International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 1221-1230 www.ijprajournal.com ISSN: 2456-4494

Formulation of Grape seed extract

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Date of Submission: 20-08-2025 Date of Acceptance: 30-08-2025

ABSTRACT
Grape seed extract (GSE), derived as a by-product from Vitis vinifera processing, is rich in polyphenolic compounds, particularly proanthocyanidins, which exhibit potent antioxidant, anti-inflammatory, and anti-diabetic properties. GSE contains a complex mix of monomers, oligomers, and polymers of catechin and epicatechin derivatives. This study investigated the clinical efficacy of GSE supplementation in a double-blind, randomized controlled trial involving 48 type 2 diabetic patients with chronic periodontitis. Over eight weeks, participants received either GSE or placebo capsules. Outcomes included oxidative, inflammatory, and glycaemic biomarkers, showing improvements in the GSE group. Advanced extraction and formulation methods, such as phytosome encapsulation and nanoparticle synthesis, were explored to enhance GSE's bioavailability. Analytical techniques including UV-vis spectrophotometry, FTIR, TEM, and dynamic light scattering were used to characterize GSE formulations. GSE demonstrated significant antioxidant capacity in vitro and in vivo and has promising therapeutic potential in managing metabolic and inflammatory conditions.

I. INTRODUCTION

The grape (Vitis vinifera) is a fruit crop widely grown all over the world. Grape seed is obtained as a waste by-product of the grape juice and wine processing industry. Global grape production is estimated to be about 75 million metric tons per year.[1]

Proanthocyanidins are also known as condensed tannins existing in GSE as monomeric (catechin and epicatechin), dimeric, trimeric and polymeric tannin structures.[2]

Findings from in vitro studies have demonstrated that these compounds act as free-radical scavengers and may prevent the oxidation of LDL-cholesterol.[3]

Chronic changes in kidney-based shape, function, or both that have an impact on a person's health are referred to as kidney disease.[4]

Cyst, tumor, malformation, and atrophy are a few examples of anatomical problems that are visible on imaging. Kidney failure, however, can cause oedema, hypertension, changes in urinary production or quality, and growth retardation in children. These changes are most frequently identified by elevated serum creatinine level and/or blood urea nitrogen (BUN). Regardless of the underlying medical condition, renal fibrosis is the most typical pathological symptom of kidney failure .[5]

There are numerous studies looking for methods to decrease amikacin (AMK), as an aminoglycoside, nephrotoxicity. Potential strategies include suppressing the signaling between cells that causes apoptosis, decreasing the production of ROS, preventing tubular absorption, and improving the kidney's capacity for regeneration. For many years, chronic kidney disease (CKD) patients have used complementary and alternative therapies, with apparently varying degrees of success in enhancing the outcomes.[6]

Surprisingly, grapes' seeds contain the largest proportion of the fruit's overall polyphenols. GSE is made up of a variety of vitamins and 3% minerals, 35% fibres, 13% fats, 11% proteins, 7% water; and a heterogeneous combination of polyphenolic substances, including 5 to 30% monomers, 17 to 63% oligomers and 11 to 39% polymers.[7]

II. MATERIALS AND METHOD

The study was a double blind randomised controlled parallel clinical trial to evaluate the oxidative, inflammatory and glycaemic status in type 2 diabetes mellitus patients with chronic periodontitis with or without GSE supplement. The patients were selected from the Outpatient Department of Periodontology, JSS Dental College and Hospital and Department of Medicine, JSS Medical Hospital, Mysore and the duration of the study was 10 months from January 2014 to October 2014. The study protocol was approved by the Institutional Review Board Ethical Committee governing the use of human subjects in clinical experimentation, JSS Dental College and Hospital, Mysore (JSS/DC/ETHICAL/2011-12). The

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Volume 10, Issue 4 July-Aug 2025, pp: 1221-1230 www.ijprajournal.com ISSN: 2456-4494

investigation was performed in accordance to the requirements of the Declaration of Helinski, 18th World Assembly in 1964 and revised in Edinburgh (2000). Informed consent was obtained from all the participants.[8]

A total of 48 diabetic patients with chronic periodontitis by purposive sampling were selected for the study. From the power analysis, it was shown that to achieve 80% power with a confidence limit of 95% and detect mean differences of clinical parameters between groups, 24 samples in each group were required.

