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REVEALING THE MIRACLE: GRAPE SEED

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ABSTRACT

Grapes have been commonly used in various fields since the ancient Greek and Roman civilizations. Grape seeds are waste products of the winery and grape juice industry. These seeds contain lipid, protein, carbohydrates, and 5–8% polyphenols depending on the variety. Grape seeds contain mainly phenols such as proanthocyanidins (oligomeric proanthocyanidins). Polyphenols in grape seeds are mainly flavonoids, including gallic acid, the monomeric flavan-3-ols catechin, epicatechin, gallocatechin, epigallocatechin, and epicatechin 3-O-gallate, and procyanidin dimers, trimers, and more highly polymerized procyanidins. Grape seed extract is known as a powerful antioxidant that protects the body from premature aging, disease, and decay. Research suggests that grape seed extract is beneficial in many areas of health because of its antioxidant effect to bond with collagen, promoting youthful skin, cell health, elasticity, and flexibility. Other studies have shown that proanthocyanidins help to protect the body from sun damage, to improve vision, to improve flexibility in joints, arteries, and body tissues such as the heart, and to improve blood circulation by strengthening capillaries, arteries, and veins. This review summarizes the phytochemical constituents, pharmacological activities, and various applications of grape seeds.

KEYWORDS: Grape seed extract (GSE), Polyphenols, Proanthocyanidins, Flavanoids.

INTRODUCTION

Grapes being one of the most highly consumed fruit across the world, has been used in traditional treatment for ages in ancient Europe. The grape (Vitis vinifera), a member of the Vitaceae family has got various kinds like wine grapes, table grapes, seedless, edible seed, and raisin grapes. Grape marc and especially the seeds in former times were only waste, nowadays the seeds have come more and more into the focus of interest. The seeds constitute about 20% of the fruit weight, and calculated on the dry material, the part of the seeds is about 40–60%. Besides being a wellspring for vitamins and fibre, the skin and seeds of grapes are highly rich in Polyphenols which can be used as a functional ingredient to address various health issues by boosting the natural bio-processes of the body.[1]

Phenolics are broadly distributed in the plant kingdom and are the most abundant secondary metabolites found in plants. All phenolic compounds possess an aromatic ring bearing one or more hydroxyl group. Phenols represent the third most abundant constituent in grapes and wines after carbohydrates and fruit acids. Scientific studies have shown that the antioxidant power of proanthocyanidins is 20 times greater than vitamin E and 50 times greater than vitamin C.[2] Extensive research suggests that grape seed extract is beneficial in many areas of health because of its antioxidant effect to bond with collagen, promoting youthful skin, cell health, elasticity, and flexibility.

Hence, grape seeds have a potential to substitute or complement in currently used drugs in the treatment of diseases by developing it into other successful pharmaceutical formulations for better future prospective. Thus, the aim of this review is to summarize the phytochemical constituents, pharmacological activities, and various applications of grape seeds.

Taxonomy

Kingdom	**Plantae**
Division	Magnoliophyta
Class	Magnoliopsida
Order	Vitales
Family	Vitaceae
Genus	Vitis
Species	V. vinifera

Active ingredients

The phenolic compounds in grape seeds are essentially all flavonoids. The presence of flavan-3-ol monomers, dimers, and trimers has been extensively reported. Flavan3-ols easily

condenses into oligomeric procyanidins and polymeric compounds (condensed tannins).[3] The dimeric procyanidins are often referred as B-series, and the trimeric procyanidins as C-series. Five different dimers (procyanidin B1, B2, B3, B4, and B5) and two trimers (C1 and C2) were identified from grape skin and seeds. These dimers and trimers are composed of catechins and epicatechins.[2] Fuleki and Silva isolated and identified a total of 11 monomers, dimers, and trimers by reversed-phase high-performance liquid chromatography (HPLC) from the seeds of red grapes.[4] Prieur et al. showed a degree of polymerization (DP) of 16 units by employing gel permeation chromatography and normalase HPLC.[5] It may be possible that the higher polymers observed by those authors are due to oxidative polymerization after extraction from seeds. Resveratrol, a polyphenol is also found in Grape seed extract (GSE).[5]

