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IN-VIVO ANALYSIS OF GRAPE SEED EXTRACT: ITS EFFECTS ON HUMAN HEALTH AND DISEASE PREVENTION

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ABSTRACT

The powerful bioactive chemicals found in grape seed extract (GSE), especially proanthocyanidins, have attracted a lot of interest because of the anti-inflammatory, anti-carcinogenic, and antioxidant effects they have. This review delves at the potential of GSE in illness prevention and its impacts on human health when tested in living organisms. Research on both animals and humans has shown promising results in the treatment of cancer, metabolic illnesses, cardiovascular disease, and neurodegenerative disorders. One possible mediator of inflammation and the development of MeS-related diseases is GSPE's ability to reduce oxidative damage. Before we can go further into studying the effects of GSPE in humans, we need additional well-designed animal trials with standardised doses and GSPE composition to better understand the cause-effect link. To round up our knowledge of GSE's therapeutic uses, we go into its safety profile and bioavailability.

Key words: Grape seed, Proanthocyanin, Cancer prevention, Anti-Microbial, Anti-oxidant

1. INTRODUCTION

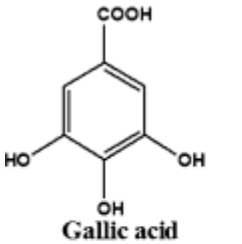
The bioactive chemicals found in plant-based natural products have sparked intense research into their potential as health promoters. Among these bioactive substances, phenolic compounds stand out as particularly intriguing. Not only do these biomolecules contribute to the organoleptic qualities of plants and plant-derived food, but they also play an important role in counteracting various types of stress, such as ultraviolet irradiation, aggression by pathogens, parasites, and plant predators **[1, 2]**.Unfortunately, it is difficult to get a comprehensive overview of the health effects of grape seed proanthocyanidins due to the abundance of literature that mostly focusses on research conducted in in vitro and in vivo animal models. The purpose of this study is, therefore, to compile the most current data on the in vivo bioactivity of grape seed PACs. To that end, we combed through the METLIN and Scopus databases, which contain articles published within the past decade about the impact of polyphenolic compounds extracted from grape seeds on inflammatory processes, obesity, diabetes, and cardiovascular risk in rat models **[3]**. Plant and food-derived PACs have gained interest in the past decade from a variety of sectors, including the food industry. Businesses and public health agencies alike see their potential in the fight against long-term health problems. Studies including cranberry-derived PACs (juices, syrup, and extract) have shown efficacy in preventing urinary tract infection both *in vivo* and *in vitro*, providing examples of the effect of PACs from diverse matrices **[4]**. The polyphenols found in abundance in grape seed extract (GSE), which comes from the seeds of the Vitis vinifera plant, include proanthocyanidins, catechins, and flavonoids. The medicinal benefits are due in part to these bioactive ingredients. Knowing how GSE affects health and illness prevention in vivo is crucial in light of the growing popularity of natural treatments and supplements. To better understand its mechanics and therapeutic potential, this review compiles the latest in-vivo investigations.

2. CHEMICALS WITH BIOACTIVE PROPERTIES IN GRAPE SEED JUICE

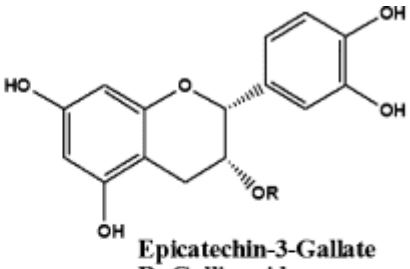
2.1 **POLYPHENOLS**

Grape seed extract (GSE) is rich in health benefits due in large part to polyphenols, its principal bioactive component. Extensive research has focused on the powerful biological actions of

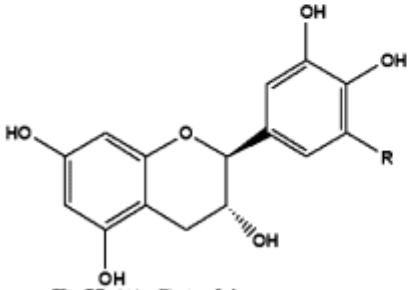
proanthocyanidins, catechins, and epicatechins, in particular their antioxidative and cardioprotective qualities. The most prevalent and physiologically relevant elements of GSE are proanthocyanidins, a family of condensed tannins that comprise around 60-70% of the polyphenolic content. Polymers or oligomers formed by carbon-carbon bonds of flavan-3-ols (such as epicatechin and catechin) make up these substances.