Inclusion criteria:

The patients were included between 30-60 years with a body mass index of 18.5-30 kg/m2 and a glycated haemoglobin in the range 6%-8% coinciding with mean plasma glucose in the range 135-205 mg/dL. Patients suffering from Type 2 diabetes receiving oral hypoglycaemic drugs only with duration of diabetes for more than 5years but less than 10 years with Chronic generalised periodontitis having probing pocket depth ≥5 mm were included in the study [9].

Exclusion criteria:

Patients were excluded if they gave history of allergy to grapes, diabetic patients with any other complications of diabetes such as cardiovascular diseases e.g., coronary heart disease, diabetic nephropathy, pregnant and lactating mothers, smokers, patients receiving any anticoagulant drugs, those receiving any antioxidant drugs in the past three months or receiving treatment for any other condition. Prior to randomisation, baseline measurements were taken and the patients fulfilling the inclusion criteria underwent scaling and root planing and were randomised by computer generated randomisation using Random Allocation Software by the statistician into two groups of 24 patients each. Test group received 200 mg of capsule containing GSE (formulation: 95% GSE powder, 1.92% lost on drying, 1.65% ash) which were consumed orally whereas the control group received a capsule without the active ingredient, also taken orally. These capsules were taken once daily for a period of eight weeks. Both the capsules were identical in formulation, shape, size, weight, texture and packing which were disclosed after the completion of the study. The participants and operator were not aware of the treatment provided hence, it was a double blinded study.[8]

Reagents

All reagents were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Organicsolvents were purchased from Fisher Scientific (Hampton, NH, USA). Certificates ofanalysis were verified for all chemicals used to confirm > 95% purity. Butylene glycol wasobtained from DAICEL (Tokyo, Japan). Hydroxypropyl-_-cylodextrin was obtained fromHenan Yibo Biological Technology Co., Ltd. (Zhengzhou, China).

Hydroxyacetophenoneand 1,2-hexanediol were sourced from Symrise (Holzminden, Germany). Soybean lecithinwas obtained from Tywei (Shanghai, China). Cholesterol was sourced from Cool Chemistry(Beijing, China).[10]

AGSE and E-AGSE Production

AGSE was prepared as described in US patent no. 10,912,812 B2. The resulting AGSE material is a glassy, purple/black-colored solid. E-AGSE was prepared by adding 10 g AGSE powder to 50–75 g butylene glycol and stirring at room temperature for 18 h to dissolve (Phase A). Subsequently, 300 g HPCD was added to 200 g water and stirred at 90 °C until dissolved, and then cooled down to room temperature to obtain a transparent cyclodextrin solution (Phase B). Next, 5–10 g soybean lecithin and 1–2 g cholesterol were added into 25–50 g butylene glycol and mixed until dissolved at 70 °C (Phase C). Meanwhile, 5 g hydroxyacetophenone and 5 g 1,2-hexanediol were dissolved in water and sterilized, and then cooled down to room temperature for later use (Phase D). Phase B was added into Phase A, and the mixture stirred at room temperature for 12 h. The mixture was then added into Phase D and stirred for 4 h. The mixture of Phase A, Phase B, and Phase D was heated up to 70 °C, and then Phase C was added into the mixture and stirred at 70 °C for 5 to 10 minutes. After stirring, the mixture was cooled to 40 °C. Subsequently, the mixture was treated with high-pressure homogenization (HPH) using a UH-200 (Union-Biotech, Shanghai, China) to obtain 1 kg E-AGSE nanoparticles. Finally, particle size was analyzed using dynamic light scattering (DLS).[11]

