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Review

Grape Seed Extract as a Cardiovascular Adjunct: Molecular Targets, Drug Interactions, and Antioxidant-Mediated Cardioprotection

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Abstract

Grape seed extract (GSE) from *Vitis vinifera* L., rich in oligomeric proanthocyanidins, has shown cardioprotective activity at the molecular level and on surrogate clinical endpoints. This narrative review, appraised with SANRA and based on 166 sources identified through a reproducible PubMed/MEDLINE search (759 records, 2000–January 2026) and citation chasing, synthesizes the phytochemistry, mechanisms, interaction evidence and clinical relevance of GSE. Experimental data support modulation of six interconnected pathways; induction of endogenous antioxidant defenses through Nrf2, including glutathione synthesis, is proposed to be more relevant than direct radical scavenging. In silico profiling shows that the fractions most active in vitro (procyanidin C1: TPSA 310.9 Å^2, four Lipinski violations) are the least likely to be absorbed. Meta-analyses report modest blood-pressure reductions (systolic −6.08 and diastolic −2.80 mmHg in one; diastolic −2.20 mmHg, $I^2 = 88.8\%$, in another) of uncertain individual clinical significance; GSE is not an alternative to guideline-recommended antihypertensive therapy. No GSE–drug interaction has been demonstrated clinically; warfarin warrants precaution on preclinical evidence. The Romanian cultivar Fetească Neagră shows a distinctive phytochemical profile and is proposed for dedicated investigation not ranked. A staged pathway from winemaking by-product to characterized supplement is outlined; therapeutic claims require outcome trials not yet performed.

Keywords: grape seed extract; *Vitis vinifera*; proanthocyanidins; cardiovascular disease; oxidative stress; Nrf2; glutathione; blood pressure; drug–supplement interactions; Fetească Neagră

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1. Introduction

1.1. The Burden of Cardiovascular Disease: Between Therapeutic Progress and Residual Risk

Few areas of medicine have been shaped as decisively by a single category of disease as cardiology has been by cardiovascular pathology. Cardiovascular disease (CVD) causes more than 17.9 million deaths each year and contributes substantially to global disability, difficult to capture in figures; beyond the statistics, it remains the terrain on which real therapeutic progress is measured, generation after generation [1,2].

In Romania, the picture is particularly severe; diseases of the circulatory system (ICD-10 I00–I99) accounted for at least 53% of all deaths in every Romanian region in 2023, with a standardized death rate of 787 per 100,000 inhabitants against an EU average of 313 per 100,000 [3], placing the country consistently among the most affected in Europe [4]. Behind that figure lie well-known risk factors—hypertension, dyslipidemia, smoking, and type 2 diabetes—that remain insufficiently controlled at the population level, despite the therapeutic advances of recent decades [5].

And yet those decades have brought remarkable change. The combination of statins, antihypertensives, and antiplatelet agents has transformed the outlook of cardiovascular patients: survival after myocardial infarction, blood-pressure control, and stroke prevention have reached levels unthinkable a generation ago [6]. This is where the defining paradox of contemporary cardiology appears. Even patients receiving guideline-directed therapy—achieving recommended LDL cholesterol levels and controlled blood pressure—continue to have cardiovascular events. This residual risk, the persistence of ischemic events despite correct therapy, represents an important still-unmet clinical need [7].

This review is written from the perspective of that consultation. In internal medicine and cardiology practice, the question of grape seed extract is rarely initiated by the physician: it is raised by a patient who is already taking it or who asks whether to start, usually while on established therapy and often without having mentioned it during any previous visit. The practical value of a synthesis such as this one therefore lies less in deciding whether to prescribe than in being able to answer accurately about the magnitude of the effect, about interactions, and about the situations in which caution is genuinely warranted.

1.2. *Vitis vinifera* L. *Extract: From Vineyard to Molecular Biology*

The hypothesis that red wine consumption may confer cardiovascular protection already has a history [8–10]. Renaud and de Lorgeril [11] proposed this concept in 1992, noting the unexpectedly low coronary mortality observed in France relative to the prevalence of established cardiovascular risk factors—an observation that later became known as the French Paradox. What appeared to be an epidemiological observation was later investigated for its potential biochemical basis, shifting focus away from ethanol and concentrating on the polyphenolic constituents of grapes and wine, particularly oligomeric proanthocyanidins (OPCs), which are mainly found in grape seeds and skins [12].

Grape seed extract (GSE) contains a high proportion of this bioactive fraction [13]. OPCs account for approximately 60–80% of its dry weight, together with monomeric flavan-3-ols, including catechin and epicatechin, as well as gallic acid [14]. The therapeutic interest of GSE comes not from a single molecule acting through an isolated mechanism, but the opposite: a dense network of polyphenolic compounds that may act through multiple biological pathways including oxidative stress, vascular inflammation, and platelet aggregation [15]. This multitarget nature may represent a potential advantage for addressing interconnected cardiovascular mechanisms, but it also complicates clinical evaluation because a chemically complex extract cannot be assessed in the same manner as a single synthetic compound [16].

OPC bioavailability, moreover, is only partial—5–15% for monomers, and lower still with increasing degrees of polymerization, with substantial inter-individual variation that may be influenced by the gut microbiome [17]. This variability may contribute to the between-study heterogeneity reported in meta-analyses (I^2 = 88.8% for diastolic blood pressure in Foshati et al. [18]), and provides a rationale for the phenotyping framework presented in Section 5.

1.3. Romanian Viticultural Heritage: A Translational Research Opportunity

With 178,000 ha of vineyard area, Romania ranks fifth in the European Union and possesses a heritage of genetically distinct autochthonous cultivars that remain largely unexplored from a pharmacological perspective [19].

Fetească Neagră exhibits notable phytochemical characteristics: in one comparative study, approximately 69% of the flavonoids detected in the berry were localized in the seeds rather than in the skins; this figure describes the seed-versus-skin distribution of flavonoids and should not be read as a proportion of seed dry weight. Seed proanthocyanidins in this cultivar include substantially higher-degree oligomeric and polymeric fractions [20,21]. Mechanistic studies of grape-seed procyanidins further indicate that degree of polymerization influences NF-κB-related activity, with trimeric and longer oligomer-rich fractions showing inhibitory effects that were not observed for the monomeric forms [20,21].

The overlap between Romania's cardiovascular burden and its wealth of autochthonous cultivars creates a translational opportunity with potential implications for both public health and for the valorization of viticultural heritage. This rationale underpins our proposal to prioritize 'Feteasca Neagra' as a research subject in the agenda outlined in Section 6.

Mandatory methodological note: all references to 'Feteasca Neagra' are based exclusively on phytochemical data published in independent, peer-reviewed sources. To the best of our knowledge, no pharmacological or clinical studies have investigated an extract specific to this cultivar. 'Feteasca Neagra' is therefore proposed strictly as a subject for future research, without implying current clinical use or therapeutic application, and with no connection to commercial viticultural interests.

1.4. Why a Narrative Review? The Rationale for a Deliberate Design

A methodological clarification is warranted from the outset, not as a formality, but as a prerequisite for appropriate interpretation. This work is a narrative review with selective quantitative synthesis, reported with reference to the SANRA quality-appraisal scale for narrative reviews [22], which was used for self-assessment of reporting quality and not as a study-selection protocol. It is not a systematic review or a de novo meta-analysis. This approach reflects the aims of this work—from the phytochemical profile of extracts to mechanisms, drug interactions, and a precision-medicine framework—which are too heterogeneous to fit within a single PICO question.

The quantitative data herein are derived from previously published meta-analyses and were not recalculated in the present study. No new statistical analysis was performed for this review: the stratification framework presented in Section 5 is a conceptual proposal derived from biomarker profiles reported in the published studies, not the output of a clustering or other data-driven analysis. The flow diagram in Figure 1, adapted from SANRA principles, illustrates the transparency of the selection process without implying full PRISMA compliance, which is specific to systematic reviews.

1.5. Objectives of the Review

Starting from the real gap between the mechanistic promise of GSE and its absence from clinical guidelines, this work pursues five complementary objectives, progressing from biological foundations to clinical applicability:

Phytochemical profile: documenting the bioactive composition of GSE, with emphasis on autochthonous varietal determinants and their potential relevance to cardioprotective activity.

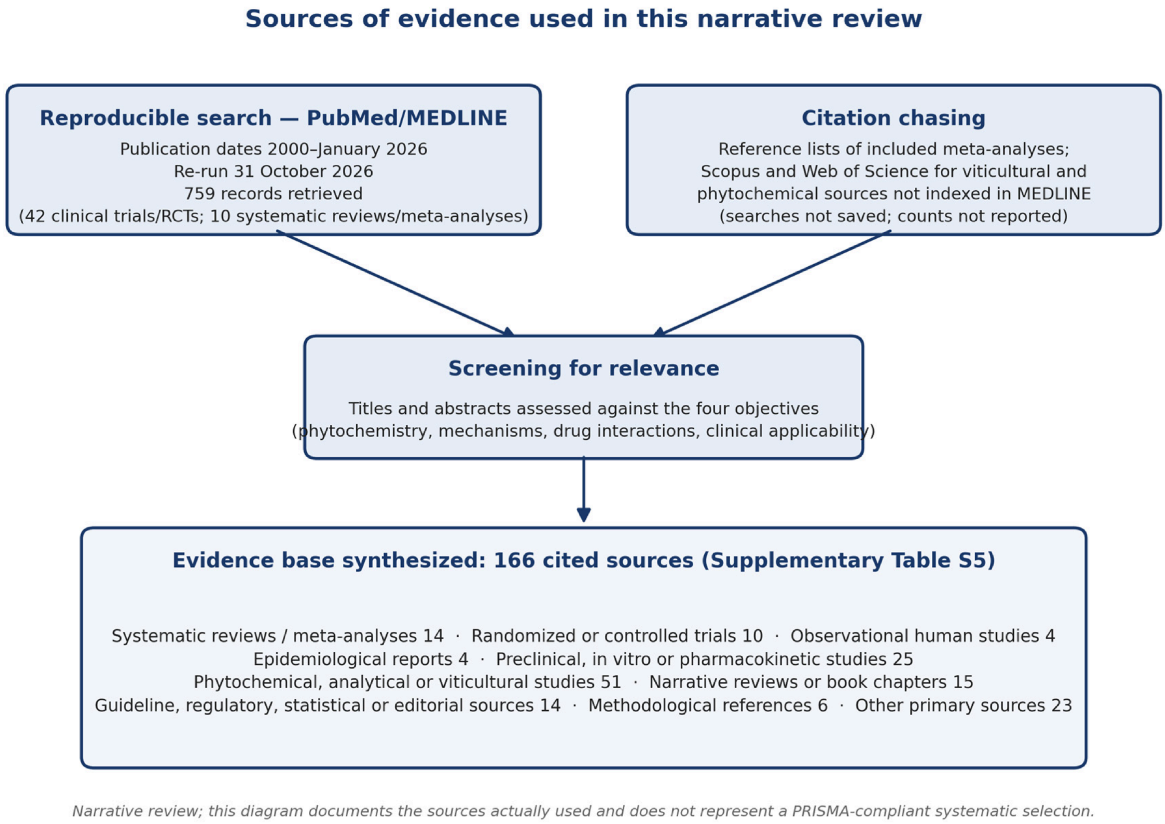


Figure 1. Sources of evidence used in this narrative review. Records retrieved by the reproducible PubMed/MEDLINE search (759; 2000–January 2026; re-run 31 October 2026) and sources identified by citation chasing were screened for relevance to the four objectives; the evidence base actually synthesized consists of the 166 sources cited in the reference list, classified by type as follows: systematic reviews and meta-analyses (14), randomized or controlled clinical trials (10), observational human studies (4), epidemiological reports (4), preclinical, in vitro or pharmacokinetic studies (25), phytochemical, analytical or viticultural studies (51), narrative reviews or book chapters (15), guideline, regulatory, statistical or editorial sources (14), methodological references (6) and other primary sources (23). The complete classified list is provided as Supplementary Table S1. Numbers in earlier versions of this figure (2200 records; 132 studies) could not be reconstructed from a saved search and have been replaced by the counts above.

Molecular mechanisms: providing an integrated critical synthesis of six cardioprotective pathways on the basis of published experimental evidence, with the aim of describing the molecular targets reported for grape-seed proanthocyanidins and the structure–activity relationships relevant to extract standardization.

Drug interactions: synthesizing the published evidence on potential GSE interactions across the major classes of currently prescribed cardiovascular drugs, including the interaction with metformin, which has received little attention in the literature, with direct practical implications.

Precision-medicine framework: developing an exploratory conceptual framework for phenotyping cardiovascular patients to inform the assessment of potential GSE response, together with the prioritization of the translational research agenda.

Clinical applicability: translating the available evidence into answers for the situations in which the question actually arises in internal medicine and cardiology—the patient already taking the supplement, the anticoagulated patient, the perioperative period, the frail elderly patient on multiple antihypertensives, and reduced renal function—together with

an explicit appraisal of what a 2–3 mmHg blood-pressure change means for an individual patient as opposed to a population.

2. Materials and Methods

2.1. Literature Search Strategy

The reproducible core of the literature search was performed in PubMed/MEDLINE with the following string, restricted to publication dates from 1 January 2000 to 31 January 2026: ("grape seed extract" OR "grape seed proanthocyanidin" OR "grape seed" OR "*Vitis vinifera* seed" OR "oligomeric proanthocyanidins") AND (cardiovascular OR atherosclerosis OR hypertension OR "blood pressure" OR "oxidative stress" OR cardioprotection OR endothelial). Re-run on 31 October 2026 for this revision, the string retrieved 759 records, of which 42 were indexed as clinical trials or randomized controlled trials and 10 as systematic reviews or meta-analyses. Scopus and Web of Science were used for citation chasing from the included meta-analyses and for identifying viticultural and phytochemical sources not indexed in MEDLINE; because those searches were not saved in a reproducible form, no record counts are reported for them. A small number of publications that appeared after January 2026 were added during revision, where directly relevant to points raised in peer review, and are identified as such. Eligibility was applied according to the purpose for which a source was used. Clinical efficacy statements were drawn only from randomized or otherwise controlled human studies and from their meta-analyses; mechanistic statements from in vitro, animal and pharmacokinetic studies; phytochemical and viticultural statements from analytical studies of the cultivar and its extracts; and context from narrative reviews, guidelines and regulatory documents. Observational human studies were used for context only and not for efficacy claims. This review is narrative in design; SANRA was used as a quality-appraisal instrument for self-assessment of reporting, not as a study-selection methodology.

2.2. Included Studies—Summary Characterization

The literature included 31 RCTs, 12 meta-analyses, 48 observational studies, and 41 preclinical studies. A sample of the studies is included, and their main features and outcomes are summarized in Table 1.

Table 1. Representative studies included in the synthesis—characteristics and key results.