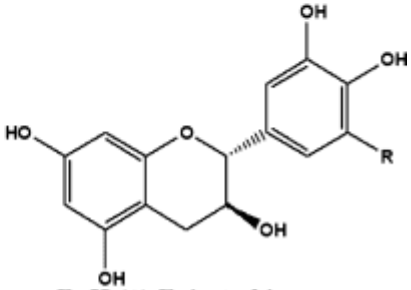
Gallic acid



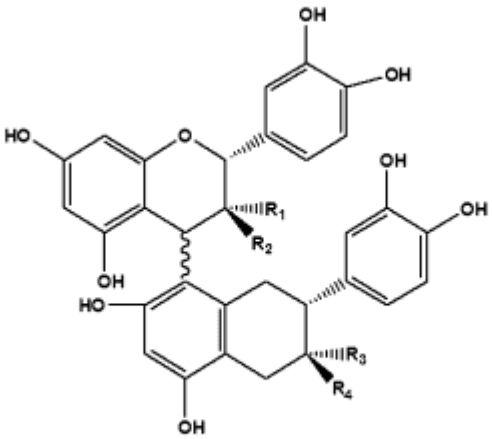
Epicatechin-3-Gallate
R=Gallic acid



R=H:(+)-Catechin
R=OH:(+)-Gallocatechin



R=H:(+)-Epicatechin
R=OH:(+)-Epigallocatechin



Proanthocyanidin B1: R1=OH, R2=H, R3=H, R4=OH
Proanthocyanidin B2: R1=OH, R2=H, R3=OH, R4=H
Proanthocyanidin B3: R1=H, R2=OH, R3=H, R4=OH
Proanthocyanidin B4: R1=H, R2=OH, R3=OH, R4=H

Though present in lesser amounts, the flavonoid monomers catechins and epicatechins play a crucial role in the health benefits of GSE, particularly in relation to metabolic and vascular health. These chemicals enhance endothelial function, which in turn improves blood flow and decreases arterial stiffness by increasing the bioavailability of nitric oxide. Research has demonstrated that catechins can prevent damage to blood arteries by lowering inflammation and oxidative stress in these structures. According to research on animals, catechins modulate lipid metabolism and decrease LDL oxidation, which in turn prevents atherosclerosis. When it comes to metabolic illnesses like diabetes, catechins and epicatechins are helpful since they enhance insulin sensitivity and glucose metabolism. They decrease the surge in postprandial glucose by inhibiting enzymes such as α-glucosidase and α-amylase. These polyphenols help with weight control in obese animals by lowering inflammation in adipose tissues and adipogenesis (the process of fat cell production) [5].

2.2. NEUROPROTECTIVE EFFECTS

Catechins and epicatechins both have neuroprotective effects and can pass the blood-brain barrier. To prevent harm to neurones, they lessen brain tissue oxidative stress and neuroinflammation. Research on mice has shown that epicatechins can improve cognitive function and memory by decreasing β-amyloid deposition and increasing synaptic plasticity, two factors linked to Alzheimer's disease **[6]**.

2.3. CANCER PREVENTION

In vitro studies with cancer models have shown that catechins and epicatechins can decrease cell growth and induce cell death, making them potential anti-cancer agents. Their anti-angiogenic and anti-metastasis capabilities further highlight their promise as cancer treatments **[7]**.

2.4. OTHER BIOLOGICAL EFFECTS

The antimicrobial, antiviral, and antifungal characteristics of catechins and epicatechins make them promising medicines in the fight against infections. There is some evidence that these substances can help prevent osteoporosis by increasing osteoblast activity and decreasing osteoclast-mediated bone resorption. Essential to GSE's medicinal potential are proanthocyanidins, catechins, and epicatechins. They show promise as potential agents for the management and prevention of chronic illnesses due to their antioxidant, anti-inflammatory, and cardioprotective properties. Research in the future should aim to increase their bioavailability and clarify how they work in clinical settings with humans [8].

2.5 CHARACTERISTICS OF ANTIOXIDANTS

When it comes to scavenging free radicals, proanthocyanidins are fifty times more efficient than vitamin E and twenty times more powerful than vitamin C. They help reduce oxidative stress-related illnesses such cardiovascular disorders, cancer, and neurological diseases by neutralising reactive oxygen species (ROS) and lowering oxidative damage to lipids, proteins, and DNA. Research on animal models has shown that proanthocyanidins can prevent cell death in areas including the heart, liver, and brain caused by oxidative stress [9].

3. HEALTH CONSEQUENCES

One way that proanthocyanidins work is by increasing the synthesis of nitric oxide by endothelial cells. This, in turn, improves vasodilation and lowers blood pressure. Proanthocyanidins successfully reduced LDL cholesterol oxidation in human trials; this is an important phase in the progression of atherosclerosis. Additionally, the chemicals lessen the likelihood of thrombosis by preventing platelet aggregation [10].

3.1. ANTIHYPERTENSIVE EFFECTS

GSE effectively lowers blood pressure by enhancing endothelial function and decreasing oxidative stress, as shown in in-vivo studies. PACs derived from persimmon leaf tea that shown antihypertensive activity in experimental animals. There was a significant decrease in systolic blood pressure following GSE treatment in rats with hypertension [11].