Cell Culture and Viability

Primary human dermal fibroblasts (HDFBs) and normal human melanocytes (NHMCs) were obtained from the Cell Bank of Guangdong Biocell Biotechnology Co., Ltd. (Dongguan, China). Primary normal human epidermal keratinocytes (NHEKs) were purchased from Thermo-Fisher (Carlsbad, CA, USA). HDFBs

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were grown in Dulbecco's modified Eagle's medium (DMEM, Gibco, New York, NY, USA) containing 10% (v/v) new bovine serum (NBS, Hangzhou, China). NHMCs and NHEKs were grown in Medium 254 and EpiLife® medium (ThermoFisher, Carlsbad, CA, USA) supplemented with human melanocyte or keratinocyte growth supplements, respectively. Skin equivalent model EpiDerm™ was purchased from MatTek Corp (Ashland, MA, USA) and acclimated for 24 h before treatments. Cells and tissues were incubated under standard conditions (37 °C; 5% CO_2). Maximum nontoxic concentrations of each material were determined by reduction of tetrazolium dye MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide to formazan and monitoring by optical density at 490 nm. Results from the MTT assay determined the concentrations tested for each cell-based assay. For cell monolayers, all actives were diluted directly into culture medium and compared to untreated cells. For 3D skin model EpiDerm™, treatments were applied topically, and the vehicle used was E-vehicle, which comprised 90% propylene glycol and 10% encapsulation carrier without AGSE.[12]

UVB-Induced Inflammation

EpiDerm™ tissues were pretreated topically for 4 h before UVB irradiation under standard culture conditions. Later, medium was removed, tissues were washed with phosphate-buffered saline (PBS), and tissues were irradiated with UVB at 200 mJ/cm^2 without test materials using FS-20/T-12 bulbs (280–340 nm). After UVB irradiation, tissues were treated and incubated for 24 h under standard culture conditions. After incubation, culture media supernatants were used to measure IL-8 levels using a Human ELISA kit (BD Biosciences; Franklin Lakes, NJ, USA).[12]

Tissue Histology

EpiDerm™ tissues were washed with PBS and fixed in 10% neutral-buffered formalin. Tissues were sent to Mass Histology Services (Worcester, MA, USA) for paraffin embedding and mounting. Briefly, tissues were dehydrated in graded alcohols and xylene and embedded in paraffin blocks. Five-micron thick sections were obtained and mounted onto microscope slides. Hematoxylin–eosin (H&E) staining was performed to analyze sunburn cells (SBCs). Antigen retrieval was performed using citrate pH 6.0 or Tris/EDTA pH 9 buffer solutions. Tissue sections were incubated with anti-thymine dimer (CPDs, clone H3) or anti-filaggrin (clone EPR21892) purchased from AbCam PLC (Waltham, MA, USA). Chromogenic visualization was obtained after incubation with appropriate secondary antibody conjugated to horseradish peroxidase (HRP) and diaminobenzidine (DAB) substrate kit (AbCam). Positive cells were counted using a light microscope.[12]

Animal

In this study, white female rats (Sprague Dawley strain), aged 2-3 months and weight about 150-200 g were provided by Bogor Agricultural University (Indonesia). [13]

Total phenolic content in grape seed extract

A calibration curve of a standard solution of gallic acid was made. Concentration of the sample solution was 1000 µg/ml. Then, it was diluted to obtain six different concentrations ranged from 100 to 600 µg/ml. The solution was taken in a test tube (0.2 mL) and added with 1.5 mL of 10% Folin-Ciocalteu reagent solution. All the experimental test tubes were kept at room temperature in a dark place for 5 min. Then 1.5 mL of 6% Na2 CO3 was added to each test tube and the mixture was kept in a dark place at room temperature for 90 min. Following the incubation, the absorbance of each sample was analyzed using UV-visible spectrophotometer at a wavelength 720 nm.[14]