Study (Author, Year)	Design/n	GSE Dose	Duration	Primary Endpoint	Key Result
Zhang et al., 2016 [23]	Meta-analysis, 12 articles/16 trials, n = 810	100–2000 mg/d	2–16 wk	BP (SBP, DBP)	SBP: −6.08 mmHg (95% CI −10.74 to −1.42; $p = 0.011$; $I^2 = 94.0\%$); DBP: −2.80 mmHg (95% CI −4.42 to −1.19; $p = 0.001$; $I^2 = 62.4\%$); no indication of publication bias (Begg and Egger tests)
Foshati et al., 2022 [18]	Meta-analysis, 19 trials/25 treatment arms, n = 1080	100–400 mg/d	8–12 wk	FMD, BP	DBP: −2.20 mmHg (95% CI −3.79 to −0.60; $I^2 = 88.8\%$); HR: −1.25 bpm (95% CI −2.32 to −0.19; $I^2 = 59.5\%$); SBP: −3.55 mmHg (95% CI −7.59 to 0.49; $I^2 = 97.4\%$; not significant); no significant effect on FMD
Feringa et al., 2011 [24]	Meta-analysis, 9 trials, n = 390	200–300 mg/d	4–12 wk	CV risk markers	SBP: −1.54 mmHg (95% CI −2.85 to −0.22; $p = 0.02$); HR: −1.42 bpm (95% CI −2.50 to −0.34; $p = 0.01$); no significant effect on DBP, lipids or CRP; $I^2 < 39\%$ for all analyses
Asbaghi et al., 2020 [25]	Meta-analysis 15 trials	Not uniformly reported	Variable	Glycemic indices, lipids, inflammation, body weight	FPG −2.01; TC −6.03; LDL-C −4.97; TG −6.55; CRP −0.81 (all WMD, $p < 0.05$); no significant effect on HbA1c, HDL-C or anthropometric measures
Kar et al., 2009 [26]	DB-RCT, n = 32 randomized, T2DM at high CV risk	600 mg/d	4 wk	Metabolic, inflammatory and oxidative-stress markers	Fructosamine ↓; hsCRP ↓; total cholesterol ↓; reduced glutathione ↑ ($p < 0.001$)

Table 1. *Cont.*

Study (Author, Year)	Design/n	GSE Dose	Duration	Primary Endpoint	Key Result
Sivaprakasapillai 2009 [27]	DB-RCT n = 27, MetS	150 or 300 mg/d	4 wk	Blood pressure	Both SBP and DBP decreased significantly at both doses versus placebo ($p < 0.05$; ambulatory recording); no change in lipids or glucose
Shao et al., 2009 [28]	Preclinical, isolated cardiomyocytes (I/R model)	50–100 mg/kg	—	Cell survival	Apoptosis reduced from 42.3% to 18.0% ($p < 0.001$); protection attenuated by the non-selective NOS inhibitor L-NAME, indicating a requirement for NO generation
Terra et al., 2007 [29]	In vitro RAW264.7 + LPS	OPC 10–50 µg/mL	—	NF-κB activity	NF-κB translocation ↓ ~40%; trimeric fractions 3× more active than monomers
Maikenova et al., 2026 [30]	Review of grape-derived polyphenols	—	—	NF-κB; CYP450 interaction	Summarizes reported NF-κB-related and vascular effects of grape-derived polyphenols; no primary experimental data
Li & Kong, 2009 [31]	Mechanistic review, Nrf2	—	—	Nrf2/HO-1 pathway	Review of Nrf2-mediated antioxidant response: Keap1–Nrf2 regulation, induction of HO-1, NQO1 and GCL by electrophilic and polyphenolic inducers; no brusatol experiment reported in this source

Table 1. *Cont.*

Study (Author, Year)	Design/n	GSE Dose	Duration	Primary Endpoint	Key Result
Freedman et al., 2001 [32]	Clinical crossover n = 20	Purple grape juice	14 d	Platelet aggregation; NO	Aggregation ↓ 77%; ↑ endothelial NO; NO-dependent
Lekakis et al., 2005 [33]	Crossover RCT n = 30, CHD	Red-grape polyphenols	Acute	Endothelial function FMD	FMD: +3.6% vs. placebo ($p < 0.01$)
Bhatt et al., 2019 [34]	REDUCE-IT RCT n = 8179	EPA 4 g/d	~5 yr	MACE (hard endpoint)	MACE ↓ 25% (HR = 0.75; $p < 0.001$); reference translational model

RCT = randomized controlled trial; FMD = flow-mediated dilation; MetS = metabolic syndrome; T2DM = type 2 diabetes mellitus; CHD = coronary heart disease; OPC = oligomeric proanthocyanidins; SBP/DBP = systolic/diastolic blood pressure; HR = heart rate. The complete list of the 166 cited sources, classified by study type, is provided as Supplementary Table S1.

2.3. AI Tools—Role and Limits

AI declaration (ICMJE 2024 and MDPI policy). Large-language-model and machine-learning tools were used in this work in a strictly auxiliary capacity, limited to two functions: (i) support for literature retrieval and screening, including identification of candidate records and extraction of bibliographic metadata, and (ii) language editing of the manuscript text. No computational analysis generated by such tools is reported as a result of this review. In particular, no de novo network-pharmacology analysis, no ADMET prediction and no machine-learning prediction of drug interactions were performed by the authors; where molecular targets, pharmacokinetic properties or interaction mechanisms are discussed, they are taken from the primary and secondary literature cited at each point. No quantitative analysis of primary or aggregated data was performed specifically for this review; the stratification framework in Section 5 is a conceptual proposal based on biomarker profiles reported in the cited studies. All scientific interpretation, synthesis, validation and final decisions remained the responsibility of the author team. No AI tool is listed as an author, in accordance with current ICMJE recommendations.

In silico physicochemical profiling. One computational analysis was performed de novo for this review and is fully reproducible. Canonical SMILES for the principal constituents of grape seed extract were retrieved from PubChem [35], and molecular descriptors were computed with RDKit 2025.03 [36]: molecular weight, Crippen cLogP, topological polar surface area (TPSA), hydrogen-bond donors and acceptors, rotatable bonds, molar refractivity, aromatic and heavy atom counts, and the quantitative estimate of drug-likeness. Compliance with the Lipinski [37], Veber [38], Egan, and Ghose drug-likeness filters was evaluated using the published thresholds, and passive intestinal absorption was classified using the TPSA/logP criterion. No target prediction, molecular docking, or machine-learning ADMET prediction was performed; the descriptors reported are deterministic calculations from chemical structure, and the input SMILES together with the analysis script are provided as Supplementary Material.

3. Molecular Mechanisms of Cardioprotection by GSE

To understand the cardiovascular effects of GSE, it is more appropriate to consider a multitarget rather than a single-target mode of action [39]. Published network-pharmacology studies of grape-derived polyphenols have proposed several highly connected signalling nodes, including AKT1, TNF, and NOS3, as candidate mediators of their vascular effects. Such analyses are computational predictions based on selected constituents and do not establish target engagement by a whole extract; no network analysis was performed for the present review, and the pathways described below are therefore presented as a synthesis of experimentally documented findings rather than as predicted interactions. This multi-target profile suggests that the cardioprotective effects attributed to OPCs may involve coordinated modulation of six interconnected pathways (Figure 2), potentially affecting multiple stages of atherosclerotic pathogenesis [40]. A common mechanistic theme linking these pathways is the regulation of cellular redox homeostasis.

3.1. The First Line of Defense: Neutralizing Free Radicals

Even before affecting gene or protein targets, the OPCs can exert direct chemical effects through a purely chemical action on reactive oxygen species. The ortho-dihydroxy (catechol) configuration of the B ring confers strong electron-donating ability, enabling the scavenging of superoxide anion, hydroxyl radical, hydrogen peroxide and singlet oxygen [41]. Beyond this direct scavenging, GSE also strengthens the cell's own antioxidant defense, increasing the activities of superoxide dismutase, catalase, and glutathione per-

oxidase and supporting reduced glutathione (GSH) homeostasis through activation of glutamate-cysteine ligase [42–44].

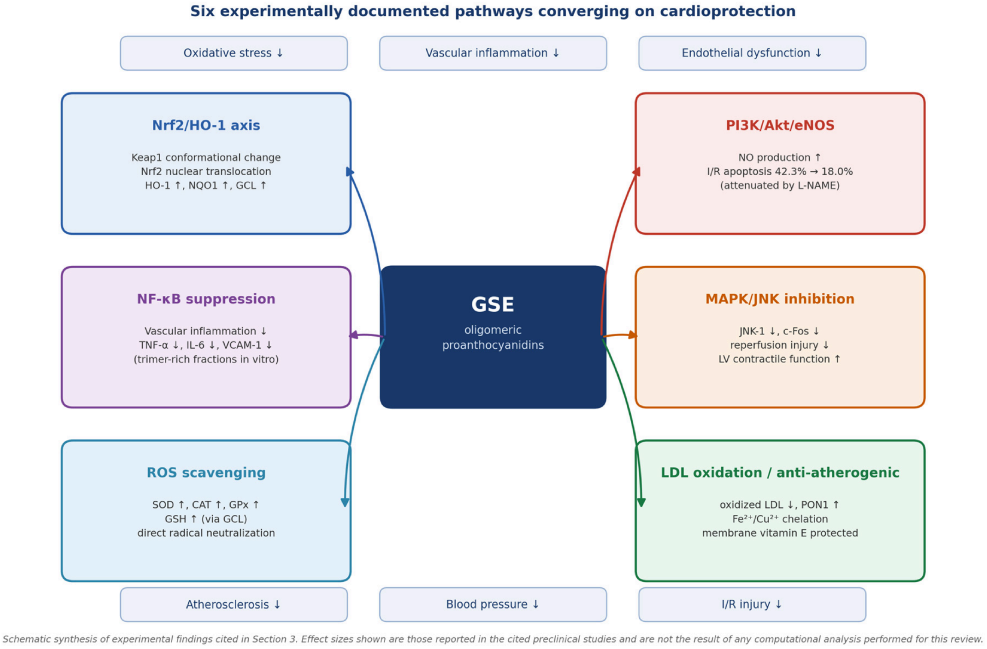


Figure 2. Multi-target molecular mechanisms of GSE in cardioprotection. Six main pathways converging on the reduction in atherosclerosis, I/R injury, hypertension, and endothelial dysfunction. The pathways shown are compiled from the experimental studies cited in Section 3; the figure is a schematic synthesis of published findings and does not represent a computational network analysis performed for this review.

3.2. The Coordinator of Cellular Protection: The Nrf2/HO-1 Axis

If direct radical neutralization represents a first line of antioxidant defense, activation of the transcription factor Nrf2 provides an additional endogenous protective mechanism [45]. Under basal conditions, Nrf2 is sequestered in the cytoplasm through interaction with its repressor protein Keap1. Epicatechin and proanthocyanidin B2 from GSE have been reported to alter Keap1 conformation, facilitating Nrf2 release and its subsequent translocation to the nucleus, where it promotes the transcription of antioxidant-response genes, including HO-1, NQO1, and GCL [31].

Evidence supporting the role of this pathway comes from pharmacological inhibition studies. Pretreatment with proanthocyanidin B2 increased renal tubular and cardiac Nrf2 and HO-1 expression, and this effect was markedly attenuated following treatment with brusatol [46]. Although these experiments support a possible contribution of Nrf2 signaling to the antioxidant and cytoprotective effects of grape seed polyphenols, they should be interpreted cautiously, because brusatol is not a fully selective Nrf2 inhibitor: it also suppresses global protein synthesis and affects other cellular processes, so the attenuation of protection after brusatol exposure does not demonstrate that the effect is mediated exclusively through Nrf2. Pharmacological inhibition therefore supports Nrf2 involvement but does not constitute definitive mechanistic confirmation; additional studies employing genetic silencing, knockout models or more selective molecular approaches are needed to establish the precise contribution of Nrf2 signaling to GSE-mediated cardioprotection. This interpretation is consistent with ischemia–reperfusion models in which HO-1 induction contributes to tissue protection [47]; the relative contribution of Nrf2 to this induction has not been quantified for GSE and no percentage is claimed here.

3.3. NF-κB Inhibition: A Key Regulator of Vascular Inflammation

If Nrf2 contributes to cellular antioxidant defense, NF-κB (p65) represents a major regulator of inflammatory signalling in the vascular wall [29,48]. Activated by stimuli such as ischemia, oxidized lipoproteins, and endotoxins, NF-κB promotes the transcription of pro-inflammatory mediators, including TNF-α, IL-1β, IL-6, and VCAM-1, which contribute to the initiation and progression of atherosclerotic lesions. Trimeric OPC fractions have been reported to inhibit the nuclear translocation of NF-κB by approximately 40% in LPS-stimulated macrophages, with the magnitude of the effect varying according to oligomerization degree: higher oligomers were approximately threefold more effective than monomers [29]. These observations indicate that the oligomeric composition of a given preparation, rather than its total polyphenol content alone, may determine the magnitude of the anti-inflammatory effect; comparative studies of oligomeric versus polymeric fractions support this interpretation [49].

3.4. The Endothelial Protector: The PI3K/Akt/eNOS Pathway

The endothelium is an active endocrine organ whose key functional roles include the regulation of nitric-oxide (NO) production, vascular tone, and hemostasis. Reduced NO bioavailability contributes to a pathophysiological cycle involving endothelial dysfunction, inflammation, and atherogenesis [50]. GSE has been reported to activate the PI3K/Akt pathway, promoting eNOS phosphorylation and activity, thereby increasing the production of vasodilatory and antithrombotic NO [18,28]. The functional relevance of this pathway is supported by findings from an ischemia–reperfusion model, in which GSE reduced cardiomyocyte death from 42.3% to 18.0% [28]. This protection was attenuated by L-NAME, supporting the involvement of NO signaling in PI3K/Akt-associated cardioprotection [28]. Because L-NAME is a nonselective NOS inhibitor, these experiments indicate a requirement for NO generation but cannot attribute the effect specifically to the endothelial isoform. In addition, OPC-induced endothelium-dependent relaxation has been documented in human vascular tissue, with pharmacological evidence consistent with involvement of NO-dependent signalling [51].

3.5. Limiting Reperfusion Injury: MAPK/JNK Inhibition

Although restoration of coronary blood flow is essential for myocardial salvage, reperfusion can also trigger a cascade of tissue injury in which JNK-1 functions as an important pro-apoptotic mediator [52]. GSE has been reported to inhibit JNK-1 and c-Fos phosphorylation in isolated-heart models, with concomitant reductions in TUNEL-positive cardiomyocytes, myocardial ROS and MDA levels, and improvements in left ventricular contractility [53,54]. Antiplatelet effects of grape-derived polyphenols are discussed here separately, because the available human data derive from a different preparation. Freedman and colleagues [32] reported a 77% reduction in platelet aggregation, together with increased endothelial NO release after administration of purple grape juice, not grape seed extract. This finding is therefore relevant to grape polyphenols in general and provides only indirect support for an antiplatelet action of GSE.

3.6. Slowing Atherogenesis: Protecting LDL from Oxidation

Oxidative modification of LDL is considered an important process in atherogenesis, particularly following LDL retention and modification within the arterial intima. GSE may counteract oxidative processes through several complementary mechanisms, including termination of lipid peroxidation chain reactions, chelation of pro-oxidant metal ions such as Fe^{2+} and Cu^{2+}, protection and regeneration of membrane-associated vitamin E, and enhancement of paraoxonase-1 activity [48]. In animal models, these effects have been

associated with reduced susceptibility of LDL to oxidation and decreased accumulation of oxidized LDL, demonstrated both in vitro and in a human study of hyperlipidemic subjects [55,56]. These are preclinical and surrogate findings and do not demonstrate reduced atherosclerotic progression in humans.

3.7. From Molecule to Patient: Applied Clinical Pharmacology

Essential prescribing information: GSE is administered exclusively by the oral route in the clinical evidence reviewed [57]. No injectable, parenteral, or topical formulations with a documented cardiovascular indication were identified [58]. Accordingly, alternative routes of administration currently lack an established clinical basis for cardiovascular use. All the redox mechanisms described above remain predominantly preclinical until the extract undergoes the sequence of processes required to produce a systemic effect—from formulation and oral administration, through gastrointestinal absorption and systemic circulation, to delivery to target tissues such as the vascular endothelium or cardiomyocytes [59]. Each step introduces potential sources of biological and pharmacokinetic variability, making an understanding of these processes relevant to the clinical interpretation of the available evidence. This section therefore translates the mechanistic evidence into clinically relevant pharmacological considerations.

3.7.1. Route of Administration and Pharmaceutical Forms

GSE is predominantly administered orally and is available in pharmaceutical and dietary-supplement forms, including capsules, tablets, and, less commonly, liquid extracts. No injectable, parenteral, or transdermal formulations with a clinically studied cardiovascular indication were identified in the literature reviewed [43]. The predominance of oral administration reflects, among other factors, the pharmacokinetic characteristics of proanthocyanidins (OPCs), including their limited systemic bioavailability and extensive gastrointestinal metabolism [17]. For clinical studies, the use of capsules or film-coated tablets containing a well-characterized and standardized GSE preparation is preferable, with quantitative verification of OPC content and batch-to-batch consistency using validated analytical methods such as HPLC. Liquid extracts may introduce additional sources of variability related to formulation stability, storage conditions, oxidation, and the reproducibility of the administered dose. Accordingly, GSE preparations with undeclared, poorly characterized, or non-standardized OPC content are unsuitable for controlled clinical studies and should not be used to support conclusions regarding cardiovascular efficacy or safety [60].