Physical properties of polyphenols

Molecular weight (MW): The molecular weights of three monomers, catechin, epicatechin, and epicatechin-(3-O)- gallate, based on their molecular structure, are 293, 294, and 445, respectively. According to the DP, the MW of procyanidin dimer, trimer, and tetramer are 580, 870, and 1,160, respectively. These molecular weight differences are the basis for separation by gel permeation chromatography and membrane fractionation.[6]

Solubility: Some phenolics are water-soluble, and some are lipid-soluble. In general, catechins are lipid-soluble, and procyanidins are water-soluble. Therefore, it is relatively easy to separate procyanidins from catechins. Since procyanidins are water-soluble, they can be extracted by water without introducing any organic solvents. This ensures the safety of grape seed extract as a dietary supplement. Their water and lipid solubilities are also of prime importance in understanding their antioxidant activities.[7]

Melting point: The melting points of catechin, epicatechin, and epicatechin-3-gallate are 174°C, 236°C, and 236°C, respectively.[2]

Absorption of light: The maximum absorption of light occurs at λ max=264–280 nm.[2]

Chemical and Biochemical properties of polyphenols

Hydrogen donation: Phenolics contain multiple hydroxyl groups (-OH). They are hydrogen-donating antioxidants and singlet oxygen quenchers. This makes polyphenols a class of reducing agents. They are also very potent metal chelating agents. They can trap and quench

free radicals and break the chain reaction. Their antioxidant potentials are four to five times that of vitamin C or E.[8]

Stability: Grape seed polyphenols are very sensitive to oxygen, light, acid, and alkaline, but relatively less sensitive to heat. Colourless phenolics such as catechin and epicatechin are easily oxidized in fruits and vegetables because of the presence of polyphenol oxidase, which is responsible for the bruising of fruits (e.g., apples, pears, and peaches) and vegetables and the browning of juice.[2]

Polyphenol–protein interaction: Phenols from grape seeds have a special affinity for some proteins and certain protein building blocks (e.g., proline-rich proteins).[9,10] There are four kinds of interactive bonds between phenolic compounds and protein: hydrogen, hydrophobic, ionic, and covalent bonds.[11] Phenols may combine with protein reversibly by hydrogen bonding, or irreversibly by oxidation followed by covalent condensations. The interaction of polyphenols with bovine serum albumin was used to study the anti-ulcer activity of grape seed extract in vitro.[12] Many proteins can be precipitated by polyphenols. This property can be used to quantify proteins, for example, the hemoglobin assay,[13] gelatin assay,[14] and bovine serum albumin assay.[15] Proanthocyanidins, the major polyphenols of grape seed extracts, are colourless.[16]

Pharmacological activity

GSE has anti-inflammatory, anti-apoptotic, anti-necrotic, cardiovascular, and anti-carcinogenic properties, making it useful in the treatment of a variety of ailments, including skin ageing (Farzaei et al. 2015).[17]

Proanthocyanidins are indeed an interesting class of phytonutrients for the prevention and treatment of various diseases due to their high antimicrobial and immune-modulatory activities.[18]

Proanthocyanidins are highly hydroxylated flavan-3-ol structures that form oligomeric structures with varying numbers of units. Catechin (C), epicatechin (EC), or their substituted derivatives linked through the C4–C8 or C6 bonds are the most common flavan-3-ol units (B-type).[18] The ability to form insoluble complexes with carbohydrates and protein is referred to as condensed tannins.[19] Proanthocyanidins are known as propelargonidin (one hydroxyl substitution), procyanidin (two hydroxyl substitutions), and prodelphinidin (three hydroxyl

substitutions) based on the number of hydroxyl substitutions in the B ring (three hydroxyl substitutions).[20]

Antioxidant properties

GSE has proved its efficacy against oxidative stress and its role in the prevention of several inflammatory diseases. Oxidative stress is a stumbling block or interruption in the development of free radicals and antioxidant defences. The signal transduction mechanism is aided by a small amount of free radicals. The vascular gene expression of Vascular Endothelial Growth Factor (VEGF) is regulated by reactive oxygen species (ROS) and oxidative stress (Kunsch and Medford 1999).[21] Mechanisms of protective effects of GSE are most likely related to their antioxidant activity and their ability to scavenge reactive oxygen species (ROS) and reactive nitrogeneous species (RNS). NO (Nitric oxide), O_2-(Superoxide radical), and their reaction product ONOO- are generated in excess during the host response against bacterial infections and contribute to pathogenesis by promoting oxidative stress, tissue injury, and even cancer. iNOS (Inducible nitric oxide synthase), the enzyme responsible for the synthesis of NO, is highly expressed in LPS(lipopolysaccharide)-activated macrophages, and this also contributes to pathogenesis of infectious diseases. The induction of iNOS by bacterial stimuli leads to organ destruction in some inflammatory and autoimmune diseases. Thus, the inhibition of NO production by blocking iNOS expression may present a useful strategy for the treatment of various inflammatory diseases.[21] Recently, the effects of selected flavonoids on NO production in LPS/ interferon-g-activated RAW 264.7 macrophages have been reported.[22]