Phytosome formulation

The required amounts of GSE and Phospholipon 90 G with three different mass ratios was dissolved in ethanol 96%. The mixture was stirred at a temperature not exceeded than 40°C for 2 h. The mixture was then evaporated and the dried residues were collected and placed into a desiccator overnight. Phytosomes were prepared by thin layer hydration method using rotary vacuum evaporator. The GSE-Phosholipon complex was dissolved in dichloromethane and then inserted into a round bottom flask. The flask was attached to a rotatory evaporator, and rotated at 180 rpm. The solvent was evaporated at 39°C under reduced pressure to obtain film inside of the wall of flask. Nitrogen gas was flown into the thin layer, and it was stored in the refrigerator up to 24 h. The casted film was dispersed into phosphate buffer solution (pH 5.5). After the phytosome suspension was formed, ultra-sonication was conducted for 10 min.[14]

Phytosome characterization

Vesicles morphology of phytosome was visually observed using a FEI Tecnai G2 20 S-Twin (USA) Transmission Electron Microscope

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(TEM).Samples were shed on a carbon-coated copper grid, then the droplet was dried at room temperature and colored using phosphotungstic acid solution. The grid was left for 30 min and the films were viewed using a transmission electron microscope and the results were documented.[14]

Particle size distribution and zeta potential

The vesicle size and potential zeta were analyzed by dynamic light scattering system spectroscopy using a Malvern Zetasizer Nano Z (UK) computerized system. [14]

Fourier transformation infrared spectroscopy (FTIR)

FTIR spectra were obtained using an FTIR spectrometer (Shimadzu® FTIR-8400). Samples were mixed with dry crystalline KBr in a ratio of 1:100 and pellets were prepared. The mixture was triturated into fine powder using an agate mortar before compressing into KBr disc. Each KBr disc was scanned for each sample within the wave number region 4000–400 cm−1. The IR spectra of Phospholipon 90 G, pure GSE, physical mixture of Phospholiphon 90 G and GSE and GSE phytosome were analyzed as comparisons.

The Entrapment Efficiency

The phytosome suspension was centrifuged at 4500 rpm for 60 min. The supernatant was discarded, and the precipitate was collected and dissolved in methanol. The solution was then analyzed by UV-Vis spectrophotometer to determine its total phenolic content as the marker of GSE.

Phytochemical Compounds in Grape Seeds

Grape seeds contain protein (11%), fiber (35%), minerals (3%), and water (7%). In addition, the lipid content of grape seeds ranges from 7 to 20%.[15] The oil content of grape seeds is traditionally extraction using mechanical methods or organic solvents. In mechanical extraction, although the quality of product is superior, the extraction gives a lower yield. While organic solvent extraction gives a higher yield, it requires solvent recovery through distillation and the final product contains traces of residual solvent. While the supercritical method is regarded as a promising method which can produce similar quantity and better quality of oil yield than mechanical and organic solvent extractions.[16] Cold-pressing is used to extract the oil from grape seeds without chemical treatment or2521 heat.[17] Although the cold pressing usually gives a lower yield than other conventional solvent extraction, it may retain more bioactive components and be safer because there are no solvent residues in the grape seed oil.[17] Several studies have been conducted on grape seeds, in order to determine their bioactive compounds.[18] Grape seed extracts contain a heterogeneous mixture of monomers (5–30%), oligomers (17–63%), and polymers (11–39%) composed of proanthocyanidins.[19]

