component form, and route of administration in the current literature. An effect-outcome relationship between the intake of grape seed either orally or systematically with dietary supplements and its health effects can only be obtained by conducting studies invivo and invitro at larger scale to properly standardize and categorize the composition of grape seeds. Grape seed though have several limitations still been used successfully in Ayurvedic medicine for centuries. Hence more clinical trials must be conducted to

support the beneficial and therapeutic use of this naturally available fruit.

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