Anti-microbial properties

The GSE have shown an effective antimicrobial property; they are efficiently used against Gram-positive bacteria (Bacillus cereus, Staphylococcus aureus, Bacillus coagulans and Bacillus subtilis), but are more effective against Gram-negative bacteria like-Pseudomonas aeruginosa or Escherichia coli(E.coli) (Jayaprakasha et al. 2003).[23] The study of Paulo et al. (2010) reported that the antimicrobial effect of GSE is attributed by changes in cell morphology and DNA content (Paulo et al. 2010).[24] Resveratrol shows a positive antimicrobial activity against many pathogens, such as Staphylococcal aureus, Psedomonas aeruginosa and Enterococcus faecalis (Chan 2002).[25] In normal skin, resveratrol applied topically increases production of cathelicidin, which inhibits the growth of Staphylococcal aureus and induces antimicrobial peptides (Park et al. 2013).[26] The antimicrobial activity

showed by resveratrol, involves the induction of oxidative damage to bacterial membrane without affecting the host cells, especially in E. coli. The higher amount of flavonoids and their derivatives in GSE were responsible for the antimicrobial-activity (Anastasiadi et al. 2009).[27] In another study, Vaquero et al. (2007), suggested that caffeic acid, quercetin, and quercetin-3-O-rutinoside of GSE are responsible for inhibition of Listeria monocytogenes (Vaquero et al. 2007).[28] Similarly, it has been brought to notice that the polymeric phenolic fractions of GSE exhibited the highest specific inhibition activity for almost all Listeria species (Rhodes et al. 2006).[29]

Anti-inflammatory properties

GSE generates its anti-inflammatory effect by calibrating the delicate balance between pro-inflammatory and anti-inflammatory cytokines through regulating their release and gene expression.

In a study that evaluated the impact of procyanidin from grape seeds on the inflammatory mediators in rat fed with a high fat diet, Terra et al. reported that rats fed with a high fat diet supplemented with procyanidins from grape seeds (345 mg/kg feed) for 19 weeks had a lower plasma C-reactive protein (CRP) level than rats fed with high-fat diet, suggesting that the decrease in plasma CRP is related to a downregulation of CRP mRNA expression in the liver and mesenteric white adipose tissue (WAT).[30] In addition, the authors also reported a decrease in the expression of the proinflammatory cytokine tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) in the mesenteric WAT of rats.

In a study that investigated whether procyanidins play a role in modulating inflammation, Chacon et al. reported that macrophage-like (THP-1) cell lines and human adipocytes (SGBS- human Simpson Golabi Behmel syndrome) pre-treated with grape-seed procyanidin extracts had a reduction in IL-6 and monocyte chemoattractant protein (MCP-1) expression after inflammatory stimulus.[31]

In addition, the authors also reported that the translocation of NFκB to the nucleus was partially inhibited in macrophage-like (THP-1) cell lines and human adipocytes (SGBS) pre-treated with grape-seed procyanidin extracts. In addition, grape-seed procyanidin extracts also increased adiponectin expression and decreased IL-6. Grape-seed procyanidin extracts are also linked to a reduced expression of epidermal growth factor module-containing mucin-like receptor 1 (EMR1) (specific marker of macrophage F4/80), suggesting a reduced

macrophage infiltration of WAT. Therefore, the regular consumption of food containing procyanidins might help to prevent low-grade inflammatory-related diseases in obesity characterized by macrophage accumulation in WAT and abnormal cytokine production.[30]

GSE was demonstrated to protect against collagen breakdown and had a bacteriostatic effect on the anaerobes that may significantly decrease the maturation of dental biofilm and therefore may be used in the prevention of periodontal disease as well.