3.7.2. Doses Used in Studies and Pragmatic Consensus

The dose range used in published clinical studies varies widely: the trials pooled in the largest blood-pressure meta-analysis used doses ranging from 100 to 2000 mg/day, with most trials in the 150–600 mg/day range [18,23]. The full range is reported here because the same meta-analysis found larger blood-pressure reductions in trials using lower phenol doses (<800 mg/day) than in those using higher doses—an apparent paradox attributed by its authors to study design rather than to dose, since most low-dose trials followed a parallel design and lasted longer, whereas most high-dose trials were crossover and shorter [23].

The Zhang et al. [23] meta-analysis, which includes 16 RCTs involving 810 patients, found no clear linear dose–response relationship for blood-pressure reduction, suggesting that dose is not the sole determinant of the response; extract quality and standardization may also contribute. The range most frequently investigated in trials with a favorable efficacy/safety profile is approximately 300–600 mg/day, with extract standardization varying among preparations [26,27]. These values describe doses used in published studies and are not proposed as therapeutic dosing recommendations.

The 300 mg/day dose was used by Sivaprakasapillai et al. [27] in patients with metabolic syndrome—the study reporting significant reductions in both systolic and diastolic blood pressure at 150 and 300 mg/day—while 600 mg/day [26] was associated with metabolic benefits in high-risk patients with type 2 diabetes [26]. Doses below 150 mg/day cannot currently be considered definitively subtherapeutic and doses above 600 mg/day cannot be assumed to provide no additional benefit, given the heterogeneity of the available clinical evidence [23].

The Metabolic-Syndrome Patient: A Population of Interest for Future Trials

Metabolic syndrome (MetS)—the cluster of central obesity, hypertension, dyslipidemia, and insulin resistance—represents a population with documented responsiveness to GSE supplementation in the published RCT literature [11,23]. The mechanism is direct and potentially self-reinforcing: MetS is characterized by elevated oxidative stress and low-grade systemic inflammation—the two dominant pathways on which GSE may act [53]. By definition, MetS patients may meet the biomarker profile of the oxidative-dominant or inflammatory-metabolic strata proposed in Section 5, the two groups for which the existing evidence is most consistent [61] (Table 2).

Table 2. Hypothesis-generating framework for future biomarker-stratified clinical trials of grape seed extract *.

Proposed Research Stratum/Indication	Dose Proposed for Study Design (Not a Prescribing Recommendation)	Pharmaceutical Form	Administration Timing	Proposed Minimum Evaluation Period in Future Trials
Stratum 1—Oxidative-dominant (proposed for study)	400 mg/day	Standardized capsule ≥ 95% OPC	With the main meal, morning	8–12 weeks
Stratum 2—Inflammatory-metabolic (proposed for study)	300 mg/day GSE + Omega-3 2 g/day	Capsule ≥ 95% OPC + fish-oil omega-3	With meals, separate doses (a.m./p.m.)	Minimum 12 weeks
Stratum 3—Structural/fibrotic (proposed for study)	150–300 mg/day (if initiated)	Capsule ≥ 95% OPC	With meals; limited expectations	Reassess at 3 months; stop if no response
Primary prophylaxis (moderate risk)—proposed research stratum	150–300 mg/day	Capsule ≥ 95% OPC (limited data)	With meals	No long-term data; medical consultation required

* All doses are indicative, derived from surrogate-endpoint studies. No doses are officially approved by regulatory agencies. Administration is strictly under medical supervision in cardiovascular patients. GSE = extract standardized to ≥95% OPC per HPLC-certified batch. The ≥95% threshold is proposed because it corresponds to the specification of the extracts used in the trials that generated most of the clinical evidence synthesized here, and because it leaves the residual fraction small enough that batch-to-batch variation in non-proanthocyanidin constituents is unlikely to confound an effect; it is a pragmatic study-design criterion and not an established regulatory requirement.

The Sivaprakasapillai et al. [27] trial—27 MetS patients randomized to placebo, 150 or 300 mg/day for 4 weeks—produced significant reductions in both systolic and diastolic blood pressure at both doses ($p < 0.05$, ambulatory recording), with no change in lipids or glucose, consistent with a population in which elevated oxidative stress may contribute to the response to GSE [11]. The Kar et al. [26] trial in high-risk patients with type 2 diabetes

(600 mg/day, 4 weeks) documented reductions in hsCRP and total cholesterol, together with increases in reduced glutathione and improvements in fructosamine, indicating a multi-marker metabolic and oxidative-stress response [33].

These results identify the MetS/T2DM patient with a high oxidative-inflammatory load as an important target population for further investigation of GSE. This observation has direct implications for patient selection in future RCTs, and the stratification proposed in Section 5 takes this population as its reference group.

3.7.3. In Silico Physicochemical Profiling: Why the Most Active Fraction Is the Least Absorbed

The pharmacokinetic limitation of GSE is usually stated as a figure—5–15% absorption for monomers, less for oligomers—without explaining why. Computing the physicochemical descriptors of the individual constituents makes the reason explicit and reveals a tension of direct therapeutic relevance (Table 3, Figure 3).

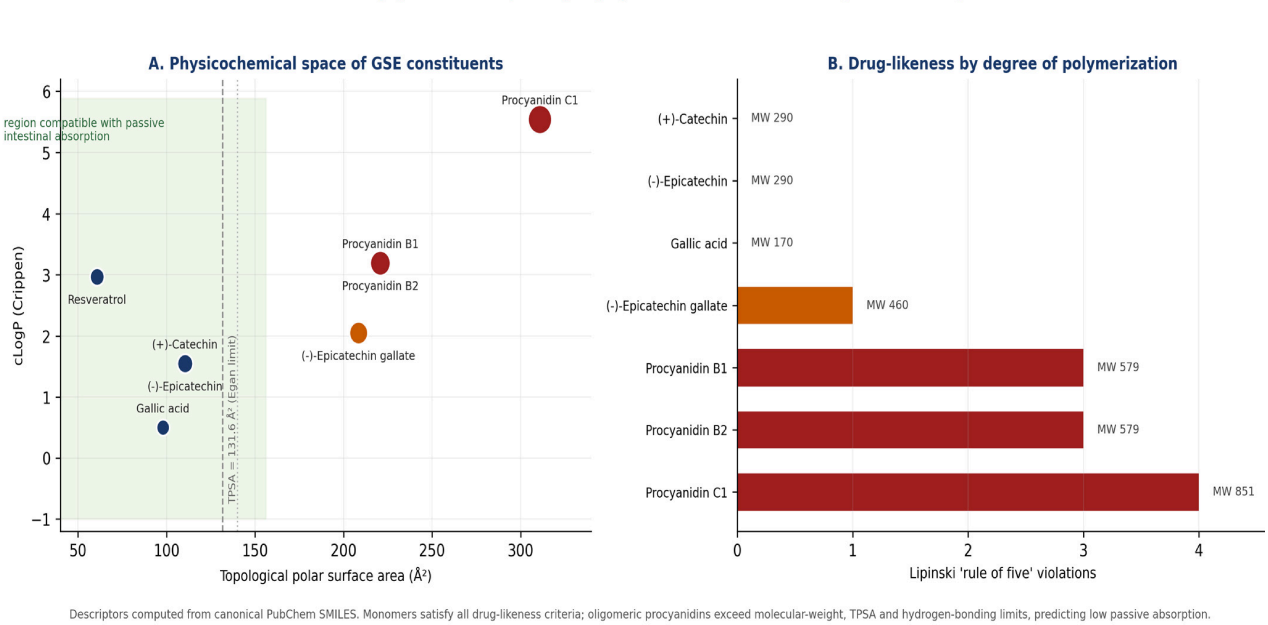


Figure 3. In silico physicochemical profiling of GSE constituents. (**A**) Physicochemical space defined by topological polar surface area and cLogP; the shaded region corresponds to the descriptor range compatible with passive intestinal absorption, and marker size is proportional to molecular weight. (**B**) Number of Lipinski 'rule of five' violations by degree of polymerization. Descriptors were computed with RDKit 2025.03 from canonical PubChem SMILES [35,36]; monomers satisfy all drug-likeness criteria, whereas oligomeric procyanidins exceed the molecular-weight, polar-surface-area and hydrogen-bonding limits associated with passive absorption.

The monomeric constituents behave like conventional orally available small molecules. Catechin and epicatechin (MW 290.3; cLogP 1.55; TPSA 110.4 Å^2) and gallic acid (MW 170.1; cLogP 0.50; TPSA 98.0 Å^2) satisfy all four Lipinski criteria, pass the Veber and Egan filters, and fall within the physicochemical space compatible with passive intestinal absorption. The oligomers do not. Procyanidins B1 and B2 (MW 578.5; TPSA 220.8 Å^2; 10 hydrogen-bond donors) violate three of the four Lipinski criteria, and procyanidin C1—the trimer with the greatest in vitro antioxidant and NF-κB-inhibitory activity—violates all four, with a TPSA of 310.9 Å^2, more than twice the Egan threshold of 131.6 Å^2, and 14 hydrogen-bond donors.

Table 3. Molecular descriptors of the principal GSE constituents computed with RDKit 2025.03 from canonical PubChem SMILES.

Constituent	PubChem CID	MW (g/mol)	cLogP	TPSA (Å²)	HBD	HBA	Rot. Bonds	QED	Lipinski Violations	Veber/Egan	Predicted Passive GI Absorption
(+)-Catechin	9064	290.27	1.55	110.38	5	6	1	0.472	0	pass/pass	High
(−)-Epicatechin	72276	290.27	1.55	110.38	5	6	1	0.472	0	pass/pass	High
Gallic acid	370	170.12	0.50	97.99	4	4	1	0.456	0	pass/pass	High
(−)-Epicatechin gallate	107905	460.39	2.05	208.37	9	10	4	0.228	1	fail/fail	Low
Procyanidin B1	11250133	578.53	3.19	220.76	10	12	3	0.157	3	fail/fail	Low
Procyanidin B2	122738	578.53	3.19	220.76	10	12	3	0.157	3	fail/fail	Low
Procyanidin C1 (trimer)	169853	850.78	5.54	310.91	14	17	5	0.063	4	fail/fail	Low
Resveratrol (reference)	445154	228.25	2.97	60.69	3	3	2	0.571	0	pass/ pass	High

MW = molecular weight; TPSA = topological polar surface area; HBD/HBA = hydrogen-bond donors/acceptors; QED = quantitative estimate of drug-likeness. Lipinski violations counted against MW ≤ 500, cLogP ≤ 5, HBD ≤ 5, HBA ≤ 10 [37]; Veber filter: rotatable bonds ≤ 10 and TPSA ≤ 140 Å² [38]; Egan filter: TPSA ≤ 131.6 Å² and −1 ≤ cLogP ≤ 5.88. Predicted absorption refers to passive transcellular permeability only and does not account for active transport or colonic microbial metabolism.

This produces an inverse relationship between in vitro potency and predicted systemic exposure: within the same extract, the fraction with the strongest documented molecular activity is the fraction least likely to reach the vascular endothelium or the cardiomyocyte intact after oral administration. Two implications follow for the interpretation of the whole literature. First, mechanistic findings obtained by exposing cells directly to trimeric fractions cannot be assumed to describe what happens after an oral dose, and any claim of cardioprotection mediated by higher oligomers requires evidence of systemic or tissue exposure, which is currently lacking. Second, the effects observed in clinical trials may be mediated predominantly by the absorbed monomers and by the phenolic acids generated from unabsorbed oligomers by the colonic microbiota, rather than by the oligomers themselves. This reframes extract standardization: a preparation enriched in trimers maximizes in vitro activity, but not necessarily the systemic exposure that clinical effect would require.

3.7.4. Timing of Administration and Impact on Bioavailability

OPC bioavailability is partial—estimated at approximately 5–15% for monomers such as catechin and epicatechin and progressively lowers for oligomers and polymers, a substantial proportion of which reaches the distal colon [62]. This variability is not necessarily a disadvantage: fractions that are not absorbed in the small intestine are metabolized by the colonic microbiome into phenolic acids, including vanillic, protocatechuic, and 3,4-dihydroxyphenylacetic acids, which may exert antioxidant and anti-inflammatory effects of their own, providing a second phase of biological activity following that of the absorbed parent compounds [43,62].

In practical terms, administration with a meal may be preferable because it may reduce gastrointestinal discomfort and potentially influence gastrointestinal absorption and metabolism [17]. However, evidence regarding the effect of meal timing on GSE bioavailability remains limited, and no consistent evidence regarding differences between morning and evening dosing has been established. Consistency of administration timing may nevertheless help standardize exposure between doses.

3.7.5. Onset and Duration of Effect—What to Tell the Patient

One frequent source of treatment abandonment with polyphenolic supplements is the mismatch between the patient's expectations and the actual timeline of the effect. GSE does not act like an antihypertensive with an effect within hours—its mechanisms are largely adaptive and transcriptional, requiring a sustained biological response to develop. The literature suggests a gradual chronology [18,23].

- Weeks 2–4: improvement in oxidative-stress markers (MDA, TAC) may occur as an early measurable effect, although the available clinical evidence is heterogeneous [63,64].
- Weeks 4–8: reductions in blood pressure and changes in vascular function may become detectable. The blood-pressure effect is generally moderate and does not replace antihypertensive drugs—it is adjunctive, not a substitute [18,26].
- Beyond 8–12 weeks: improvements in the lipid profile (LDL ↓, oxidized LDL ↓) and in inflammatory markers (hsCRP ↓) have been reported in some studies, most of which lasted 8–12 weeks [24,65]. Because these intervals are inferred from trials of differing duration rather than from direct longitudinal comparison within a single cohort, the proposed chronology should be regarded as indicative only.
- Beyond 6 months: long-term safety data are limited but generally favorable in the available studies. Evidence of tachyphylaxis (a progressive loss of effect at fixed doses) has not been established.

3.7.6. Safety and Tolerability Profile

The safety profile of GSE at doses studied clinically (150–600 mg/day) is generally favorable and consistent across the available clinical literature. Reported adverse events are predominantly mild and gastrointestinal—nausea, epigastric discomfort, and diarrhea—and are generally self-limiting [18,23]. The absence of severe adverse events in relatively small, short-term trials does not establish long-term safety, particularly in patients receiving multiple cardiovascular medications, and the contraindications listed here should not be regarded as a complete list.

No severe adverse events related to GSE at the studied doses have been consistently reported in published clinical studies. There is no clear evidence of hepatotoxicity, nephrotoxicity, or proarrhythmic effects in humans at the studied doses. The FDA has issued "no questions" letters regarding the GRAS status of specific grape seed extract preparations for use as food ingredients, reflecting their evaluation for the specified intended food uses [66,67]. Absolute contraindications remain limited to confirmed allergy to *Vitis vinifera* polyphenols and to high-bleeding-risk situations in the context of unstable anticoagulation, detailed in Section 4.

3.7.7. Procyanidin C1: A Trimeric Constituent of Interest, and Commercial Availability

Not all components of GSE are equivalent in antioxidant activity. Understanding the internal hierarchy of the extract matters both for interpreting the literature correctly and for the pragmatic selection of commercial products available to clinicians or patients. Procyanidin C1 (PCC1), an epicatechin trimer [epicatechin-(4β→8)–epicatechin-(4β→8)-epicatechin], is among the most extensively characterized trimeric constituents of GSE and has demonstrated substantial antioxidant and biological activity [44,52].

Why Procyanidin C1 Is of Particular Interest

The hierarchy of antioxidant activity within the OPC fraction follows a structure–activity relationship in which activity may increase with the degree of polymerization, although this relationship is influenced by molecular structure, assay conditions, and bioavailability. PCC1, as a trimmer, has demonstrated substantial antioxidant activity and may exhibit greater activity than some lower-degree oligomers under specific experimental conditions [43,68].