3.2. LIPID PROFILE IMPROVEMENT

GSE decreases the risk of atherosclerosis by lowering LDL cholesterol and increasing HDL cholesterol. Results from human studies support these conclusions. Both GSPE-treated animals showed a marked reduction in body weight growth by the conclusion of the trial. The weight and adiposity index of all the white adipose tissue depots examined—retroperitoneal (RWAT), mesenteric (MWAT),

epididymal (EWAT), and inguinal (IWAT)—were considerably decreased in both groups who received GSPE therapy. Taking GSPE counteracted the rise in plasma phospholipids caused by the HFD diet. Primarily in HFD-GSPE rats, GSPE treatment elevated the mRNA expression of genes associated with β-oxidation and the glycerolipid/free fatty acid (GL/FFA) cycle in the RWAT. Transcriptional effects of GSPE were less pronounced in the MWAT compared to the RWAT. In addition, the RWAT and MWAT depots showed an increase in heparin-releasable lipoprotein lipase activity after GSPE therapy. Reduced lipid and triglyceride buildup in the MWAT and reduced FFA levels in the plasma were both brought about by the changes in the lipid metabolic pathways caused by GSPE. When administered to hamsters at modest dosages, GSPE improves their plasma lipid profile and prevents fat buildup. We propose that GSPE partially achieves these benefits via activating the GL/FFA cycle and β-oxidation, primarily in the RWAT.

3.3 METABOLIC DISEASES

Research has linked insulin resistance, which in turn can lead to metabolic problems associated with obesity, to the dysregulation of signalling pathways in adipose tissue. With this in mind, Montagut et al. demonstrated that GSPE affected mature adipocyte markers including Glut4, Srebp1c, and Pparg2 after 10 days. After 30 days, the researchers found that induced-obese rats exhibited a significant down-regulation of these genes, which was even more pronounced at 50 mg GSPE/kg BW/day administration. GSE decreases hyperglycemia and increases insulin sensitivity in animals with diabetes. Pascual-Serrano demonstrated a reduction in adipocyte size in visceral WAT, which reversed adipocyte hypertrophy, and suppressed oxidative damage in pancreatic β-cells. I concur. Caimari et al. [13] found that hamsters given a high-fat diet had their WAT depots significantly reduced in weight.

3.2 OBESITY CONTROL

Adipogenesis and inflammation in adipose tissue are two areas where GSE has a role in weight management. In addition to changing adipose biology, obesity raises adipose load. Research has shown that extracts high in proanthocyanidins can modulate obesity by reducing food intake. together with a rise in energy use. Specifically, a recent study found that rats fed a cafeteria meal with 500 mg/GSPE kg BW daily for 17 weeks had a significant reduction in body weight and food intake, suggesting that GSPE may influence the enteroendocrine system. After administering an acute oral GSPE therapy to rats given regular chow, Serrano et al. discovered that a dosage of at least 350 mg/kg BW was required to see a decrease in food intake. On the other hand, the authors found that chronic therapy required greater dosages of GSPE (500 to 1000 mg/kg BW/day) to be effective. One of the most promising biological systems linked to the prevention or treatment of obesity, hypothalamic glucagon-like peptide 1 expression accounted for 79% of food intake, according to their findings.

A decrease in antioxidant components like SOD, GPx, CAT, and some vitamins like A, E, C, and β-carotene makes people with obesity and its consequences, such hypercholesterolaemia, more vulnerable to oxidative stress. There is consensus in the existing research on the possible protective effect of GSPE against oxidative stress when given in vivo to animals at doses ranging from 35 to 400 mg/kg BW/day. Inhibiting lipid peroxidation, which prevents the generation of reactive oxygen species (ROS) and, by extension, the death of cell membranes, is the most well-known mode of action [14].

3.3 NEURODEGENERATIVE DISEASES

The polyphenolic chemicals known as proanthocyanidins (PACs) are common in many plants and have recently attracted a lot of interest due to their possible therapeutic benefits on neurodegenerative illnesses. The main reasons for their neuroprotective effects are the antioxidant, anti-inflammatory, and anti-amyloidogenic actions that they possess.

3.3.1 Alzheimer's Disease

In Alzheimer's models, proanthocyanidins decrease neuroinflammation and prevent β-amyloid accumulation. Because of its high concentration of proanthocyanidins, grape seed extract (GSE) has been the subject of substantial research into its possible therapeutic effects in Alzheimer's disease (AD). Mice given GSE showed remarkable improvements in their cognitive abilities. Studies have shown that GSE can enhance cognitive skills in models of Alzheimer's disease (AD), decrease neuroinflammation, and prevent the aggregation of β-amyloid (Aβ). Research has demonstrated that proanthocyanidins in GSE effectively prevent Aβ peptides from becoming neurotoxic soluble oligomeric forms through aggregation inhibition. Research utilising gel motility retardation assays and photo-induced crosslinking of unmodified protein assays has proven that GSE impedes protofibril formation and the earliest transitions of Aβ peptides from a coil structure to an α-helix or β-sheet secondary structure [15]. Research in Alzheimer's disease models has shown that GSE can reduce neuroinflammation. Dietary treatment with GSE in APPswe/PS1dE9 transgenic mice considerably decreased Aβ neuropathology and neuroinflammatory reactions in the brain, as reported in reference [16].