Grape phenolics and human health

Anti-hypertensive properties

Study carried out by Quinones et al. (2013) assessed the antihypertensive effect of GSE in male spontaneously hypertensive rats. The outcome was that the GSE produces a significant decrease in systolic diastolic blood pressure. The study opined GSE exerts antihypertensive activity by increasing the antioxidant endogen system.[32] GSE also shows positive impacts on the blood pressure and it is more obvious to obese and the patients with metabolic syndrome or disorders (Zhang et al. 2016).[33] The effects of white grape pomace flour on thirty-eight male human subject of age between 30 and 65 years having metabolic syndrome was performed. At the end of study, it was seen that the systolic-diastolic blood pressure was significantly decreased. This indicates that the consumption of grapes rich in polyphenols at regular basis improves the blood pressure (Urquiaga et al. 2015).[34]

Anti-Cholesterol property

During a study that investigated the impact of supplementing one high-fat meal with three hundred mg of proanthocyanidin-rich grape seed extracts in eight male adults, Natella et al. reported that grape seed extracts cut back postprandial oxidative stress by increasing the plasma inhibitor concentration and preventing the rise of lipid hydroperoxides. Consequently, this improves the resistance to oxidative modification of LDL(low density lipoprotein) cholesterol. It's advised that the polyphenols in grape seed extracts activate serum paraoxonase (PON) that prevents the postprandial increase in lipoid peroxides.[35] Serum paraoxonase is an enzyme related to high-density {lipoprotein|HDL|alpha-lipoprotein|lipoprotein} (HDL) that hydrolyzes lipoprotein peroxides and inhibits LDL oxidation.[36]

Effect on Cardiovascular disease (CVD)

Studies and evidences show that consumption of grapes rich in polyphenols has cardioprotective benefits and also decreases the cardiovascular mortality. There are many mechanisms by which GSE prevent the atherosclerosis, including inhibition or limit the oxidation of low-density lipoprotein (LDL), lowering the blood pressure, reducing inflammation, inhibition of the platelet aggregation, and activating some proteins which prevents the cell senescence (Dohadwala and Vita 2009).[37] The in vitro and in vivo study provides evidence that there is a relation between presence of antioxidant phenolics and the reduction of oxidized LDL particles and consumption of diets rich in phenolic antioxidant reduced the rate of occurrence of cardiac disease (Kinsella et al. 1993).[38] The capability of the (poly)phenols present in GSE avert radical oxidation of the polyunsaturated fatty acids of low-density lipoproteins (LDL), which occurs frequently through oxidative modification of the apoprotein toward an atherogenic form, has a direct follow up on the prevention of CVD (Rimm et al. 1993).[39]

It was also reported that antioxidants contained in the red GSE are able to inactivate superoxide anions and prevent lipid peroxidation. Red GSE has cardio protective effect against reperfusion-induced injury by free radicals after ischemia (Bagchi et al. 2003).[40] GSE can also minimize the accumulation of fat in adipose tissue and dietary fat absorption by inhibiting fat metabolizing enzymes; pancreatic lipase and lipoprotein lipase (Moreno et al. 2003).[41]

Effect on wound healing activity

Wound healing involves 3 steps that include: inflammation, proliferation and transformation. In inflammation, the inflammatory cells like monocytes and macro phages begin depositing at the injury site and this step starts instantly when the injury happens. Proliferative phase of wound healing includes many steps like angiogenesis, epithelialization, collagen aggregation, and formation of granulation tissue and wound interaction. Angiogenesis process is stimulated by vascular endothelial growth factor (VEGF) which is the most effective growth factor involved in the process of healing of wounds. VEGF could be a signal glycoprotein produced by the cells, also called vascular permeability factor.[42]

GSE contains polyphenyl phenolic bioflavonoids, proanthocyanidins that accelerates the process of wound healing (Soto et al. 2015).[43] Proanthocyanidins specifically induces the expression of VEGF in human keratinocytes cells accountable for wound healing (Sen et al.