Proanthocyanidins are the major compound in grape seed extracts.The red color and astringent taste of grape seed extracts can be attributed to proanthocyanidins. However, higher concentrations of proanthocyanidins may affect the sensory and color properties of the product.[20]reported that the total phenols (gallic acid equivalent (GAE)), total flavonoids (catechin equivalent (CE)), catechin equivalent (CE), and proanthocyanidins (cyanidin equivalent (CyE)) in red grape seed extracts were 8.58 g/100 g dry matter (DM), 8.36 g/100 g DM, 6.41 g/100 g, DM and 5.95 g/100 g DM, respectively. Another study bydocumented that the total phenolic content and total flavonoid content of Ahmeur Bouamer grape seeds were 265.15 mg GAE/g of dry mass and 14.08 mg catechin equivalent (CE)/g of dry mass, respectively. In a study analyzing 26 samples of six white grape varieties and 44 of four red grape varieties from different areas of Castilla-La Mancha, Spain, Rodríguez Montealegre et al. reported that the grape seeds were shown to contain catechin, epicatechin, epicatechin gallate, protocatechuic acid, procyanidin B1, procyanidin B2, procyanidin B3, and procyanidin B4. Small quantities of gallic acid and protocatechuic acid were also present in grape seeds.[21]

Pharmacological Properties

Proanthocyanidins are present in substantial amounts in grape seeds and have attracted the attention of consumers because of their potential health effects.[22] In vitro, proanthocyanidins have been shown to exhibit strong antioxidant activity and scavenge reactive oxygen and nitrogen species, modulate immune function and platelet activation, and produce vasorelaxation by inducing nitric oxide (NO) release from endothelium.In addition, proanthocyanidins also inhibits the progression of atherosclerosis and prevent the increase of low-density lipoprotein (LDL) cholesterol concentration.[23]

Anti-Diabetic

body weight per day for 30 days had an

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improved homeostatis model assessment-insulin resistance index accompanied by downregulation of primers Glut4, Irs1, and Pparg2 in mesenteric white adipose tissue (WAT), suggesting that grape seed procyanidin has a positive long term-effect on glucose homeostasis. Another study by Montagut et al.[24] demonstrated that the oligomeric structures of grape seed procyanidin extracts activated the insulin receptor by interacting and Montagut et al.[25] reported Wister female rats treated with 25 mg grape seed procyanidin extract/kg inducing the autophosphorylation of the insulin receptor in order to stimulate the glucose uptake.

Antioxidant

Different methods including the 1,1-diphenyl-2-picryhidrazyl (DPPH) method and oxygen radical absorbance capacity (ORAC) have been employed to evaluate the antioxidant capacity of phenolic compounds from grape seeds. Poudel et al. reported that the antioxidant capacity of grape seed extract using DPPH ranged between 17 and 92 mmol Trolox® antioxidant equivalent (TE)/g. While the ORAC method was 42 mmol TE/g.[25]

Process of Drying and Grinding of Grape Seeds

Prior to the extraction process of grape seed oil, grape seeds must undergo a series of drying (Figure 1a) and grinding processes (Figure 1b). Initially, the seeds are separated from the skins manually or mechanically. Then, the seeds are dried in a drying chamber (oven) at 55 ◦C for 48 h [26], until reaching a constant weight with less than 10% moisture. A study found that in oils extracted using the Soxhlet and Soxtherm apparatus, reducing the moisture content of the seeds from 10 to 2.5% increased the yield by nearly 1% [27]. A second procedure was carried out by drying the pomace (seeds and skins) in a drying chamber until a constant weight of <10% moisture was obtained; subsequently, the researchers separated the seeds from the skins using vibrating sieves [28]. After dehydrating the seeds using one of these two procedures, they were placed in vacuumsealed bags and stored in darkness at room temperature [29], or −18 or −20 ◦C [30]. The dried seeds were then ground into a powder with a particle size of less than 0.5 mm (indicated by several researchers later on). Reducing particle size increases the surface area per unit volume, enhancing oil diffusion. In one study, it was observed that decreasing the particle size from 0.75 to 0.41 mm increased the yield from 8 to 16% . This sievingprocess is part of the characterization but will not be included in the final procedure.This stage allows for the separation of particles of different sizes using sieves or mesheswith specific openings, resulting in finer particles or particles of uniform size. This couldpotentially affect the oil extraction process. However, further studies are recommendedto specifically examine the impact of particle size on the obtained grape seed oil. Finally,the grape seed flour is stored in vacuum sealed polypropylene bags at −20 ◦C withoutlight [31]. Considering the drying and grinding stages before the extraction processcould enhance the yield. Therefore, optimization studies for the parameters at each stageare recommended.