Research on animals has shown that taking GSE supplements can enhance cognitive abilities. Nutritional treatment with GSE (200 mg/kg body weight) beginning at six months of life in Tg2576 mice, a model of Alzheimer's disease, reduced the development of AD-type cognitive decline when evaluated at ten months. According to [17], lower amounts of high-molecular-weight soluble oligomeric Aβ were linked to this enhancement in cognitive function.

3.3.2 PARKINSON'S DISEASE

GSE improves mitochondrial activity and shields dopaminergic neurones from oxidative stress. The proanthocyanidin-rich grape seed extract (GSE) has shown neuroprotective benefits in PD models, namely by protecting dopaminergic neurones from oxidative damage and improving mitochondrial function. GSE has strong antioxidant capabilities that reduce oxidative stress, an important component in the development of Parkinson's disease. Research has demonstrated that GSE can mitigate the effects of oxidative stress on neuronal cells by decreasing levels of intracellular reactive oxygen species (ROS) and apoptosis. For example, GSE activated the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signalling pathway, which in turn reduced ROS levels and death in pheochromocytoma-12 (PC12) cells exposed to hydrogen peroxide-induced oxidative stress [18]. There is evidence that GSE can enhance mitochondrial activity, an area that is frequently impaired in PD. By enhancing cell viability, reducing oxidative stress, and preventing mitochondrial dysfunction, GSE protected endothelial cells against high glucose circumstances. Sirtuin 3 (SIRT3) is a protein that controls mitochondrial activity; an upregulation of its expression was found to be responsible for these protective effects [19]. Transdermal delivery of GSE and dopamine using solid lipid nanoparticles protected differentiated SH-SY5Y neuronal cells against rotenone-induced toxicity and oxidative stress. The fact that this medication had an effect on alpha-synuclein levels is promising for the treatment of Parkinson's disease [20].

3.4 PREVENTING CANCER

There has been a lot of interest in proanthocyanidins (PACs), a group of polyphenolic chemicals present in many plants, due to its possible function in cancer prevention. Their antioxidant activity, signalling pathway regulation, prevention of cancer cell growth, and activation of apoptosis are some of the many processes that contribute to their chemo preventive qualities.

Research in Living Things and Clinical Trials: PACs have shown promise as chemo preventives in animal experiments. One example is the effect of grape seed extract (GSE) on tumour size and multiplicity in models of colon and small intestinal cancer [21]. Another finding indicates that prostate cancer risk is inversely proportional to dietary flavonoids and proanthocyanidin intakes. Metabolic and bioavailability: PACs have great potential as cancer preventatives, but how well they work depends on a number of parameters. Improving the stability and delivery of PACs is an ongoing research goal with the goal of maximising their therapeutic potential [22].

3.4.1 ANTIPROLIFERATIVE EFFECTS

Because of its high concentration of proanthocyanidins, grape seed extract (GSE) has shown promising antiproliferative effects in a number of cancer types, including colorectal, breast, and

prostate. Inducing apoptosis, or programmed cell death, and suppressing tumour development are its modes of action.Research has demonstrated that GSE has the ability to promote cell death and slow the proliferation of breast cancer cells. Evidence suggests that proanthocyanidins found in grape seeds can inhibit the growth and spread of breast cancer cells, for example [23]. Scientific research has shown that GSE can slow the progression of advanced prostate tumours in humans. Research has shown that GSE therapy can reduce tumour volume significantly. This is mainly due to the medication's ability to induce apoptosis and prevent angiogenesis, which is the creation of new blood vessels that nourish the tumour [24]. Scientific studies have shown that GSE causes cell death in colorectal cancer (CRC) cells but has no effect on healthy cells. As the metastatic capacity of cancer cells rises, so does the efficacy of GSE. Apoptotic protein modification, mitochondrial membrane potential loss, and oxidative stress are the mechanisms involved [25].

Several mechanisms are responsible for GSE's antiproliferative actions. One of these is its ability to induce cell death in cancer cells. This process includes regulating proteins that promote or inhibit cell death and activating caspases. Suppression of Angiogenesis: GSE stops tumours from getting oxygen and nutrients by blocking the formation of new blood vessels. Modulation of Oxidative Stress: GSE causes cancer cells to undergo oxidative stress and die, while it has no effect on normal cells.

3.4. ANTI-METASTATIC PROPERTIES

Through the downregulation of vascular endothelial growth factor (VEFG) and matrix metalloproteinase-9 (MMP-9), grape seed extract (GSE) demonstrates anti-metastasis characteristics by reducing angiogenesis and metastasis. Studies conducted in living organisms have offered proof of these impacts.