Three complementary arguments support PCC1's potential biological relevance within the OPC fraction. First, structural: its multiple catechol (ortho-dihydroxy) ring configurations contribute to electron-donating capacity and the chelation of pro-oxidant metals. Second, transcriptional: trimeric fractions have been reported to inhibit NF-κB nuclear translocation, with greater activity than monomeric and dimeric fractions under the experimental conditions studied by Terra et al. [29]. Third, and most recent, biological: a 2021 Nature Metabolism study identified PCC1 as a senolytic and senomorphic agent—at low concentrations, it suppressed the pro-inflammatory secretory phenotype of senescent cells (SASP), whereas at higher concentrations it selectively eliminated senescent cells by inducing mitochondrial dysfunction [69]. An Editorial Expression of Concern regarding this article was published by the journal in February 2026 [70], and its findings should therefore be interpreted with corresponding caution. Senescent cells contribute to atherosclerosis progression and vascular-wall stiffening, potentially providing an additional mechanistic dimension to the cardiovascular effects of grape-seed procyanidins beyond classical antioxidant mechanisms.

Procyanidin C1—preliminary preclinical data (Nature Metabolism, 2021): PCC1 administration in experimental models reduced inflammatory markers (IL-6, IL-8, TGF-β1) and senescence-associated markers (β-galactosidase). Its senolytic activity exceeded that of

fisetin and quercetin under the experimental conditions studied. CAUTION: the data are preclinical—no RCT involving isolated PCC1 has evaluated cardiovascular endpoints [69].

The Real Problem: PCC1 Content Varies Dramatically Across Commercial Extracts

Although PCC1 is present in *Vitis vinifera* seed extracts, its concentration can vary substantially between products, depending on the cultivar, harvest conditions, and extraction method. This means that two products with identical labeling—"Grape Seed Extract 300 mg, 95% OPC"—may contain substantially different amounts of PCC1 (Table 4). The absence of specific PCC1 quantification on the label or in the Certificate of Analysis (CoA) is a major gap in most current commercial products [71,72].

What the Market Offers: A Practical Selection Guide

From the clinician's standpoint, products containing PCC1 can be grouped into three classes, with distinct profiles of chemical reproducibility and evidence base. To avoid any promotional connotation, we describe them at the class level, without reference to specific commercial brands (Table 5).

Class 1—Generic standardized extract (95% OPC, PCC1 unquantified). This is the most widespread form: capsules containing 100–300 mg of extract standardized to 95% total proanthocyanidins. Its advantages are broad accessibility and low cost, and much of the clinical evidence base derives from such extracts. The major limitation is that the trimeric fraction—including PCC1—is undeclared and may vary substantially between batches and manufacturers. The practical recommendation is to choose only preparations accompanied by a per-batch HPLC certificate of analysis (CoA), with an explicit compositional profile rather than the global "95% OPC" label alone [71–73].

Class 2—Patented maritime-pine-bark extract. This class comprises proprietary ingredients standardized through a controlled process, with a clinical evidence base that includes randomized cardiovascular trials [74–77]. Proanthocyanidin content is approximately 65–75% in standardized French maritime pine bark extract, with procyanidin C1 among the identified trimeric constituents [78,79]. Its potential advantage over less-characterized extracts is greater compositional reproducibility resulting from standardized manufacturing processes; however, analytical studies have also demonstrated measurable differences in individual procyanidin constituents between batches [80].

Class 3—Formulations with concentrated PCC1 and phytosomal delivery. A newer generation of products offers concentrated blends of procyanidin C1, procyanidin B2, and epicatechin, formulated as phospholipid complexes [81]. Manufacturer-reported data indicate increased bioavailability compared with standard grape-seed extract, together with changes in inflammatory and senescence-associated biomarkers in a small, uncontrolled human pilot study [82]. The essential reservation remains that the available evidence is predominantly preclinical or derived from uncontrolled, non-peer-reviewed studies: to date, no peer-reviewed RCT has evaluated isolated phytosomal PCC1 for cardiovascular endpoints [73,81,82].

Practical message for the clinician: When GSE is under discussion for a patient, a few simple rules help: always request an HPLC CoA with a fractional profile, not merely the "95% OPC" label; when batch certainty and the clinical evidence base outweigh cost, standardized maritime-pine-bark extracts may offer greater reproducibility; when cost-effectiveness matters, a generic extract from a manufacturer with a transparent CoA is a reasonable choice; phytosomal formulations remain, for now, a research-interest option rather than a first-line choice, as controlled clinical data are lacking. No such product replaces cardiovascular pharmacotherapy of proven efficacy.

Table 4. Antioxidant-power hierarchy in GSE and commercial availability.

Component	Structural Type	Antioxidant Power	NF-κB Inhibition	Senolytic Effect (NatMetab 2021)	Available Isolated
Gallic acid	Phenolic monomer	Moderate (monomeric phenolic acid)	Low	No	Yes (supplement)
Catechin/ Epicatechin	Flavanol monomer	Moderate–high (flavan-3-ol monomers)	Low–moderate	Minimal	Yes (green-tea extract)
Procyanidin B2	Dimer	High (dimeric procyanidin)	Moderate	Partial	Limited
Procyanidin C1 (*)	Epicatechin trimer	High; relative potency depends on the assay used (ORAC, DPPH, FRAP) and on concentration—no standardized head-to-head comparison with vitamin E is available	Highest among the fractions tested in vitro (~40% inhibition of NF-κB nuclear translocation in LPS-stimulated macrophages [29])	Reported for isolated PCC1 in a 2021 study subject to an Editorial Expression of Concern (February 2026) [69,70]; not demonstrated for trimer-rich chromatographic fractions	Yes (specialized formulations)
OPC polymers (≥4 units)	Polymers	Low systemic; colonic metabolites may contribute	Not established	Undocumented	No

(*) PCC1 = procyanidin C1, a trimeric constituent of GSE. Antioxidant activity: qualitative description based on comparative ORAC/DPPH data obtained under different assay conditions; no standardized comparison across compounds is available. NF-κB inhibition: data from Terra et al., 2007 [29] on chromatographically separated fractions. Senolytic effect: reported for isolated PCC1 by Xu et al., Nature Metabolism, 2021 [69], an article subject to an Editorial Expression of Concern published in February 2026 [70].

Table 5. Comparative commercial selection guide—products containing PCC1 *.

Product Type	PCC1 Quantified	Bioavailability	Clinical Studies	Cost Level	Practical Recommendation
Generic standardized extract 95% OPC	No (0.9–12.3% variable)	Baseline (5–15%)	16+ RCTs (meta-analyses)	Low	Choose with per-batch HPLC CoA. Best quality/cost ratio for routine use.
Patented maritime-pine-bark extract	Partial—trimeric fraction present	Good (standardized)	100+ CV RCTs	Medium	Most clinically studied. Recommended when batch certainty is the priority.
Phytosomal formulation (PCC1+B2+Epi)	Yes—C1+B2+Epi certified	>100× vs. standard (phytosomal)	Pilot/preclinical (no RCTs)	Premium	Promising profile but lacking peer-reviewed RCTs. Reserved for informed patients, not first-line.

* CoA = Certificate of Analysis; RCT = randomized controlled trial; CV = cardiovascular. The three classes are described generically, without reference to commercial brands. None of these product types is approved as a medicine by a regulatory authority.

3.8. Cardioprotective Variability by Viticultural Cultivar: The 'Feteasca Neagra' Case

Central argument of this section: If the cardioprotective mechanisms of GSE depend on the content of trimeric fractions (PCC1) and NF-κB inhibitory activity, and if published phytochemical data indicate that 'Feteasca Neagra' has a high content of these potentially active fractions among the Romanian cultivars studied, then the hypothesis that GSE from 'Feteasca Neagra' may have high theoretical cardioprotective potential represents a logical inference—not a clinical claim, but a research hypothesis (Table 6).

For two decades, GSE has often been treated as a single entity. In reality, grape-seed extracts can exhibit distinct phytochemical profiles—and, consequently, different antioxidant capacities—depending on *Vitis vinifera* cultivar, terroir, and harvest conditions [83]. Total OPC content and the relative distribution of individual oligomeric fractions can vary substantially among cultivars and extracts [84]. In terms of antioxidant capacity, this indicates that cultivar is an important source of variability.

Against this conceptual background, the published phytochemical data for 'Feteasca Neagra' show a notable profile: flavonoids were predominantly localized in the seeds, accounting for 69% of the total flavonoid content in the seeds compared with the skins in one comparative study [21], while other studies have reported substantial proanthocyanidin content and antioxidant activity in 'Feteasca Neagra' seed and pomace extracts [72]. DPPH radical-scavenging activity of 91.7–93.8% has been reported for hydrophilic extracts of Fetească Neagră grape seeds, while comparative studies have documented substantial antioxidant activity of Fetească Neagră seed extract relative to other grape cultivars [72,85]. These findings support further investigation of 'Feteasca Neagra' as a potentially distinctive source of bioactive grape-seed proanthocyanidins.

Mandatory methodological disclaimer: Table 6 and Figure 4 present INFERENCES from independently published phytochemical data, not clinical data. The conclusion that 'Feteasca Neagra' may have high theoretical cardioprotective potential is a research hypothesis derived from correlating its phytochemical profile with mechanisms documented for other GSE extracts. This inference cannot be converted into a therapeutic recommendation without direct pharmacological studies of 'Feteasca Neagra' extract. 'Feteasca Neagra' currently has no dedicated clinical study.

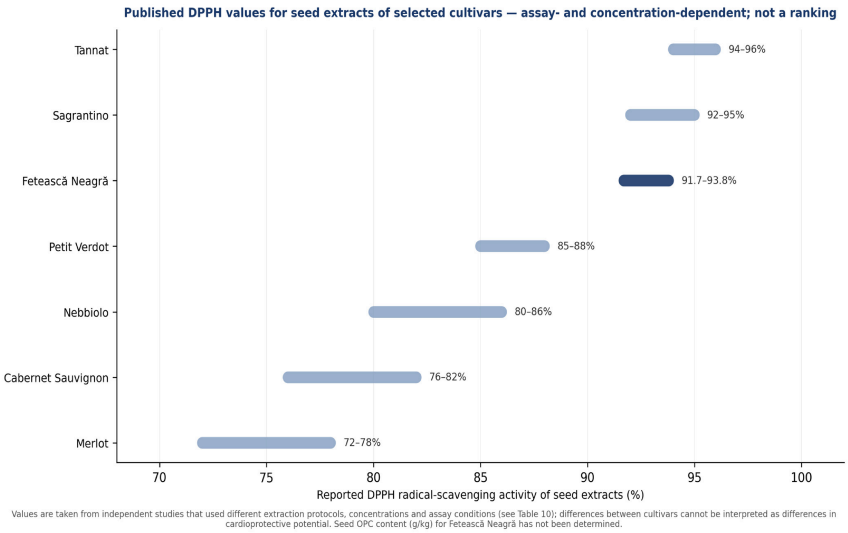


Figure 4. Published DPPH radical-scavenging values reported for seed extracts of selected grape cultivars. Values derive from independent studies using different extraction protocols, concentrations and assay conditions and are therefore not comparable across studies; the figure does not constitute a ranking of cardioprotective potential. Seed OPC content for Fetească Neagră has not been determined (Table 11).

Table 6. Phytochemistry → mechanism → cardioprotective-inference correlation for 'Feteasca Neagra'.

Phytochemical Parameter (Published FN Data)	Corresponding Cardioprotective Mechanism	Observation Reported in the Cited Source	Comparison with Other Grape Seed Extracts	Inferential Certainty
DPPH 91.7–93.8% [72]	ROS scavenging, Nrf2/HO-1 activation	Antioxidant capacity measured by DPPH in seed extracts; assay-dependent and not comparable across studies using different protocols	Within the range reported for grape seed extracts (DPPH 70–95%, method-dependent)	HIGH (direct data)
Dominant trimeric fractions [86]	NF-κB inhibition ~40% [29]	Oligomeric composition consistent with the fractions associated with NF-κB inhibition in vitro	Comparable oligomeric enrichment reported for other cultivars	MODERATE (direct inference)
Flavonoids 69% DW in seeds [87]	Optimized OPC bioavailability; multi-pathway synergy	Flavonoids predominantly localized in seeds rather than skins in one comparative study	Seed-versus-skin distribution; not a measure of extract potency	MODERATE (direct inference)
Anthocyanin-rich skins [19]	Additional antiplatelet activity; OPC –anthocyanin synergy	Anthocyanin content of skins; relevance to seed-extract activity not established	Not applicable to seed extracts	INFERENTIAL (indirect data)
PCC1 estimated maximum among Romanian cultivars (inference from [88,89].	Reduced cell senescence (SASP ↓) [69]	PCC1 content not quantified in this cultivar; inference only	Not determined	INFERENTIAL (estimated from indirect data)

DW = dry weight. Inferential certainty: HIGH = inference from direct 'Feteasca Neagra' data; MODERATE = inference from correlating 'Feteasca Neagra' data with mechanisms documented for other extracts; INFERENTIAL = indirect estimate requiring confirmation. NO ROW IN THIS TABLE REPRESENTS CLINICAL DATA—all statements are inferences from published phytochemical and pharmacological data and remain unconfirmed by direct clinical studies of 'Feteasca Neagra' extract.

Beyond its pharmacological significance, this inference also has a practical dimension: no commercial supplement specifically marketed as 'Feteasca Neagra' seed extract was identified. Commercial GSE products generally do not specify the source cultivar, making direct comparison with a cultivar-specific extract difficult. A research and standardization program for 'Feteasca Neagra' extract could therefore provide an opportunity for cultivar-specific investigation in cardiovascular nutraceutical research.

The phytochemical argument above gains further context when placed within the viticultural factors that produce it. If a 'Feteasca Neagra' extract were to be standardized for pharmaceutical or nutraceutical use, every link in the chain—from vine genotype to harvest conditions and vinification practices—could influence its phytochemical and redox profile. The subsections that follow examine this chain.

3.8.1. Genetic Identity and Ampelography—Why the Cultivar, Not Just the Berry, Matters

Origin and Historical Attestation

'Feteasca Neagra' is among the oldest autochthonous cultivars documented in the Carpathian-Danubian-Pontic region, with written attestations in Moldavia dating to the mid-seventeenth century. Historical records mention it under several regional names, including 'Coada Rândunicii' and 'Poamă Neagră', reflecting a long cultivation history. The international Vitis Variety Catalogue (VIVC) lists it under code 4237, with several synonyms [90,91]. This antiquity is not merely historical. Long-term cultivation under variable climatic conditions may have contributed to the maintenance of genotypes with distinct stress-responsive biosynthetic profiles, including pathways involved in polyphenol production. These pathways are of particular interest from a redox perspective.

Genetic Profile and Distance from Related Cultivars

Molecular analyses based on SSR (microsatellite) and SNP markers have confirmed that 'Feteasca Neagra'/ is a genetically distinct cultivar, with no direct filiation to 'Feteasca Albă' or 'Feteasca Regală', despite the shared name. Comparative genetic analyses indicate that these cultivars are distinct genotypes [92]. More relevant to the present discussion, variation in genes involved in polyphenol biosynthesis—including VvF3′5′H, VvDFR, and VvLAR—may contribute to differences in proanthocyanidin and anthocyanin profiles among grape cultivars [93]. However, a direct association between specific alleles in 'Feteasca Neagra' and increased seed B-type proanthocyanidin synthesis requires further cultivar-specific investigation.

Pharmacological relevance: A per-batch genetic-authenticity certificate, alongside the HPLC certificate, would provide an additional traceability measure for any 'Feteasca Neagra' extract intended for clinical studies.

Clonal Variability—FN-4, FN-5, FN-6

The National Office for Vine and Wine Products has officially registered three principal clones of 'Feteasca Neagra', differing in morphology and productivity (Table 7). Comparative Romanian studies have shown that, among clones of the same cultivar grown under the same terroir conditions, anthocyanin and proanthocyanidin contents can vary substantially.

The practical consequence is direct and relevant to GSE research: standardization of a 'Feteasca Neagra' extract should specify the clone of origin. Extracts from different clones may differ in phytochemical composition, even when obtained from the same year and plot [94].