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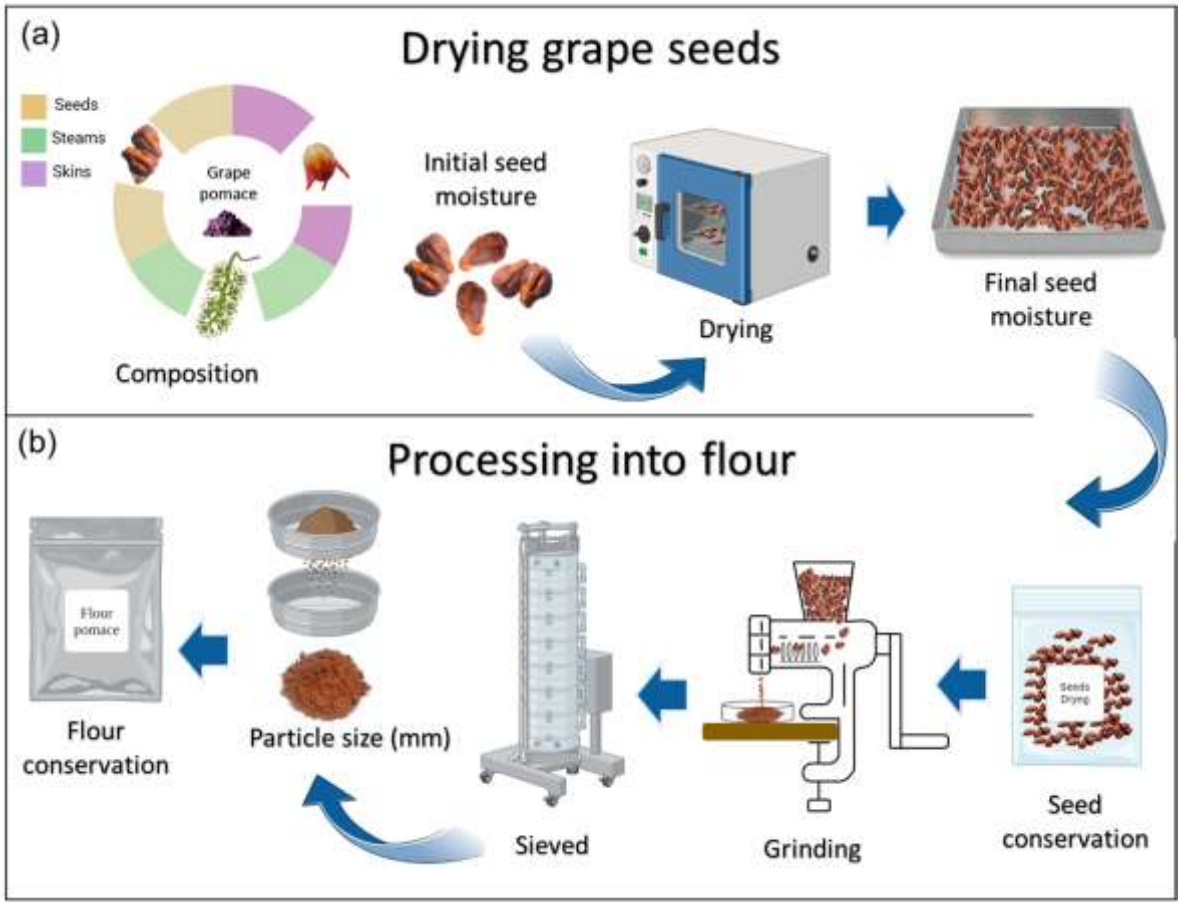

Figure 1. Grape seed drying process (**a**) and grinding processing into flour (**b**).