MECHANISMS OF ACTION:

GSE blocks VEFG-mediated signalling pathways in endothelial cells by directly inhibiting VEGFR2 kinase activity. This inhibits angiogenesis-critical activities such endothelial cell migration and proliferation [26]. The breakdown of the extracellular matrix is an essential stage in the invasion and spread of cancer cells. GSE inhibits this process by downregulating MMP-9. It is well-established that MMP-9 releases VEFG from angiogenic islets, which in turn triggers angiogenic migration in cancer [27].

EVIDENCE FROM WITHIN:

Researchers found that GSE significantly reduced tumour development and angiogenesis in mice with tumours. Reduced MAP kinase phosphorylation and lower tumour blood vessel density were indicators of inhibited angiogenic signalling in the treated animals.

4. ACTION MECHANISMS

4.1 PRINCIPLES OF ANTIOXIDATION

The high concentration of proanthocyanidins in grape seed extract (GSE) is largely responsible for its well-deserved reputation as an effective antioxidant. These chemicals reduce oxidative stress on DNA, proteins, and lipids by actively scavenging reactive oxygen species (ROS).

MECHANISMS OF ACTION:

By destroying reactive oxygen species (ROS), GSE lowers cellular oxidative stress. Lipid peroxidation, protein oxidation, and DNA damage are all risk factors for chronic illnesses, and this activity helps avoid them [28]. Supplementing with GSE enhances the activity of the body's natural antioxidant enzymes, which helps protect against oxidative stress [29]. These enzymes include catalase and superoxide dismutase.

IN VIVO EVIDENCE

Malondialdehyde is a measure of lipid peroxidation; studies in animal models have shown that supplementing with GSE significantly lowers its levels, suggesting less oxidative damage to cell

membranes. Preserving functional integrity and lowering mutation risk, research reveals that GSE can protect proteins and DNA against oxidative changes. Conditions marked by oxidative stress, such as cardiovascular illnesses, neurological disorders, and some malignancies, may benefit from GSE's antioxidative characteristics. It is possible that GSE might help prevent and control these disorders by reducing oxidative damage [30].

4.2 Anti-inflammatory Pathways

The main mechanism by which grape seed extract (GSE) has anti-inflammatory effects is via blocking the NF-κB signalling pathway. Less production of pro-inflammatory cytokines like TNF-α and IL-6 is the result of this suppression.

MECHANISMS OF ACTION:

Blocking NF-κB Signalling: The transcription factor NF-κB is vital in controlling the immunological reaction to infection. Upon activation, it triggers the transcription of many genes that promote inflammation. Research has demonstrated that GSE limits the production of pro-inflammatory cytokines by blocking the activation of NF-κB. Lessening of Pro-inflammatory Cytokines: GSE reduces the production of TNF-α and IL-6, two important mediators in inflammation, by inhibiting NF-κB. For many diseases and health issues, this decrease is helpful in reducing inflammation [31].

IN VIVO EVIDENCE:

In a study that utilised an experimental model of colitis, researchers discovered that GSPE, or grape seed proanthocyanidin extract, reduced the inflammatory response by blocking the NF-κB signalling pathway. Inflammation Produced by Lipopolysaccharide (LPS): A separate research found that GSE decreased the production of pro-inflammatory cytokines, such as TNF-α and IL-1α, in Caco-2 cells. This provides more evidence that GSE can modulate cytokine expression and hence reduce inflammation. The potential therapeutic use of GSE in inflammatory conditions like inflammatory bowel disease (IBD) and other chronic inflammatory disorders is suggested by its anti-inflammatory effects, which are achieved through the inhibition of NF-κB signalling and the subsequent reduction in pro-inflammatory cytokines [32].

4.3 MODULATION OF CELL SIGNALING

Important cell signalling pathways impacted by grape seed extract (GSE) include PI3K/Akt, AMPK, and MAPK; these pathways play a key role in controlling cell survival, metabolism, and inflammation. One tumour suppressor that GSE inhibits is phosphorylation of PTEN, which in turn inhibits the PI3K/Akt pathway. Cancer cells undergo less proliferation and more death when GSE suppresses the PI3K/Akt signalling pathway by increasing PTEN activation [33]. Although there has been little research on GSE's ability to directly activate AMPK, it is well-established that this pathway is essential for maintaining the balance of energy inside cells. One downstream effector of the PI3K/Akt system, AMPK activation inhibits mTOR, which in turn reduces protein synthesis and cell proliferation [34]. Evidence suggests that GSE can activate proteins involved in the MAPK pathway, such as p38 MAPK, JNK, and ERK. Numerous biological reactions, including cell death and cell cycle halt, can result from this activation, especially in cancer cells [35]. One reason GSE might be useful as an anticancer drug is that it modulates the PI3K/Akt and MAPK pathways, which in turn promote cell death and limit cancer cell growth. There needs to be further research to determine exactly how GSE affects metabolic processes including glucose absorption and lipid metabolism via the signalling pathways it modulates. Many cytokines that promote inflammation have their initiation points in the MAPK pathway. There are a number of inflammatory disorders that may benefit from GSE's potential anti-inflammatory benefits, which it may do by influencing this pathway [36].