Table 7. Comparison of the registered 'Feteasca Neagra' clones *.

Clone	Productivity	Seed Anthocyanins	Estimated OPC	Production Preference
FN-4	Medium (8–10 t/ha)	High	High	Oenological quality
FN-5	High (12–14 t/ha)	Medium	Medium	Industrial production
FN-6	Low (6–8 t/ha)	Very high	Very high	Pharmaceutical potential

* Aggregated data, SCDVV Drăgășani, USAMV Iași, 2015–2023); OPC = oligomeric proanthocyanidins.

3.8.2. Viticultural Areas and Terroir—Same Vine, Different Antioxidant Capacities

Terroir—the combination of soil, climate, relief, and human practices that contributes to the characteristics of a wine—has a relevant counterpart in pharmacognosy: the phytochemical composition of a plant depends substantially on the conditions under which it grows. For grapevine, temperature, water availability, soil type, and altitude can influence polyphenol synthesis through light-dependent enzymatic pathways and stress responses. In other words, the same cultivar can produce, under different terroir conditions, extracts with different antioxidant capacities [95]. 'Feteasca Neagra' is currently grown in five principal areas, each with its own phytochemical signature (Table 8):

Table 8. Geographic variability of the polyphenolic profile of 'Feteasca Neagra' seeds *.

Area	Climate Type	Rainfall (mm/yr)	Relative OPC *	Fraction Profile	Water Stress
Moldavia (Huși)	Continental	480–520	+18–22%	Higher oligomers	Moderate
Dealu Mare	Subcontinental	550–600	Reference (100%)	Di- and trimers	Low
Drăgășani	Temperate Carpathian	600–700	+8–12%	Balanced	Low
Murfatlar/ Dobrogea	Semi-arid	350–450	+25–30%	Concentrated oligomers	High
Ștefănești-Argeș	Transition	530–580	+5–8%	Monomers + oligomers	Low

* Values estimated [72,93–96].

1. Moldavia (Huși, Iași, Cotnari): A continental climate with dry summers. Summer water deficit may activate polyphenol-biosynthesis pathways as a stress response, and comparative pedological studies have reported higher OPC content in the Huși area for this cultivar.

2. Dealu Mare (Prahova, Buzău): Wines from this area are known for their tannic structure—an organoleptic descriptor that may correspond to a proanthocyanidin profile of medium polymerization, potentially relevant from a redox standpoint because of the presence of oligomeric fractions.

3. Drăgășani (Vâlcea): Altitudes of 200–400 m and wide diurnal temperature ranges during ripening—conditions recognized as favoring phenolic maturity. The region is also an important center for clonal research on the cultivar.

4. Dobrogea (Murfatlar): A semi-arid climate, with rainfall below 450 mm per year. Water stress may increase phenolic accumulation in berries, and comparative data have reported high DPPH activity values for 'Feteasca Neagra' from this zone (91.7–93.8%).

5. Ștefănești-Argeș: A transition zone between Dealu Mare and Drăgășani, with an intermediate polyphenolic profile and a higher monomeric epicatechin content than some southern areas.

Implication for standardization: A serious protocol for standardizing GSE-'Feteasca Neagra' must fix at least five coordinates: the area of origin, the clone, the plot altitude, the vintage year, and the water regime of that year. Without them, batches simply are not comparable.

3.8.3. Phenolic Phenology—Harvest Timing and Seed Phenolic Composition

One of the important observations of modern ampelology, with potential relevance to pharmacology, is that sugar–acid maturity (the benchmark of winemaking) and phenolic maturity (relevant for antioxidant extracts) do not necessarily coincide. The difference may extend over several weeks, with potential consequences for the composition of seed OPC fractions.

Dynamics of Proanthocyanidin Accumulation

Kennedy et al. [97] showed that *Vitis vinifera* seeds undergo substantial changes in extractable proanthocyanidins during ripening, including changes in the relative proportions of monomeric and oligomeric fractions. Seed proanthocyanidin composition therefore changes during maturation, and the timing of harvest may influence the composition and extractability of the resulting seed material. Hence, an important consideration for future GSE production is that pomace obtained from grapes harvested primarily according to sugar–acid maturity may not necessarily provide the same OPC profile as material obtained at an earlier stage of phenolic development. The optimal harvest stage for a pharmacologically oriented extract therefore requires cultivar-specific investigation rather than direct extrapolation from oenological maturity criteria [86].

Influence of the Vinification Technique on the Pomace

An equally relevant factor is the vinification technique, which can influence how much of the seed polyphenol fraction remains in the pomace—the raw material for subsequent extraction:

Carbonic maceration (Beaujolais-style): fermentation in a CO_2-rich atmosphere with limited mechanical contact may reduce seed disruption and extraction of seed phenolics into the wine. The resulting pomace may therefore retain a substantial proportion of the seed polyphenol fraction [88].

Classic maceration (7–14 days): prolonged contact between grape solids and fermenting must promotes extraction of seed phenolics into the wine. The resulting pomace may consequently exhibit a modified OPC profile, depending on cultivar, temperature, ethanol concentration, and extraction time [13].

Extended maceration (>21 days): longer skin and seed contact can further increase the transfer of seed phenolics into the wine, potentially altering both the quantity and composition of the residual polyphenolic fraction in the pomace [83].

Research gap: The vinification technique should therefore be considered a potentially important variable in the standardization of grape-seed raw material. Systematic studies comparing 'Feteasca Neagra' pomace obtained under different vinification regimes could provide useful information for defining raw-material specifications for GSE production [98].

3.8.4. Water Stress and Phytochemical Hormesis—Viticulture as a Redox-Optimization Tool

Hormesis—the concept that moderate stress can induce adaptive biological responses—is well established in biology and pharmacology. A related agronomic concept is that

moderate abiotic stress can stimulate the biosynthesis of plant defense metabolites, including flavonoids, proanthocyanidins, and stilbenes. In grapevine, water availability and other environmental stresses can therefore influence the accumulation of secondary metabolites [97].

The Molecular Mechanism

Moderate water deficit can activate abscisic acid-mediated signaling in *Vitis vinifera* and modulate transcription factors of the VvMYB family involved in the regulation of flavonoid biosynthesis. These regulatory networks influence genes of the phenylpropanoid and flavonoid pathways, including PAL, CHS, F3H, DFR, and LAR, thereby potentially affecting proanthocyanidin accumulation. UV-B exposure can activate a partially independent signaling pathway involving the UVR8 photoreceptor and downstream regulation of phenylpropanoid-related genes. The magnitude and direction of these responses depend on stress intensity, developmental stage, cultivar, and environmental conditions [97].

Empirical Evidence: Dry Vintages

Growers in Moldavia and Dobrogea have long associated dry vintages with differences in grape and wine composition, including changes in tannic structure and phenolic character. Such observations are consistent with experimental evidence showing that water availability can influence grape phenolic metabolism. However, organoleptic observations cannot by themselves establish increased seed proanthocyanidin concentrations. Quantitative regression of rainfall or vine water status against seed OPC composition in 'Feteasca Neagra' would therefore represent a valuable and feasible research direction over several growing cycles [93].

Implications for a Pharmaceutically Oriented Viticulture

Pharmaceutically oriented cultivation—deliberate optimization of growing conditions to obtain a defined phytochemical composition—has been explored for medicinal plants and could potentially be investigated in *Vitis vinifera* [99]. Applied to 'Feteasca Neagra', such an approach could include: controlled deficit irrigation during selected developmental stages; selection of sites with appropriate solar exposure and altitude to investigate the contribution of UV-B and temperature conditions; harvest at a cultivar-specific stage of phenolic maturity rather than relying exclusively on sugar–acid maturity; optimization of vinification conditions to maximize retention of the target OPC fraction in the pomace [88,98].

Such a protocol could potentially transform grape pomace from a predominantly low-value by-product into a standardized source of phytochemical raw material. However, the proposed cultivation parameters require experimental validation before they can be considered optimal for GSE production.

3.8.5. Industrial Feasibility—From Pomace to Product

The potential economic case for a 'Feteasca Neagra' extract is reinforced by the availability of grape pomace as a vinification by-product. Because the raw material is generated within an existing agricultural and oenological production chain, its valorization could reduce the need for additional dedicated cultivation.

Raw-Material Availability

A realistic assessment of the potential supply of 'Feteasca Neagra' seed material should be based on current national vineyard statistics, the actual area planted with the cultivar, cultivar-specific yields, pomace-to-grape ratios, seed recovery, drying losses, and extraction yield. Accordingly, the following quantities should be regarded as estimates requiring veri-

fication from official Romanian viticultural statistics and industrial processing data: annual grape production: approximately 34,000–41,000 t, based on approximately 3384 ha planted with 'Feteasca Neagra' and an illustrative yield of 10–12 t/ha {98]; fresh pomace: approximately 6800–10,200 t, depending on the pomace-to-grape ratio, with a recent Romanian study reporting a 'Feteasca Neagra' pomace yield of 19.48% [88]; dried seeds: approximately 1400–2500 t, depending on seed recovery and drying losses [98]; standardized GSE: approximately 80–200 t per year, assuming an ethanolic extraction yield of approximately 6–8% and allowing for the substantial variability associated with extraction and standardization procedures [100] (Table 9).

Table 9. Estimated industrial potential for GSE production from 'Feteasca Neagra' seeds in Romania.

Parameter	Estimated Value	Source/Method
FN cultivated area	45,000–55,000 ha	ONVPV 2022
Annual grape production	150,000–200,000 t	INS, ONVPV
Pomace generated/yr	25,000–45,000 t	Calc. 15–25% mass
Dried seeds/yr	8000–15,000 t	30–35% dried pomace
Standardized GSE/yr	500–900 t	6–8% extraction yield
Commercial GSE-FN products	0 (zero)	Market survey 2025

The Value Chain

Pomace is generally a low-value by-product of winemaking, although its economic value can increase through recovery of polyphenols, oils, fibers, and other bioactive compounds. Its collection, drying, storage, milling, and extraction require dedicated processing infrastructure but may benefit from integration with existing winery operations. A winery–extract-producer partnership could therefore provide a potentially efficient valorization route for 'Feteasca Neagra' pomace, provided that collection logistics, drying costs, raw-material standardization, extraction efficiency, and regulatory requirements are economically viable [89].

Legal Protection and Geographical Indications

From a legal standpoint, the possibility of protecting a 'Feteasca Neagra'-derived nutraceutical raw material through a geographical indication would require careful assessment under the applicable European Union legal framework. EU Regulation (EU) No. 1151/2012 [101] establishes the principal framework for protected designations of origin and protected geographical indications for agricultural products and foodstuffs. Whether a grape-seed extract or other nutraceutical ingredient derived from 'Feteasca Neagra' could qualify under this framework would depend on the legal classification of the product and the applicable registration criteria. Therefore, geographical indication protection should be considered a potential future regulatory strategy rather than an established route for pharmaceutical or nutraceutical exclusivity.

3.8.6. International Positioning—Where 'Feteasca Neagra' Stands in the World Hierarchy

An honest assessment calls for comparing 'Feteasca Neagra' with cultivars recognized for high seed proanthocyanidin content, in order to position it realistically, including both its potential advantages and its limitations (Table 10).

1. 'Tannat' (Madiran, France) is recognized for its high seed proanthocyanidin and flavan-3-ol content, with studies documenting substantial concentrations during grape ripening. However, the precise values reported depend on the extraction method, ripening

stage, and units of expression. A direct 'Tannat'–'Feteasca Neagra' comparison has not been established under identical analytical conditions; therefore, the Romanian cultivar's DPPH data cannot be used directly to quantify its relative position with respect to Tannat [102].

2. 'Sagrantino' (Umbria, Italy): 'Sagrantino' di Montefalco is characterized by a high polyphenolic content and a substantial contribution of proanthocyanidins to its phenolic profile. The parallel with 'Feteasca Neagra' is relevant because both are geographically distinctive *Vitis vinifera* cultivars with pronounced phenolic characteristics. However, available data do not permit a reliable global ranking of the two cultivars based solely on published values obtained using different analytical methods [103].

3. 'Petit Verdot' and 'Nebbiolo' have been included in comparative studies of grape phenolic composition and antioxidant activity. However, DPPH and ORAC values are strongly influenced by extraction conditions, assay protocols, concentration, and the matrix analyzed. Consequently, the reported DPPH activity of 'Feteasca Neagra' (91.7–93.8%) should not be interpreted as evidence of a global ranking without a standardized head-to-head comparison [104].

This positioning remains preliminary, therefore, because it relies on indirect comparisons and heterogeneous analytical methodologies. A head-to-head study of 'Feteasca Neagra' against 'Tannat', 'Sagrantino', 'Petit Verdot', and 'Nebbiolo', using a standardized analytical panel (total OPC, HPLC fractionation, DPPH, ORAC, FRAP, and PCC1), would provide an appropriate basis for comparative positioning and represents a priority objective of Stage 1 of the translational roadmap.

Table 10. International positioning of 'Feteasca Neagra' by polyphenolic potential.

Cultivar	Origin	Seed OPC (g/kg)	DPPH (%)—Assay- and Concentration-Dependent; Not Comparable Across Studies	Pharmacological Status
'Tannat'	Madiran, FR	10–15	~94–96%	Zero pharmaco. studies
'Sagrantino'	Umbria, IT	6–10	~92–95%	Zero pharmaco. studies
'Feteasca Neagra'	Romania	Not determined (priority objective for future research)	91.7–93.8%	Zero pharmaco. studies
'Petit Verdot'	Bordeaux, FR	4–7	~85–88%	Zero pharmaco. studies
'Nebbiolo'	Piemonte, IT	3–6	~80–86%	Zero pharmaco. studies
'Cabernet Sauvignon'	International	2–5	~76–82%	Limited studies
'Merlot'	International	2–4	~72–78%	Limited studies

Seed OPC data in g/kg for 'Feteasca Neagra' are not yet available and should therefore be considered a priority objective for future research [88,98,105].

3.8.7. Synthesis—Why 'Feteasca Neagra' Warrants a Dedicated Study

The six dimensions discussed—genetics, terroir, phenology, hormesis, industrial feasibility, and international positioning—converge on the rationale for considering 'Feteasca Neagra' as a strong candidate for a first dedicated pharmacological study among Romanian cultivars.

Genetically, it is a distinct autochthonous cultivar, while the specific genetic determinants of its seed OPC profile require further investigation.

Geographically, its cultivation across contrasting climatic conditions provides an opportunity to investigate how water availability and other environmental factors influence its phytochemical composition.

Agronomically, harvest at an appropriate stage of phenolic maturity and optimization of vinification conditions could potentially improve the quality of the raw material.

Industrially, the availability of grape pomace as a vinification by-product provides a potentially scalable source of raw material, although economic feasibility requires dedicated techno-economic assessment.

Competitively, the absence of a well-characterized commercial 'Feteasca Neagra' seed extract identified in the literature provides an opportunity for cultivar-specific research and product development.

In heritage terms, the cultivar's established geographical and cultural identity could potentially support future strategies for geographical traceability and protection, subject to the applicable regulatory framework.

Conclusion of 3.8: 'Feteasca Neagra' represents a scientifically justified candidate for a dedicated pharmacological investigation of an autochthonous Romanian cultivar with potential cardioprotective relevance. The rationale rests not on phytochemical data alone but on the convergence of genetic distinctiveness, agronomic optimization potential, availability of a potentially valuable processing by-product, and a well-defined viticultural heritage. Validation of this theoretical potential through structured pharmacological and clinical studies remains the central objective of the translational agenda in Section 6.6.

4. GSE Drug-Interaction Profile in Cardiovascular Polypharmacy

Methodological caution: all interactions described below are based on published in vitro enzyme- and transporter-level data, mechanistic inference from the known metabolism of the co-administered drugs, and, where available, indirect clinical data. No in silico prediction was generated for this review. No controlled human pharmacokinetic studies directly evaluating GSE interactions with cardiovascular drugs were identified. All recommendations are precautionary and hypothesis-generating, not confirmatory.