2002).[44] Researchers of Ohio University's heart and lung Research institute reported that the GSE helps in wound healing by 2 ways: (1) GSE helps body in the regeneration of the damaged blood vessels and (2) GSE will increase the quantity of free radicals present at the wound site. Free radical helps in killing and clearing of morbific microorganism and endotoxin from the site and helps in curing of wounds.[1]

Effect on peptic ulcer

Reports show that GSE wealthy in proanthocyanidin protects and provides immunity against chronic and acute gastric and intestinal oxidative injury through membrane microviscosity in gastric and duodenal membrane and inhibition of lipid peroxidation (Bagchi et al. 1999).[40] It exhibited inhibitor activity and better gastro protecting as compared to ascorbic acid and E (Cuevas et al. 2011).[45] This gastro protecting impact of GSE can be due to macromolecule binding ability of procyanidins covering the abdomen surface (Saito et al. 1998).[46] Resveratrol, a polyphenol found in GSE, suppresses the growth of Helicobacter pylori (H. pylori), Interleukin-8 secretion evoked by H. pylori, generation of reactive oxygen species, and changes in human gastric epithelial cells morphology (Zaidi et al. 2009).[47] It had been found that low dose of resveratrol (2 mg kg-1) exhibits ulcer healing activity, whereas, in high dose (10 mg kg-1) it becomes ulcerogenic. The mechanism behind low dose ulcer healing activity is attributed to stimulation of COX1 (Cycloxygenase1), inhibition of neutrophil aggregation, PGE_2 (Prostaglandin E_2) & eNOS (Endothelial nitric oxide synthase) and improvement of angiogenesis (Dey et al. 2009).[48]

Anti-cancer properties

Phenolic compounds present in GSE exhibits anticancer and cell cycle modulation activity (Huang et al. 2012).[49] These phenolic compounds show cytotoxic activity against growth cells while not poignant the conventional healthy cells (Engelbrecht et al. 2007).[50] The urged mechanisms of anticancer activity attributed to expression of pro-angiogenic factors like-angiopoietins and therefore the vascular epithelial tissue protein (Huang et al. 2012),[49] and therefore the inactivation of phosphoinositide 3-kinase (PI3K)/protein enzyme B (PKB) signal pathway that results in induction of programmed cell death of cancer cells (Engelbrecht et al. 2007).[50] Cheah et al. (2014) reported that the low mass procyanidins, present in GSE, accrued the toxicity of the chemotherapeutical agent 5-fluorouracil on cancer cells. This study opined that GSE may be used as a supplement in treatment of cancer.[51] In 2015 a study was conducted by Lacatusu et al. within

which the macromolecule nanocarriers of Grape seed oil and laurel leaf oil (natural oils) was developed and therefore the effectiveness of nanocarriers in combating certain growth cells and counteracting free radicals were evaluated between growth cells of MDA-MB 231 and hela cell lines and traditional cells of L929 and B16 cell lines. A major decrease in proliferation of growth cell was discovered. Thus, macromolecule nanocarriers supported natural oils like- Grape seed oil and laurel leaf oil might considerably improve the therapeutic effectuality of anticancer medication in clinical applications (Lacatusu et al. 2015).[52]

Anti-diabetic properties

In a study that investigated the effect of grape seed procyanidins on glucose metabolism in streptozotocin-induced diabetic rats, Pinent et al. reported that grape seed procyanidins stimulated the glucose uptake in L6e9 myotubes and 3T3-L1 adipocytes in a dose-dependent manner. In addition, grape seed procyanidins also stimulated glucose transported-4 translocation to the plasma membrane. The authors suggested that procyanidins possesses insulin-like effects in insulin sensitive cells. Therefore, all these findings suggest that procyanidins in grape seeds inhibited mRNA levels and decreased the risk of diseases associated with obesity and high fat diets.[53]

CONCLUSION

Grape seed extract exerts potential health benefits against numerous diseases, which include protection against oxidative damage, and anti-diabetic, anti-cholesterol properties etc. The health benefits of grape seed consumption are thought to arise mainly from bioactivities of their polyphenols. Potential health benefits of dietary polyphenols on major chronic noncommunicable diseases have been shown in several meta-analyses. Therefore, the screening of individual polyphenol constituents that exhibit health-promoting properties in grape seed requires further investigation. This is because a cause-effect relationship between the intake of grape seed and its health effects can only be established when the composition of grape seeds is properly characterized and standardized. Further research is needed to evaluate the effectiveness of grape seed extract in the food ecosystem and to establish their role as an antimicrobial agent in food safety.

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