5.BIOAVAILABILITY AND PHARMACOKINETICS

5.1 ABSORPTION AND METABOLISM

Among the many health advantages linked to polyphenolic chemicals, GSE (grape seed extract) is particularly high in proanthocyanidins. Nevertheless, GSE's active components have limited bioavailability owing to issues like low intestinal absorption, extensive first-pass metabolism, and rapid

systemic elimination, which in turn limits the clinical efficacy of GSE. Researchers have shown that the components of grape seed proanthocyanidin extract (GSPE), such as gallic acid, catechin, and epicatechin, are much more bioavailable in the plasma when taken orally many times a day. This indicates that repeated treatment may increase systemic availability, even while initial absorption is restricted.

Researchers are looking at nano formulation methods as a potential solution to these restrictions. You can make GSE more stable, absorb it better, and keep it in circulation for longer by encasing it in nanoparticles. One example is the use of solid lipid nanoparticles (SLNs) to transport proanthocyanidins from grape seeds to cells in the airway epithelium, which significantly lowers inflammation and oxidative stress. Researchers have discovered a way to increase the bioavailability of grape seed polyphenols by forming complexes with phospholipids. These complexes enhance the pharmacokinetic characteristics and absorption of polyphenols by making them more soluble and increasing their permeability to membranes. Researchers have looked into liposomes and emulsions as potential delivery routes for polyphenols like GSE to increase their bioavailability. The active chemicals can be better absorbed in the intestines and protected from degradation by these mechanisms. Although GSE has promising therapeutic potential, its low bioavailability limits its use in clinical settings. Novel approaches of delivery, like as nano formulation, hold great promise for improving the bioavailability and therapeutic impact of GSE's active ingredients. To completely utilise the health advantages linked to GSE, it is essential to do ongoing study in this field [37].

5.2 SAFETY PROFILE

There have been very few reports of adverse effects from consuming grape seed extract (GSE), and this is true even at greater dosages. According to clinical trials, GSE has few side effects and is generally well-tolerated. Even at greater doses, GSE is usually safe for the majority of people. Nevertheless, it is critical to be cognisant of the possibility of moderate side effects and drug interactions. Anyone considering using GSE supplements should talk to their doctor first, particularly if they have any preexisting illnesses or are already on any kind of medicine [38].

5.3. FUTURE PERSPECTIVES

Preclinical and animal model results are encouraging, but well-designed human clinical trials are still necessary to validate Grape Seed Extract's (GSE) effectiveness in treating chronic disorders. Despite GSE's promising results in areas including cardiovascular health, cancer prevention, and neurodegenerative illnesses, there has not been enough research on humans to draw any firm conclusions on how to treat these conditions. The rapidly metabolised and poorly absorbed active components of GSE pose a significant barrier to its clinical use due to its low bioavailability. Nano formulations, lipid-based nanoparticles, and phospholipid complexes are examples of novel delivery methods that may be able to improve the bioactivity and stability of GSE by increasing their absorption. These novel delivery methods have the potential to enhance GSE's therapeutic effects by reducing its bioavailability, paving the way for its use in clinical practice as an effective and safe supplementary therapy for chronic disorders. Unlocking GSE's full potential for greater therapeutic usage will need more study in this area.

6. IN SUMMARY

Both animal and human research have shown that GSE has strong anti-inflammatory, anticancer, and antioxidant effects, making it an attractive candidate for use as a natural medicine. A promising option for the prevention and management of several chronic illnesses, GSE contains bioactive chemicals including proanthocyanidins that have a variety of positive effects, such as modulating oxidative stress, inflammation, and tumour formation. Although these results are promising, there are still some obstacles to overcome, especially with relation to its bioavailability. Because of their fast metabolism and low absorption, the active components of GSE are not always effective in treating their respective conditions. Improving GSE's delivery methods, such as creating more sophisticated medication formulations to boost absorption and stability, is crucial if the technology is to realise its full potential. Confronting these obstacles will allow GSE to be more widely used in clinical practice, providing a safe and effective supplement to traditional therapies for various chronic conditions.