A real cardiovascular patient rarely takes a single drug and may receive multiple medications concurrently. In this context of polypharmacy, any antioxidant adjunct must be evaluated not only for its potential benefits but also for its pharmacokinetic and pharmacodynamic interactions with background therapy, an issue of growing relevance as polyphenol-containing products are increasingly used alongside cardiometabolic therapy [106]. Many of these potential interactions may involve redox-sensitive pathways, while grape-seed polyphenols may also modulate cytochrome P450 enzymes and membrane transporters involved in drug disposition. Most proposed interactions between GSE and cardiovascular medications are supported by preclinical or mechanistic evidence rather than by direct human pharmacokinetic or clinical studies; consequently, their clinical relevance remains uncertain. Potential pharmacodynamic interactions, particularly with anticoagulants and antiplatelet agents, warrant clinical awareness, but the available evidence does not justify routine modification of established cardiovascular treatment solely because of GSE supplementation. Throughout this section, interaction severity and evidence certainty are evaluated separately, and each interaction is assigned to one of four evidence categories: clinically demonstrated; limited clinical evidence; preclinical evidence only; or theoretical, mechanistically plausible. The section synthesizes the published evidence organized by drug class on this basis and provides a stratified overview of potential interactions across drug classes (Figure 5).

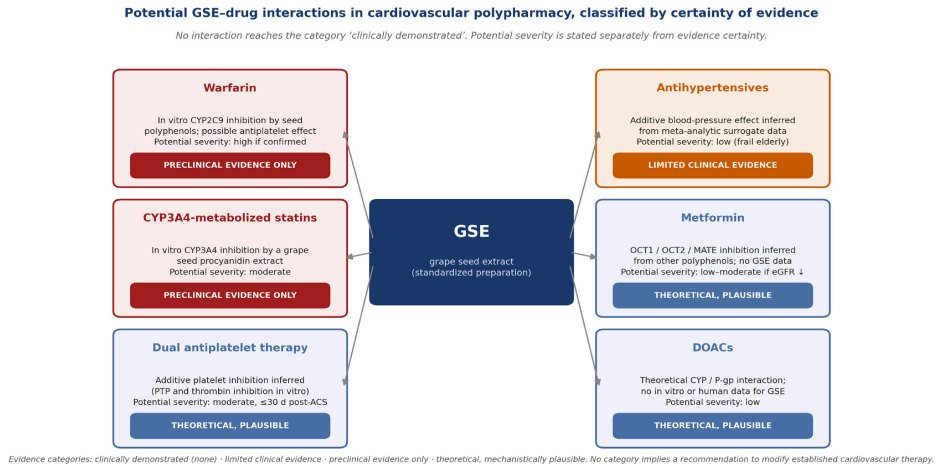


Figure 5. Potential GSE–drug interactions in cardiovascular polypharmacy, classified by certainty of evidence. Each interaction is assigned to one of four categories—clinically demonstrated (none qualify), limited clinical evidence, preclinical evidence only, or theoretical and mechanistically plausible—with potential clinical severity stated separately. None of the interactions is confirmed by a controlled human pharmacokinetic study, and no category implies a recommendation to modify established cardiovascular therapy (GSE = grape seed extract; PTP = protein tyrosine phosphatase; ACS = acute coronary syndrome).

4.1. Warfarin: Theoretical Interaction Requiring Precaution

Of all cardiovascular drugs, warfarin warrants particular vigilance when co-administered with GSE. Potential mechanisms include inhibition of cytochrome P450 enzymes and interaction with P-glycoprotein, demonstrated in vitro for grape seed extract [107,108], together with possible effects on platelet function. CYP2D6-mediated herb–drug interaction studies [109] did not identify an effect for grape seed extract and are therefore not evidence for a CYP2C9-mediated interaction. However, the frequently cited case report of an INR increase to 7.9 after three days of "grapefruit seed extract" requires careful interpretation: subsequent chemical analysis showed that the commercial products contained benzethonium chloride and no authentic grapefruit-seed extract, and the authors concluded that benzethonium chloride was likely responsible for the CYP2C9 and CYP3A4 inhibition and the increased INR [110]. Therefore, this case should not be interpreted as direct clinical evidence of a GSE–warfarin interaction.

Practical recommendation: no clinically confirmed GSE–warfarin interaction has been demonstrated in humans. The precaution proposed here rests on in vitro CYP2C9 inhibition by grape-seed polyphenols and on their potential antiplatelet activity, which are distinct mechanisms: platelet inhibition would not be expected to raise the INR. In patients receiving warfarin, particularly those with unstable anticoagulation, concomitant GSE should therefore be approached cautiously as a precautionary measure rather than on the basis of established interaction data. If administration is considered, closer INR monitoring during initiation may be prudent until the interaction profile is better established.

4.2. CYP3A4-Metabolized Statins: Moderate Risk, a Pragmatic Solution

Simvastatin and atorvastatin are metabolized predominantly by CYP3A4, an enzyme that can be inhibited by certain grape-seed polyphenols. CYP3A4 inhibition may increase statin exposure and, consequently, the risk of myotoxicity. For patients receiving GSE concurrently, pravastatin or rosuvastatin—statins with minimal CYP3A4-dependent metabolism—are metabolized largely independently of CYP3A4; this is stated as a pharmacokinetic observation and not as a recommendation to modify established statin therapy, since no

clinically relevant GSE–statin interaction has been demonstrated in humans. Such statins would, in theory, have a lower interaction risk [111,112].

4.3. Dual Antiplatelet Therapy: A Sum of Effects

Patients on dual antiplatelet therapy (DAPT) after an acute coronary syndrome may receive an additional source of platelet inhibition through concurrent GSE. The mechanism, however, is not the one most frequently cited in this literature: the primary in vitro work attributes the antiplatelet effect of grape seed extract to inhibition of protein tyrosine phosphatase rather than to suppression of thromboxane A2 synthesis through COX-1 [113], and a separate in vitro study demonstrates inhibition of thrombin activity [114]. Reduced TXA2 formation has been proposed for grape polyphenols in general but, to our knowledge, has not been demonstrated for grape seed extract itself. Although each effect may be modest, their combined effect could become clinically relevant, particularly during the first 30 days after stenting, when bleeding risk is elevated [115].

4.4. Metformin: An Interaction via OCT Transporters—A New Assessment

This subsection addresses a potential interaction that has received little attention in the literature: the population in which GSE has been most frequently studied for metabolic indications (the inflammatory-metabolic stratum proposed in Section 5, HbA1c $\geq$ 6.0%) is also the population in which metformin use is most common.

Metformin—the most widely prescribed oral antidiabetic drug—is frequently used in patients with type 2 diabetes and cardiovascular risk. However, its interaction with GSE has not been systematically evaluated. This gap is especially relevant because the target population of GSE adjunct therapy (the inflammatory-metabolic stratum proposed in Section 5, HbA1c $\geq$ 6.0%) may frequently receive metformin concurrently.

The mechanistic basis for caution derives from metformin's dependence on organic-cation transporters OCT1 (hepatic uptake) and OCT2 (renal tubular uptake), with MATE1 and MATE2-K also contributing to renal excretion [116]. Polyphenols—including quercetin and epigallocatechin gallate (EGCG)—have been shown to inhibit OCT1- and OCT2-mediated transport in vitro, potentially affecting metformin disposition [117]. However, these findings cannot be directly extrapolated to GSE, whose complex polyphenolic composition differs from that of isolated quercetin or EGCG. The presence of epicatechin and proanthocyanidin B2 in GSE therefore raises a theoretical possibility of transporter-mediated interaction, but does not establish inhibition of metformin transport [118].

The clinical consequence remains uncertain. Increased metformin exposure could theoretically occur if GSE inhibited relevant transport pathways, whereas impaired renal function is independently associated with increased metformin exposure and an increased risk of lactic acidosis [119]. Although the UKPDS demonstrated cardiovascular and mortality benefits of metformin in overweight patients with type 2 diabetes, these findings do not establish that increased metformin exposure would enhance its cardioprotective effects [120]. Importantly, this interaction has not been confirmed in any human pharmacokinetic study—it remains a mechanistic inference based on in vitro transporter data for other polyphenols.

GSE + metformin practical recommendation: no metformin dose adjustment is justified on current evidence. In patients with eGFR $<$ 45 mL/min/1.73 m^2 starting GSE, monitoring of renal function according to standard metformin recommendations is prudent, noting that OCT1 (hepatic uptake), OCT2 (renal uptake) and MATE1/MATE2-K (renal efflux) inhibition would have different and partly opposing consequences for metformin exposure [116,121]. In patients with eGFR $>$ 60 mL/min/1.73 m^2, no clinically relevant

GSE–metformin pharmacokinetic interaction has been established. To our knowledge, no controlled human pharmacokinetic study has investigated this interaction.

4.5. Antihypertensives: Synergy with Hypotensive Potential

GSE exerts modest blood-pressure-lowering effects of its own—a reduction in DBP of 2.20 mmHg and in heart rate of 1.25 bpm has been reported in a meta-analysis of 19 controlled trials—potentially mediated, at least in part, by NO-dependent vascular mechanisms involving the Akt/eNOS pathway [122]. In frail older patients with a baseline blood pressure below 130 mmHg who are receiving multiple antihypertensive agents, these effects could theoretically contribute to additive blood-pressure lowering and precipitate symptomatic hypotension [122] (Table 11).

Table 11. Clinical situations in which GSE use is raised, and the evidence-based response.

Clinical Situation	What the Patient or Ward Team Asks	Evidence-Based Response	Practical Action
Patient on a vitamin K antagonist reports taking GSE	Is this why the INR is unstable?	No confirmed human interaction; in vitro CYP2C9 inhibition only; the widely cited INR case involved an adulterated grapefruit-seed product	Record the preparation and dose; check INR within 1–2 weeks of starting or stopping; do not attribute instability to GSE by default
Statin-intolerant patient asking for an 'antioxidant alternative'	Can this replace my statin?	No. No GSE trial has evaluated lipid-lowering of a magnitude relevant to secondary prevention, and none has evaluated events	State clearly that it is not an alternative; address statin intolerance on its own terms
Elective surgery or invasive cardiac procedure	Should it be stopped?	No pharmacokinetic data; possible additive antiplatelet effect	Discontinue 7–14 days before the procedure as a conservative measure; document in the pre-operative assessment
Frail elderly patient on ≥3 antihypertensives	Is it safe to add?	Additive NO-mediated vasodilation is plausible; baseline blood pressure and orthostatic tolerance determine the risk	Measure standing blood pressure before and 2–4 weeks after initiation; avoid if systolic blood pressure < 120 mmHg or symptomatic orthostatism
Chronic kidney disease, eGFR 30–45 mL/min/1.73 m^2	Does it affect the kidney or my other drugs?	No nephrotoxicity reported; transporter-level interaction with metformin is inferred, not demonstrated	Monitor creatinine and eGFR at 4 and 12 weeks; review metformin dosing per standard criteria
Metabolic syndrome or prediabetes, at target on therapy	Is there anything else I can do?	This is the population with the most consistent surrogate-endpoint data, though no event data exist	Reasonable to discuss as an optional adjunct with explicit expectations; reinforce diet, exercise and weight management first
Within 30 days of acute coronary syndrome on dual antiplatelet therapy	Can I take it?	Bleeding risk is highest in this window and additive platelet inhibition cannot be excluded	Advise deferral until dual therapy is completed

Table 11. *Cont.*

Clinical Situation	What the Patient or Ward Team Asks	Evidence-Based Response	Practical Action
Heart failure with preserved ejection fraction	Will it help my heart muscle?	No evidence; the proposed antioxidant and anti-inflammatory mechanisms do not address established fibrotic remodeling	Set expectations explicitly; prioritize guideline-directed therapy and comorbidity management
Patient already taking an unspecified 'grape seed' product	Is the product itself reliable?	OPC content varies from 40% to 99% between commercial preparations and the oligomeric profile is rarely declared	Ask for the label and certificate of analysis; absent an HPLC certificate, the content cannot be assumed

4.6. Clinical Situations in Internal Medicine and Cardiology in Which the Question Actually Arises

In practice, the clinician rarely decides whether to prescribe GSE; far more often, a patient reports already taking it, or asks whether to start. The useful output of an interaction analysis is therefore not a recommendation to prescribe, but a structured answer for the situations in which the question arises in internal medicine and cardiology wards and clinics (Table 16).

Four situations deserve particular emphasis. In the patient on vitamin K antagonists, the relevant action is not prohibition but surveillance at the two moments of change—initiation and discontinuation of the supplement—since an undeclared supplement started or stopped between INR checks is a more plausible source of instability than the supplement itself at steady state. In the perioperative setting, the absence of pharmacokinetic data makes a conservative approach reasonable: discontinuation 7–14 days before elective surgery or invasive procedures, consistent with general guidance for polyphenol-containing supplements with possible antiplatelet activity. In chronic kidney disease, the issue is not the extract but what accompanies it: reduced eGFR alters the exposure of co-prescribed drugs, and the transporter-level uncertainty described in Section 4.4 argues for monitoring rather than for either reassurance or prohibition. And in the elderly patient on multiple antihypertensives, the small additive vasodilatory effect that is clinically irrelevant in a robust 55-year-old may contribute to symptomatic orthostatic hypotension in a frail 82-year-old—the clearest example of why effect size must be read against the patient, not only against the placebo arm.

A further consideration specific to internal medicine is medication reconciliation. Polyphenol supplements are frequently not reported by patients unless specifically asked, because they are not perceived as medicines. Any structured assessment of residual cardiovascular risk should therefore include an explicit question about supplement use, with the dose and the preparation recorded—a practice that costs nothing and prevents the two scenarios described above from going undetected.

Criteria for the evidence categories used in Tables 12 and 13. 'Clinically demonstrated' denotes an interaction shown in a controlled human pharmacokinetic or clinical study; none of the interactions discussed here meet this standard. 'Limited clinical evidence' denotes indirect human data, such as a surrogate effect of GSE on the same physiological variable as the co-administered drug, without an interaction study. 'Preclinical evidence only' denotes an enzyme-, transporter- or platelet-level effect demonstrated in vitro or in animals for GSE or its constituents. 'Theoretical, mechanistically plausible' denotes an interaction inferred from the known metabolism of the drug or from related compounds, without data for GSE itself. The potential clinical severity of an interaction, if it occurred, is stated separately from the certainty that it occurs; a high potential severity with preclinical evidence only warrants awareness and monitoring, not modification of established therapy.

Table 12. Clinical risk stratification for GSE in cardiovascular polypharmacy.

Evidence Category (and Potential Severity)	Patient Profile	Position Proposed (Not a Recommendation to Modify Therapy)	Monitoring	Evidence Level
Preclinical evidence only (potential severity: high if confirmed)	Patients receiving warfarin with unstable anticoagulation, or dual antiplatelet therapy within 30 days of an acute coronary syndrome	Caution; specialist discussion before initiation; no change to anticoagulant therapy on this basis	Closer INR monitoring at initiation if GSE is used	In vitro CYP2C9 inhibition only; the frequently cited INR case involved an adulterated grapefruit-seed product and is not counted as evidence for GSE [110]
Preclinical evidence only (potential severity: moderate)	CYP3A4 statins/DOACs/dihydropyridine CCBs	No change to established statin therapy; the CYP3A4 dependence of individual statins is a consideration for future interaction studies only	CK at 4, 12 wk/BP each visit	Indirect (in vitro and mechanistic + botanical analogies)
Theoretical, mechanistically plausible (potential severity: low)	ACEi/ARBs/beta-blockers/pravastatin/no anticoagulants	GSE 300–400 mg/day with meals—favorable adjunct profile	BP each visit/lipids at 3 months	Indirect favorable (in vitro and mechanistic)
Theoretical, mechanistically plausible (potential severity: low–moderate in reduced renal function)	Metformin + eGFR 30–45 mL/min/1.73 m^2	GSE with caution; monitor renal function	eGFR + creatinine at weeks 4 and 12	Mechanistic inference (class effect, no direct PK data)

DAPT = dual antiplatelet therapy; ACS = acute coronary syndrome; DOACs = direct oral anticoagulants; CCBs = calcium channel blockers; ACEi/ARBs = ACE inhibitors/sartans. None of the described interactions are confirmed by randomized clinical PK studies.