Grape Seed Oil Extraction Process

Pre-treatment: Since conventional grape seed oil extraction methods present certain limitations regarding extraction yield and solvent use, it is necessary to resort to pretreatmenttechniques to improve the extraction yield and the quality of the oil obtained.

Below are some reports of the pretreatments used (Figure 2); for example, ultrasonic pretreatment before the Bligh Dyer and supercritical fluid CO2 extraction, where the seedswere immersed in a polyethylene package in an ultrasonic bath at 30 ◦C for 30 min ofsonication (best condition for pre-treatment), which contributed to increasing the contentof α-tocopherol about 56 and 99% in Bligh Dyer and supercritical fluids, respectively [32].

In another study, it was observed that before extraction via pressing, by using various optimized parameters (amount of enzyme additive, hydrolysis temperature, hydrolysis time, degree of crushing, screw speed, squeezed water), with 1 g of added enzyme (proteaseand cellulase), 60 mesh, and 8% squeezed water, it was possible to reduce the percentageof waste in the process of obtaining oil via pressing from 33.24 to 57.79% [33]. A recentstudy employed a pretreatment using pulsed electric fields (PEFs) before extraction withsupercritical fluids. This pretreatment with PEFs increased the extraction yield (with valuesranging from 78.4 to 81.8 g/kg) compared to extraction using supercritical fluids (rangingfrom 76.3 to 78.6 g/kg) and cold pressing (67.1 g/kg). Furthermore, the extraction of sterols and non-flavonoid phenolic compounds saw significant enhancements, reaching 5347.0 and1378.3 mg/kg, respectively, under optimized conditions for supercritical fluid extraction with CO2 (35 MPa and 45 ◦C) and pulsed electric fields (5 kV/cm at 120 Hz for 5 min) [34].

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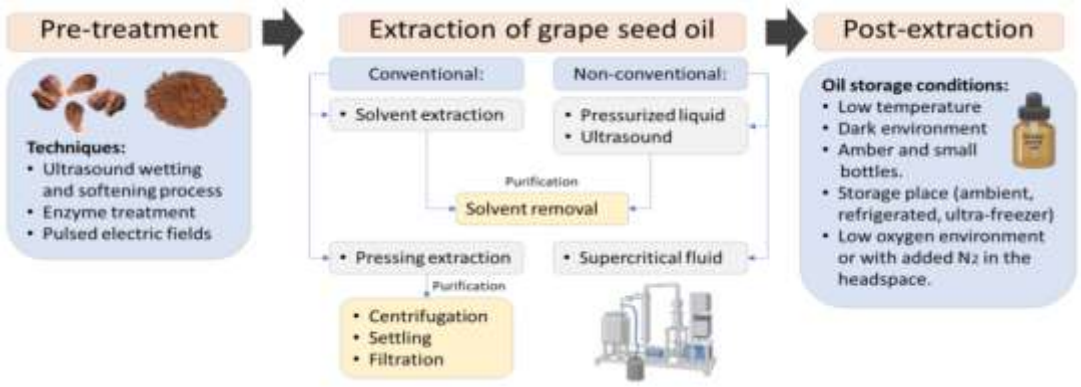

Figure 2. Grape seed oil extraction process stages.

Extraction. Grape seed oil can be obtained either through direct pressing of whole seeds or from grape seed flour. Conventional methods for oil extraction involve mechanicalpressing and solvent extraction techniques. Furthermore, alternative methods such asultrasound-assisted extraction [35], supercritical fluids with CO2 [36], andsupercritical fluids with CO2 + ethanol [37] are available (Figure 3). Below are explanations of the various methods employed for extracting grape seed oil.