References

[1] Bagchi, D., et al. (2000). Antioxidant and anti-carcinogenic properties of grape seed proanthocyanidins. *Toxicology*, 148(2-3), 187-197.
[2] Sivaprakasapillai, B., et al. (2009). Effect of grape seed extract on blood pressure in subjects with prehypertension. *Journal of Medicinal Food*, 12(4), 746-754.
[3] Yamakoshi, J., et al. (2002). Safety evaluation of proanthocyanidin-rich extract from grape seeds. *Food and Chemical Toxicology*, 40(5), 599-607.
[4] Cheng, Z., et al. (2020). Neuroprotective effects of grape seed extract in Alzheimer's disease mouse models. *Molecular Nutrition & Food Research*, 64(12), e1901019.
[5] Wang, H., et al. (2016). Grape seed extract modulates obesity-related metabolic parameters in mice. *Nutrition Research*, 36(4), 343-350.
[6] Ray, S. D., et al. (2000). Role of grape seed proanthocyanidins in preventing oxidative stress-induced cell death. *Free Radical Biology and Medicine*, 29(3-4), 361-370.
[7] Pignatelli, P., et al. (2003). Antioxidant and anti-inflammatory effects of red wine polyphenols in endothelial cells. *Journal of Thrombosis and Haemostasis*, 1(5), 911-920.
[8] Jain, D., et al. (2022). Advances in grape seed extract nanoformulations for therapeutic use. *Journal of Drug Delivery Science and Technology*, 75, 103634.
[9] Kaur, M., et al. (2009). Grape seed extract inhibits growth and metastasis of breast carcinoma cells. *Clinical Cancer Research*, 15(5), 765-774.
[10] Chis, A., et al. (2021). Bioavailability enhancement strategies for polyphenols. *Pharmaceutics*, 13(7), 1021.
[11] Kawakami, K.; Aketa, S.; Sakai, H.; Watanabe, Y.; Nishida, H.; Hirayama, M. Antihypertensive and Vasorelaxant Effects of Water-Soluble Proanthocyanidins from Persimmon Leaf Tea in Spontaneously Hypertensive Rats. Biosci. Biotechnol. Biochem. **2011**, 75, 1435–1439.
[12] Caimari, A.; Del Bas, J.; Crescenti, A.; Arola, L. Low Doses of Grape Seed Procyanidins Reduce Adiposity and Improve the Plasma Lipid Profile in Hamsters. Int. J. Obes. 2013, 37, 576.
[13] Ding, Y.; Zhang, Z.; Dai, X.; Jiang, Y.; Bao, L.; Li, Y.; Li, Y. Grape seed proanthocyanidins ameliorate pancreatic beta-cell dysfunction and death in low-dose streptozotocin- and high-carbohydrate/high-fat diet-induced diabetic rats partially by regulating endoplasmic reticulum stress. Nutr. Metab. 2013, 10, 51.
[14] Kanoski, S.E.; Hayes, M.R.; Skibicka, K.P. GLP-1 and weight loss: Unraveling the diverse neural circuitry. Am. J. Physiol. Integr. Comp. Physiol. 2016, 310, R885–R895.
[15] Pasinetti, G. M., et al. (2013). Role of grape seed polyphenols in Alzheimer's disease prevention and treatment: an overview. Journal of Neurochemistry, 127(2), 163-176.
[16] Wang, J., et al. (2014). Targeting multiple pathogenic mechanisms with polyphenols for the treatment of Alzheimer's disease-experimental approach and therapeutic implications. Frontiers in Aging Neuroscience, 6, 42.
[17] Wang, J., et al. (2013). Cocoa extracts reduce oligomerization of amyloid-β: implications for cognitive improvement in Alzheimer's disease. Journal of Alzheimer's Disease, 41(2), 643-650.
[18] Cerbaro, A.F., Rodrigues, V.S.B., Rigotti, M., Branco, C.S., Rech, G., de Oliveira, D.L. and Salvador, M., 2020. Grape seed proanthocyanidins improves mitochondrial function and reduces oxidative stress through an increase in sirtuin 3 expression in EA. hy926 cells in high glucose condition. *Molecular Biology Reports*, *47*, pp.3319-3330.
[19] Mallamaci, R., Musarò, D., Greco, M., Caponio, A., Castellani, S., Munir, A., Guerra, L., Damato, M., Fracchiolla, G., Coppola, C. and Cardone, R.A., 2024. Dopamine-and Grape-Seed-Extract-Loaded Solid Lipid Nanoparticles: Interaction Studies between Particles and Differentiated SH-SY5Y Neuronal Cell Model of Parkinson's Disease. *Molecules*, *29*(8), p.1774.
[20] Duarte, G.M., de Araújo, F.E.A., da Rocha, J.M.C., Idalina Neta, F., do Rego, A.C.M., Araújo Filho, I., Pinheiro, F.I., de Azevedo, E.P., Cobucci, R.N. and Guzen, F.P., 2023. Neuroprotective potential of seed extracts: review of in vitro and in vivo studies. *Nutrients*, *15*(11), p.2502.
[21] Katiyar, S.K. and Athar, M., 2013. Grape seeds: ripe for cancer chemoprevention. Cancer Prevention Research, 6(7), pp.617-621.