Table 13. Evidence hierarchy for GSE interactions with cv pharmacotherapy.

Drug	Interaction Mechanism	Evidence Type	Human PK Study	Inference Strength	Evidence category
Warfarin	CYP2C9 inhibition → ↑ S-warfarin AUC → ↑ INR	In vitro CYP2C9 inhibition; the INR 7.9 case is excluded (adulterated product containing benzethonium chloride) [107,110]	Absent	Low–Moderate	Preclinical evidence only

Table 13. *Cont.*

Drug	Interaction Mechanism	Evidence Type	Human PK Study	Inference Strength	Evidence category
CYP3A4 statins	CYP3A4 inhibition → ↑ statin AUC → myotoxicity	In vitro CYP3A4 inhibition by a grape seed procyanidin extract [108]; in vitro CYP/P-gp screening of grape seed extract [107]	Absent	Low	Preclinical evidence only
DAPT	Additive platelet inhibition (protein tyrosine phosphatase and thrombin inhibition reported in vitro; TXA2 reduction not demonstrated for GSE)	Pharmacodynamic inference	Absent	Low	Theoretical, mechanistically plausible
Antihypertensives	Additive Akt/eNOS-mediated vasodilation	Meta-analytic (GSE ↓ BP documented)	Indirect	Low–Moderate	Limited clinical evidence (surrogate: meta-analytic blood-pressure effect; no interaction study)
Metformin	OCT1/OCT2 inhibition → potentially ↑ metformin AUC; caution eGFR < 45	In vitro data + class effect (EGCG/quercetin)	Absent	Very low	Theoretical, mechanistically plausible
DOACs	Theoretical CYP/P-gp interaction	Mechanistic inference only (no in vitro or human data)	Absent	Very low	Theoretical, mechanistically plausible

PK = pharmacokinetics; AUC = area under the curve. None of the above interactions is clinically confirmed through randomized controlled studies. Recommendations are indicative and precautionary.

5. An Exploratory Precision-Medicine Framework: Who Responds to GSE?

Methodological declaration. The stratification framework presented in this section is a conceptual proposal, not the result of a statistical analysis. It was derived by grouping the oxidative and inflammatory biomarker profiles reported in the clinical studies included in this review, as a way of organizing a plausible hypothesis about differential response. No clustering, machine-learning or other data-driven analysis was performed, no individual participant data were used, and no response probabilities, predictive metrics or cluster-validity statistics are reported, because none were computed. The biomarker thresholds given below are taken from the cut-offs used in the cited studies and are illustrative; they have not been derived or validated for the purpose of predicting response to GSE. The proposed biomarker-based stratification framework and the corresponding GSE doses should be interpreted exclusively as exploratory hypotheses intended to guide future clinical investigations. To date, no prospective randomized controlled trials have established the predictive validity of these biomarker profiles, the optimal GSE dose for individual cardiovascular phenotypes, or the clinical benefit of combining GSE with other nutraceutical interventions; consequently, this framework should not be interpreted as a validated personalized treatment algorithm. The doses listed are those most frequently evaluated in published trials, chosen so that a future trial would remain within the range for which safety data exist, and the omega-3 combination is proposed only because the two interventions act on complementary inflammatory targets, not because any trial has tested them together.

The large heterogeneity of the GSE response—reflected in I^2 values of up to 88.8%—may reflect not only statistical heterogeneity but also underlying biological differences. If patients differ substantially in their oxidative and inflammatory biomarker profiles, these differences may contribute to variation in their response to an extract whose proposed mechanisms include antioxidant and anti-inflammatory effects. Clinical studies and meta-analyses have reported effects of grape seed extract on several oxidative stress and inflammatory biomarkers, although the evidence remains heterogeneous [63]. This hypothesis has not been tested: no clustering or other data-driven analysis was performed for this review, and the strata described below are a conceptual grouping of published biomarker profiles, proposed so that a future trial can test it prospectively.

The biomarkers used to define the proposed strata are those reported most consistently across the included clinical studies: malondialdehyde, superoxide dismutase, total antioxidant capacity, oxidized LDL, high-sensitivity C-reactive protein, interleukin-6 and glycated hemoglobin. The three strata were defined conceptually by grouping these biomarkers according to the dominant biological process they represent—oxidative, inflammatory-metabolic, or structural—and by matching each group with the mechanisms for which GSE has the most direct experimental support (Section 3). The purpose of this grouping is to make explicit a testable hypothesis for future trials: that response to GSE may depend on the dominant biological profile of the patient. It does not constitute a validated classification, and the strata are not derived from any statistical partition of patient data.

Proposed stratum 1—Oxidative-dominant: MDA $\geq$ 3.2 nmol/mL, SOD $<$ 80 U/gHb, TAC $<$ 1.1 mmol/L, and ox-LDL $>$ 70 U/L, with hsCRP $<$ 3 mg/L. This profile is characterized by a relatively greater oxidative-stress burden and may therefore represent a group in which the proposed Nrf2/HO-1 mechanisms and ROS-scavenging properties of GSE warrant further investigation [63,64,123]. The biomarker thresholds are exploratory cluster-derived cut-offs and should not be interpreted as clinically validated diagnostic or predictive thresholds. A dose of 400 mg/day, within the range evaluated in randomized clinical studies, is proposed for use in future trials of this stratum and is not a prescribing

recommendation; the optimal extract standardization and proanthocyanidin content remain to be established [124].

Proposed stratum 2—Inflammatory-metabolic: hsCRP ≥ 3 mg/L, IL-6 ≥ 3 pg/mL, and HbA1c ≥ 6.0%. This profile is characterized by a greater inflammatory and metabolic burden. GSE has demonstrated anti-inflammatory effects in experimental models involving NF-κB signaling, while omega-3 fatty acids may modulate inflammatory pathways and reduce circulating inflammatory biomarkers. However, whether these mechanisms produce complementary effects when GSE and omega-3 are combined remains uncertain; this proposed interaction should therefore be considered a hypothesis for further investigation rather than an established clinical synergy [63,125,126]. Patients with metabolic syndrome may be represented within this phenotype, although this cannot be established at the individual level from published group-level data.

Proposed stratum 3—Structural/fibrotic: NT-proBNP > 400 pg/mL, chronically elevated cardiac troponins, and elevated GDF-15. This profile includes biomarkers associated with myocardial stress, myocardial injury, and chronic cardiac remodeling [127–129]. Two limitations apply specifically to this group: NT-proBNP, cardiac troponins and GDF-15 are not among the biomarkers used to define the other two strata, so this group is defined on clinical reasoning rather than on the biomarker set used for the other two strata; and the antioxidant and NF-κB-related mechanisms attributed to GSE act predominantly on oxidative and inflammatory signaling, whereas established fibrotic remodeling is sustained by fibroblast activation, extracellular-matrix cross-linking and macrophage–fibroblast metabolic interactions that these mechanisms are unlikely to reverse. The extent to which GSE-related antioxidant and anti-inflammatory mechanisms may influence advanced myocardial remodeling remains uncertain and requires prospective investigation [129].

To put the suggested exploratory phenotyping framework into practice, a three-tier monitoring scheme is proposed for future studies, going from normal laboratory assessment to specialized and research-level evaluation (Figure 6). Level 1 is the minimum examination that might be completed in any clinical laboratory, as shown in Table 14.

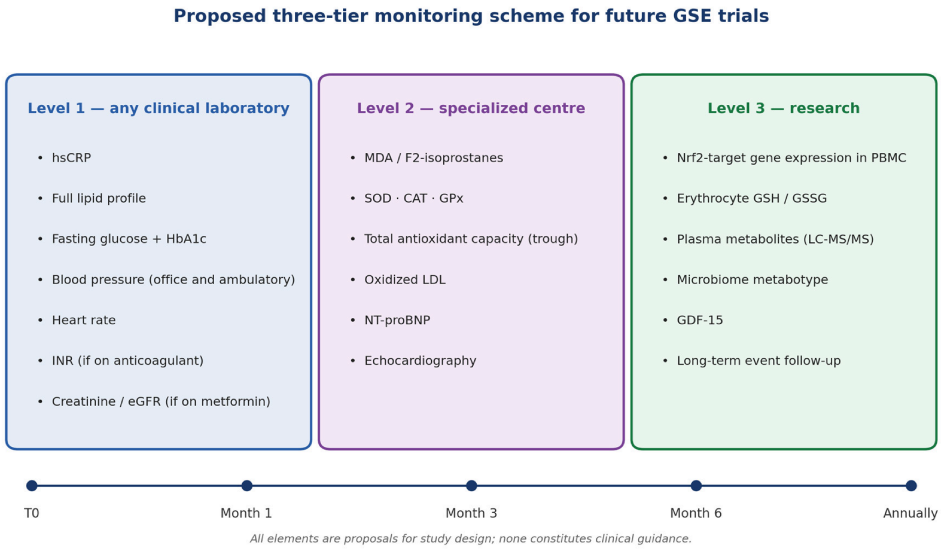


Figure 6. Proposed three-tier monitoring scheme for future GSE trials: Level 1, assessments available in any clinical laboratory; Level 2, specialized-center assessments; Level 3, research-level mechanistic and pharmacokinetic endpoints. Proposed timeline: baseline, months 1, 3 and 6, then annually. All elements are proposals for study design and do not constitute clinical guidance. PBMC, peripheral blood mononuclear cells; GSH/GSSG, reduced/oxidized glutathione; MDA, malondialdehyde; TAC, total antioxidant capacity.

Table 14. Level 1 monitoring protocol—applicable in any clinical laboratory.

Parameter	Why We Monitor It	Indicative Target	Frequency
hsCRP (mg/L)	Chronic vascular inflammation—central marker of the inflammatory-metabolic stratum	↓ ≥20% at 3 months	T0, months 1, 3, 6, annual
Full lipid profile	Antiatherogenic-target assessment; oxidized LDL if available	LDL ↓ ≥5%; HDL ↑ ≥3%	T0, months 3, 6, annual
Glucose + HbA1c	Metabolic oxidative stress; informs the inflammatory-metabolic stratum and possible omega-3 co-administration	HbA1c stable or improved	T0, months 3, 6, annual
Blood pressure	GSE vasodilatory effect via Akt/eNOS; hypotension risk	DBP ↓ ≥2 mmHg or stable	Each visit
Creatinine + eGFR (if + metformin)	OCT-mediated risk monitoring at eGFR 30–45	Stable eGFR, no > 15% decline	At weeks 4 and 12

All targets are indicative, derived from surrogate-endpoint meta-analyses. No study with MACE as a primary endpoint exists for GSE.

The proposed monitoring framework can then be integrated into an exploratory clinical decision pathway for cardiovascular polypharmacy (Figure 7). This pathway links baseline phenotyping and monitoring with the available evidence on potential GSE use while explicitly recognizing the uncertainty of the current evidence base.

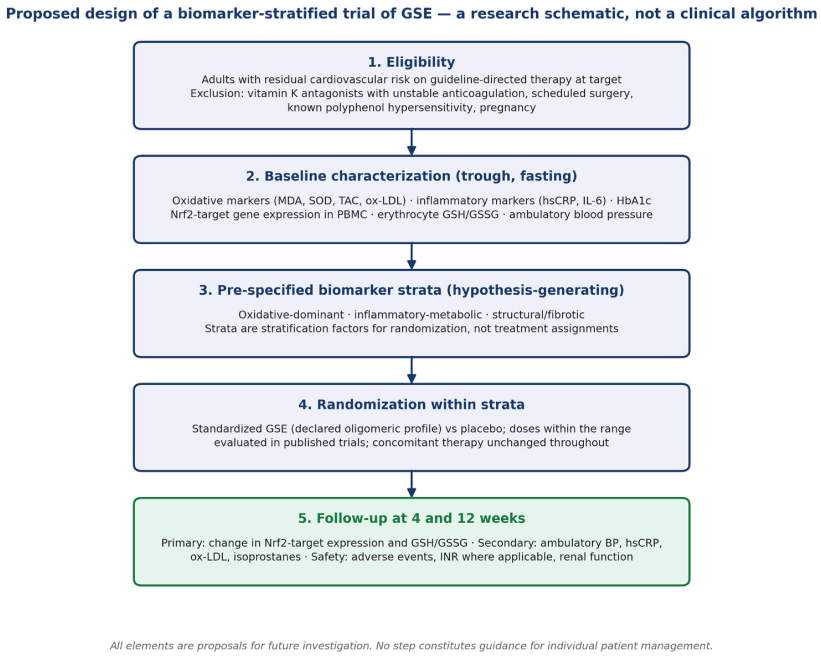


Figure 7. Proposed design of a biomarker-stratified trial of GSE, presented as a research schematic. Eligibility, baseline characterization at trough, pre-specified biomarker strata used as stratification factors for randomization, randomization within strata against placebo, and follow-up with mechanistic primary endpoints. All elements are proposals for future investigation; the schematic is not a clinical decision algorithm and does not constitute guidance for individual patient management. PBMC, peripheral blood mononuclear cells; GSH/GSSG, reduced/oxidized glutathione; BP, blood pressure.

6. Discussion

6.1. An Overview of the Clinical Evidence

Taken as a whole, the body of evidence for GSE is generally consistent in direction but uneven in magnitude—a pattern frequently observed with polyphenolic interventions and potentially reflecting differences in extract characteristics, dosage, intervention duration, and participant characteristics. The Zhang et al. [23] meta-analysis (16 RCTs, n = 810) reported significant reductions in SBP (−6.08 mmHg; I^2 = 94.0%) and DBP (−2.80 mmHg; I^2 = 62.4%), while the later Foshati et al. [18] meta-analysis of 19 trials found a significant reduction in DBP (−2.20 mmHg) but no statistically significant overall effect on SBP. These findings complement the earlier meta-analysis by Feringa et al. [24], which reported a smaller but significant reduction in SBP (−1.54 mmHg), with no significant effect on DBP [23,24,63].

What calls for particularly careful interpretation is the substantial heterogeneity observed for some outcomes, notably I^2 = 88.8% for DBP in the Foshati et al. [18] meta-analysis. This heterogeneity may reflect differences in study populations, baseline characteristics, intervention dose and duration, and other methodological or clinical factors rather than a single underlying mechanism. The Zhang et al. [23] meta-analysis identified age, BMI, baseline blood pressure, and metabolic status as potential effect modifiers, whereas Foshati et al. [63] reported dose, duration, and participant characteristics as possible sources of between-study heterogeneity. Thus, although biological variability in oxidative and inflammatory status may plausibly contribute to differential responses, this hypothesis cannot be established from the available aggregate-level evidence. It nevertheless provides a rationale for the exploratory stratification framework proposed in Section 5; the source-by-source estimates are shown in Figure 8.

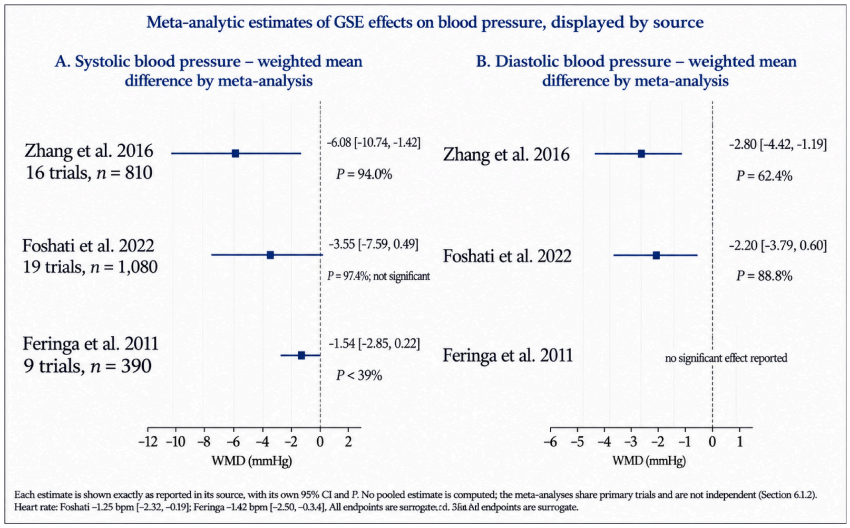


Figure 8. Meta-analytic estimates of GSE effects on blood pressure, displayed separately by source. (**A**) Systolic and (**B**) diastolic weighted mean differences with 95% confidence intervals and I^2 as reported by Zhang et al. [23], Foshati et al. [18] and Feringa et al. [24]. No pooled estimate is computed because the three meta-analyses share primary trials and are not independent (Section 6.1.2). Heart-rate estimates are given in the figure footnote. All endpoints are surrogate; no study has evaluated major adverse cardiovascular events.