Yield and Composition of Grape Seed Oil

The extraction yield of grape seed oil varies from 3.9 to 18.5% (g of oil per 100 g of dryweight of byproduct) depending on the method used. The pressing method provides thelowest yields, while the Soxhlet method and the method using supercritical fluids providethe highest yields (see Supplementary Materials). The yield depends on extrinsic factorssuch as the extraction technique, type of solvent, operating conditions, and environmentalaspects of the grape crop, as well as intrinsic factors such as grape variety. Grape seedoil is composed mainly of triglycerides (usually about 99%) and unsaponifiable materials(typically 1%). Triglycerides are ester derivatives of glycerol and fatty acids. The mainunsaponifiable compounds include phytosterols, phenols, vitamin E, and others (refer to Figure 3)

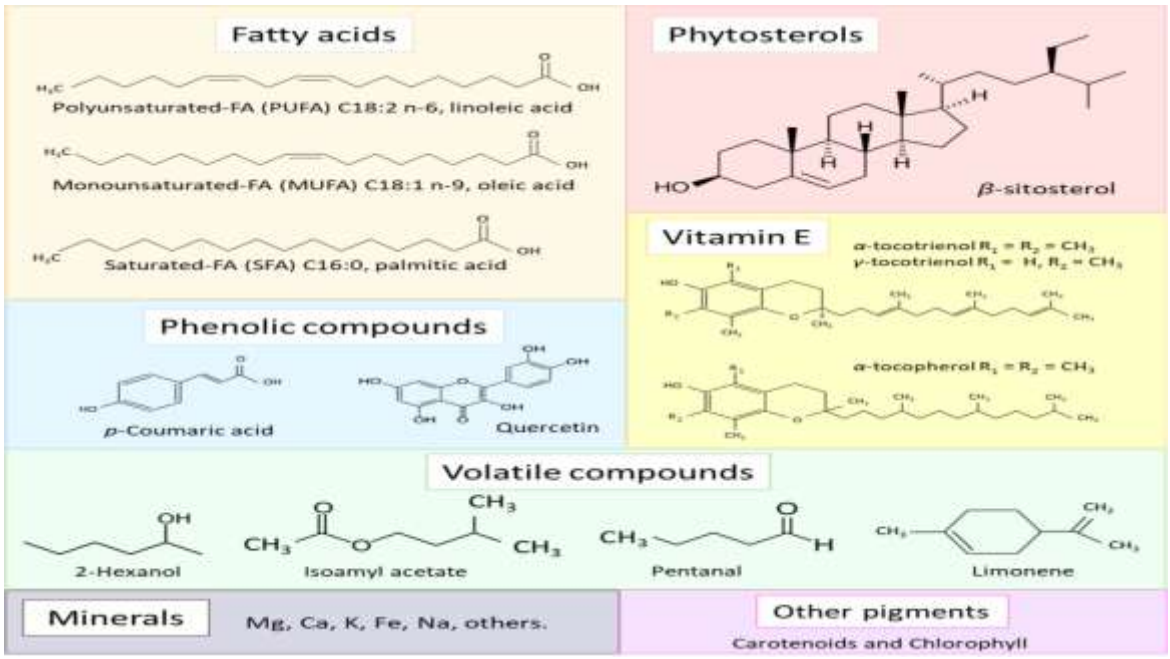

Figure 3. Main compounds of grape seed oil.

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III. CONCLUSION

Grape seed extract (GSE), rich in proanthocyanidins and polyphenolic compounds, has demonstrated significant antioxidant, anti-inflammatory, and anti-diabetic properties through both in vitro and in vivo studies. Clinical evidence suggests that GSE supplementation in patients with type 2 diabetes mellitus and chronic periodontitis may improve oxidative stress, inflammatory markers, and glycemic control. Additionally, phytosome and encapsulated formulations of GSE enhance bioavailability and therapeutic efficacy. GSE's protective role against oxidative damage, particularly in renal and skin health, underscores its potential as a natural therapeutic agent. The extraction method, particle size, and formulation significantly influence its phenolic content and pharmacological activity, suggesting the need for optimized processing methods. Given these findings, GSE emerges as a promising complementary therapy for managing chronic conditions related to oxidative stress and inflammation.

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