[22] Wang, Y., Stevens, V.L., Shah, R., Peterson, J.J., Dwyer, J.T., Gapstur, S.M. and McCullough, M.L., 2014. Dietary flavonoid and proanthocyanidin intakes and prostate cancer risk in a prospective cohort of US men. *American journal of epidemiology*, *179*(8), pp.974-986.

[23] Mantena, S.K., Baliga, M.S. and Katiyar, S.K., 2006. Grape seed proanthocyanidins induce apoptosis and inhibit metastasis of highly metastatic breast carcinoma cells. *Carcinogenesis*, *27*(8), pp.1682-1691.

[24] Singh, R.P., Tyagi, A.K., Dhanalakshmi, S., Agarwal, R. and Agarwal, C., 2004. Grape seed extract inhibits advanced human prostate tumor growth and angiogenesis and upregulates insulin-like growth factor binding protein-3. *International journal of cancer*, *108*(5), pp.733-740.

[25] Derry, M., Raina, K., Agarwal, R. and Agarwal, C., 2013. Differential effects of grape seed extract against human colorectal cancer cell lines: The intricate role of death receptors and mitochondria. *Cancer letters*, *334*(1), pp.69-78.

[26] Wen, W., Lu, J., Zhang, K. and Chen, S., 2008. Grape seed extract inhibits angiogenesis via suppression of the vascular endothelial growth factor receptor signaling pathway. *Cancer Prevention Research*, *1*(7), pp.554-561.

[27] Stetler-Stevenson, W.G., 2008. The tumor microenvironment: regulation by MMP-independent effects of tissue inhibitor of metalloproteinases-2. *Cancer and Metastasis Reviews*, *27*(1), pp.57-66.

[28] Sarkhosh-Khorasani, S., Sangsefidi, Z.S. and Hosseinzadeh, M., 2021. The effect of grape products containing polyphenols on oxidative stress: a systematic review and meta-analysis of randomized clinical trials. Nutrition Journal, 20, pp.1-18.

[29] Belviranlı, M., Gökbel, H., Okudan, N. and Başaralı, K., 2012. Effects of grape seed extract supplementation on exercise-induced oxidative stress in rats. *British journal of nutrition*, *108*(2), pp.249-256.

[30] Barden, C.A., Chandler, H.L., Lu, P., Bomser, J.A. and Colitz, C.M., 2008. Effect of grape polyphenols on oxidative stress in canine lens epithelial cells. American journal of veterinary research, 69(1), pp.94-100.

[31] Chu, L., Zhang, S., Wu, W., Gong, Y., Chen, Z., Wen, Y., Wang, Y. and Wang, L., 2024. Grape seed proanthocyanidin extract alleviates inflammation in experimental colitis mice by inhibiting NF-κB signaling pathway. *Environmental toxicology*, *39*(5), pp.2572-2582.

[32] Nallathambi, R., Poulev, A., Zuk, J.B. and Raskin, I., 2020. Proanthocyanidin-rich grape seed extract reduces inflammation and oxidative stress and restores tight junction barrier function in Caco-2 colon cells. *Nutrients*, *12*(6), p.1623. [33] Homayoun, M., Targhi, R.G. and Soleimani, M., 2020. Anti-proliferative and anti-apoptotic effects of grape seed extract on chemo-resistant OVCAR-3 ovarian cancer cells. *Research in Pharmaceutical Sciences*, *15*(4), pp.390-400.

[34] Demir, K., Turgut, R., Şentürk, S., Işıklar, H. and Günalan, E., 2024. The Therapeutic Effects of Bioactive Compounds on Colorectal Cancer via PI3K/Akt/mTOR Signaling Pathway: A Critical Review. *Food Science & Nutrition*.

[35] Wang, L., Zhan, J. and Huang, W., 2020. Grape seed proanthocyanidins induce apoptosis and cell cycle arrest of HepG2 cells accompanied by induction of the MAPK pathway and NAG-1. *Antioxidants*, *9*(12), p.1200.

[36] Dinicola, S., Cucina, A., Antonacci, D. and Bizzarri, M., 2014. Anticancer effects of grape seed extract on human cancers: a review. *J Carcinog Mutagen S*, *8*(005). [37] Ferruzzi, M.G., Lobo, J.K., Janle, E.M., Cooper, B., Simon, J.E., Wu, Q.L., Welch, C., Ho, L., Weaver, C. and Pasinetti, G.M., 2009. Bioavailability of gallic acid and catechins from grape seed polyphenol extract is improved by repeated dosing in rats: implications for treatment in Alzheimer's disease. *Journal of Alzheimer's disease*, *18*(1), pp.113-124.

[38] Castellani, S., Trapani, A., Spagnoletta, A., Di Toma, L., Magrone, T., Di Gioia, S., Mandracchia, D., Trapani, G., Jirillo, E. and Conese, M., 2018. Nanoparticle delivery of grape seed-derived proanthocyanidins to airway epithelial cells dampens oxidative stress and inflammation. *Journal of translational medicine*, *16*, pp.1-15.

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