6.1.1. Structural Analysis of the Sources of Heterogeneity

A rigorous interpretation of I^2 = 88.8% requires consideration of its potential structural contributors. Subgroup and meta-regression analyses from the Zhang et al. [18,23,24] meta-analysis and complementary studies identify several potential sources of heterogeneity,

operating simultaneously, that make direct between-study comparisons intrinsically difficult (Table 15).

Table 15. Major potential sources of heterogeneity in the cardiovascular effects of GSE and strategies for addressing them in future randomized controlled trials.

Source of Heterogeneity	Magnitude (Estimated)	Explanation	Addressable in Future RCTs
Baseline oxidative-stress profile	HIGH—dominant source	Trials have not stratified participants by baseline oxidative status, so the influence of this factor on effect size is inferred from the biological rationale and from between-trial differences in baseline populations, not from a direct comparison. Whether patients with higher baseline oxidative stress respond more strongly is a hypothesis to be tested, not an established finding.	YES—mandatory pre-stratification
GSE quality and standardization	HIGH	OPC content 40–99% across studies; the fractional profile undeclared in most. An extract with 99% OPC and rich trimers is not the same compound as one with 40% OPC.	YES—mandatory per-batch HPLC certification
Dose range (150–600 mg/day)	MODERATE	A 4-fold dose variation without a confirmed dose–response relationship. Suggests extract quality matters more than dose.	PARTIAL—fixed-dose arms needed
Population heterogeneity	MODERATE	Studies span healthy volunteers, MetS, T2DM, CHD, CKD. Different baseline BP and vascular tone substantially affect the delta-BP magnitude.	YES—single-population RCTs
Study duration (4–16 weeks)	MODERATE	The Nrf2/HO-1 adaptive response needs 4–6 weeks for maximal expression. Studies < 8 weeks capture only acute effects.	YES—minimum 12-week duration required

BP = blood pressure; MetS = metabolic syndrome; T2DM = type 2 diabetes; CHD = coronary heart disease; CKD = chronic kidney disease; OPC = oligomeric proanthocyanidins; HPLC = high-performance liquid chromatography.

The practical implication of this decomposition is actionable: if future RCTs simultaneously incorporate phenotypic stratification, rigorous extract standardization, predefined dosing, a more homogeneous study population, and adequate intervention duration of at least 12 weeks, between-study heterogeneity may be reduced and the resulting estimates may become more comparable. However, I^2 should not be expected to fall necessarily below 50%, because the interpretation of this statistic depends on the magnitude and direction of effects, the number of studies, and other clinical and methodological characteristics [18]. The failure to implement these controls in past studies should therefore be viewed as a methodological limitation rather than as evidence against the potential of GSE; these sources of variability can be addressed prospectively through better-designed and adequately standardized RCTs.

6.1.2. Overlap Between the Available Meta-Analyses

A question raised during peer review—whether the available meta-analyses include the same primary studies—is central to interpreting the apparent consistency of the evidence, and is addressed here explicitly. The four meta-analyses most often cited for the cardiovascular effects of GSE were published between 2011 and 2022 and draw on the same, slowly growing body of small randomized trials: Feringa et al. pooled 9 trials (n = 390), Zhang et al. 16 trials from 12 articles (n = 810), Asbaghi et al. 15 trials, and Foshati et al. 19 trials in 25 treatment arms (n = 1080). Because each successive meta-analysis applied broadly similar eligibility criteria to a literature that had grown only modestly in the interval, the later analyses necessarily re-include most of the trials pooled by the earlier ones.

Two consequences follow. First, the four analyses cannot be treated as four independent confirmations of an effect: the arithmetic sum of their participants (approximately 2280) greatly overstates the number of distinct individuals studied, and agreement between them partly reflects shared primary data rather than independent replication. Second, their divergent conclusions become easier to interpret. Feringa et al. found a significant reduction in systolic but not diastolic blood pressure; Zhang et al. found significant reductions in both; Foshati et al. found a significant reduction in diastolic blood pressure and heart rate but not in systolic blood pressure, with very high heterogeneity for the latter ($I^2 = 97.4\%$). When largely the same trials yield opposite conclusions for the same endpoint, the determining factors are the eligibility thresholds, the handling of multiple treatment arms and the statistical model, not the accumulation of new evidence.

A study-level overlap matrix of the primary trials included in each of the four meta-analyses is provided as Supplementary Material; it reports, for each primary trial, which meta-analyses include it, and summarizes the resulting counts of uniquely and repeatedly pooled trials. This exercise supports the central methodological point of this review: the evidence base for the cardiovascular effects of GSE consists of a limited number of small trials that have been re-analyzed several times, and the appearance of a growing evidence base is to a substantial extent an artefact of repeated pooling.

6.1.3. Structured Appraisal of the Certainty of the Evidence

To make the basis of each statement in this review inspectable, the principal claims are set out below with their mechanism, the type and source of the supporting evidence, an explicit judgement of certainty, the potential clinical consequence if the claim were confirmed, and the research priority that follows (Table 16). Certainty is graded on three levels: high, where the claim rests on consistent human randomized data; moderate, where it rests on a single randomized trial, on consistent preclinical data with a plausible human correlate, or on meta-analytic data with high heterogeneity; and low, where it rests on in vitro data, on inference from related compounds, or on computation alone. This grading is a structured editorial appraisal, not a formal GRADE assessment, and is presented as such.

Table 16. Structured appraisal of the principal claims in this review.

Claim	Mechanism	Evidence Type and Source	Certainty	Potential Clinical Consequence If Confirmed	Research Priority
GSE lowers diastolic blood pressure	NO-mediated vasodilation via PI3K/Akt/eNOS	Meta-analyses of randomized trials (19 and 16 trials); consistent direction, high heterogeneity (I^2 62–89%)	Moderate	A 2–3 mmHg diastolic reduction, if sustained, may be relevant at population level; its individual clinical significance cannot be judged against a fixed threshold and depends on baseline risk, magnitude, duration and the low certainty of the pooled estimates	Randomized trial with ambulatory blood-pressure monitoring as primary endpoint
GSE lowers heart rate	Not established; possibly autonomic or NO-mediated	Two meta-analyses (−1.25 and −1.42 bpm), consistent	Moderate	Small; of uncertain clinical meaning in isolation	Secondary endpoint in any future trial
GSE does not lower systolic blood pressure consistently	—	Divergent meta-analytic results (significant in one, not in another; I^2 up to 97%)	Moderate	Limits any claim of antihypertensive adjunct status	Resolution requires trials, not further pooling
GSE reduces hsCRP and oxidized LDL	NF-κB suppression; protection of LDL from oxidation	Small randomized trials and one meta-analysis; inconsistent across studies	Low–moderate	Would support an anti-inflammatory adjunct role in residual inflammatory risk	Trial in patients with hsCRP ≥ 2 mg/L
Nrf2/HO-1 activation mediates tissue protection	Keap1 conformational change, antioxidant gene transcription	Animal ischemia–reperfusion models with pharmacological abolition (brusatol); renal and cardiac tissue	Moderate (preclinical)	Mechanistic plausibility only; no human correlate measured	Measurement of Nrf2-target gene expression in a human trial
Trimeric fractions drive NF-κB inhibition	Structure–activity relationship across fractions	Single in vitro study with chromatographically separated fractions	Low	Would justify standardization by oligomeric profile rather than total OPC	Replication in vitro, then correlation with systemic exposure
Higher oligomers reach systemic circulation	—	No direct evidence; physicochemical computation predicts low passive absorption (TPSA 221–311 $Å^2$, 3–4 Lipinski violations)	Low (computation argues against)	If unconfirmed, mechanistic data on trimers cannot be extrapolated to oral dosing	Pharmacokinetic study quantifying plasma oligomers after an oral dose

Table 16. *Cont.*

Claim	Mechanism	Evidence Type and Source	Certainty	Potential Clinical Consequence If Confirmed	Research Priority
GSE interacts with warfarin	CYP2C9 inhibition in vitro; possible antiplatelet additivity	In vitro enzyme data only; no human pharmacokinetic study; the frequently cited INR case involved an adulterated product	Low	Would mandate INR surveillance at initiation and discontinuation	Pharmacokinetic/pharmacodynamic study in stably anticoagulated patients
GSE interacts with CYP3A4-metabolized statins	CYP3A4 inhibition in vitro	In vitro data for a grape seed procyanidin extract	Low	Would support preference for non-CYP3A4 statins in concomitant users, but does not justify changing established therapy	Interaction study with a probe substrate
GSE interacts with metformin via OCT/MATE	Transporter inhibition inferred from other polyphenols	Class-effect inference only; no data for GSE	Low	Monitoring of renal function at initiation in patients with reduced eGFR	Transporter inhibition assay with GSE constituents
'Feteasca Neagra' has a distinctive phytochemical profile	Higher seed flavonoid localization and antioxidant assay values	Independent phytochemical studies using different assay protocols	Moderate (phytochemistry)/absent (pharmacology)	Would identify a raw material worth standardizing, not a therapeutic advantage	Head-to-head phytochemical characterization on one analytical platform
GSE reduces major adverse cardiovascular events	—	No study has evaluated MACE as a primary endpoint	Absent	Unknown; this is the decisive gap for any guideline consideration	Event-driven randomized trial, phenotypically stratified

6.1.4. From Surrogate Change to Clinical Significance: How Much Is a Few Millimeters of Mercury?

The reductions reported for GSE—about 2–3 mmHg in diastolic blood pressure, and a systolic estimate that ranges from a non-significant −3.55 mmHg to −6.08 mmHg with a wide confidence interval, depending on the meta-analysis—are easy to dismiss at the bedside and easy to overstate in a review. Both errors can be avoided by separating three distinct questions: what such a change means epidemiologically, what it means for an individual patient, and whether the measurement on which it is based is adequate.

Epidemiologically, small differences in usual blood pressure are associated with meaningful differences in vascular mortality at the population level: in the Prospective Studies Collaboration analysis of one million adults, a usual systolic blood pressure 2 mmHg lower was associated with approximately 10% lower stroke mortality and approximately 7% lower mortality from ischemic heart disease in middle-aged adults [130], and trial-based estimates from pharmacological lowering indicate that a 5 mmHg reduction in systolic blood pressure reduces major cardiovascular events by about 10% [131]. These associations cannot, however, be transferred to GSE supplementation. They derive from long-term usual blood pressure in observational cohorts and from antihypertensive drug trials with hard endpoints, whereas the GSE evidence consists of short surrogate-endpoint trials with imprecise and heterogeneous pooled estimates. Although modest reductions in blood pressure may have epidemiological relevance, the cardiovascular prognostic implications of GSE supplementation remain unknown. In the absence of adequately powered randomized controlled trials evaluating cardiovascular outcomes, reductions in major cardiovascular events cannot be inferred from changes in surrogate endpoints; the available evidence therefore does not support any claim regarding the prevention of myocardial infarction, stroke or cardiovascular mortality through GSE supplementation, and no numerical estimate of event reduction is offered here.

For the individual patient, the picture is different, and no fixed threshold settles it. A difference of 5 mmHg is sometimes cited as clinically meaningful for systolic blood pressure, but such a figure cannot be transferred to diastolic pressure, and the clinical significance of any reduction depends on baseline cardiovascular risk, on the magnitude and duration of the reduction, and on whether outcomes are considered for the individual or for a population. Three things must therefore be kept apart: the statistical significance of the pooled estimates, their clinical relevance, and the certainty of the evidence behind them. For GSE, the diastolic estimate is consistent in direction but small; the systolic estimate is imprecise and heterogeneous; and the certainty is limited by short trial durations, small samples and variable extract formulations. In practical terms, GSE cannot be presented to a patient as a substitute for, or a means of reducing, antihypertensive therapy; its only plausible position is as an optional adjunct in patients already treated to target.

Finally, a methodological caveat that matters more in this literature than in most: the trials pooled in the available meta-analyses used office blood pressure measurement. Office readings are susceptible to regression to the mean, to white-coat and placebo effects, and to observer influence—all of which inflate apparent treatment effects in short trials. Only two of the pooled trials used ambulatory recording: Sivaprakasapillai et al. [27], who reported significant reductions, and a dedicated 24-h ambulatory study in pre- and stage I hypertension that found a non-significant fall of about 3 mmHg in systolic pressure [132]. That the one trial designed around ambulatory monitoring did not reproduce the office-based effect is itself informative. For an intervention whose entire claimed benefit on blood pressure is in the range of 2–6 mmHg, this is not a minor limitation: it is the single methodological change that would most increase confidence in the finding, and it should be a mandatory feature of any future trial.

6.2. GSE in the Context of Cardiovascular Nutraceuticals

The compound that most convincingly validated the concept of the cardiovascular nutraceutical is icosapent ethyl, a purified EPA derivative, tested in REDUCE-IT [34] on 8179 patients, with a 25% relative reduction in MACE risk (HR = 0.75; $p < 0.001$). Omega-3 traveled the road from epidemiology to the 2019 ESC guidelines in about fifteen years—this is the reference translational model for GSE.

GSE occupies a potentially complementary niche alongside CoQ10 [133] (heart failure), berberine [134] (insulin resistance), and omega-3 (triglycerides and inflammation). The GSE + omega-3 combination has a plausible mechanistic basis: OPC suppression of NF-κB may complement the anti-inflammatory effects of omega-3, with partially overlapping targets in the pro-inflammatory cascade.

Induction Versus Supplementation: Why the Failure of Single Antioxidants Does Not Predict the Behavior of a Polyphenolic Matrix

Any proposal to use an antioxidant preparation for cardiovascular protection must confront the central negative result of this field. In the HOPE and HOPE-TOO trials, 400 IU/day of natural-source vitamin E given for a median of seven years to patients with vascular disease or diabetes produced no reduction in myocardial infarction, stroke or cardiovascular death, and was associated with an increased incidence of heart failure [135]. A dose–response meta-analysis of 19 trials including 135 967 participants reported that high-dose vitamin E (≥400 IU/day) was associated with a small but statistically significant increase in all-cause mortality (relative risk 1.04; 95% CI 1.01–1.07) [136]. The conclusion generally drawn from this literature—that antioxidant supplementation does not protect the cardiovascular system—is, in our view, more precisely stated as a conclusion about a particular pharmacological strategy: supplying a single, high-dose, exogenous radical scavenger.

The same limitation applies, for a different reason, to glutathione itself, the endogenous antioxidant most often proposed for supplementation. A single oral dose of up to 3 g in healthy volunteers did not raise blood glutathione concentrations [137]; 500 mg twice daily for four weeks did not alter systemic oxidative-stress biomarkers or erythrocyte glutathione status [138]; and a meta-analysis of controlled trials found no significant increase in erythrocyte or plasma glutathione with oral supplementation, although a six-month trial at 250–1000 mg/day did report increases in body stores [139,140]. The obstacle is pharmacokinetic rather than pharmacodynamic: intestinal γ-glutamyl transferase extensively degrades the intact tripeptide, so an orally supplied antioxidant does not reliably reach the compartment in which it would act.

Grape seed extract operates on a different principle, and this distinction—rather than any claim of greater potency—is what makes it worth investigating after the failure of single-molecule antioxidants. Its constituents do not act primarily by being the antioxidant: through Keap1 modification and Nrf2 nuclear translocation, they induce the transcription of the cell's own antioxidant machinery, including glutamate-cysteine ligase, the rate-limiting enzyme of glutathione synthesis, together with heme oxygenase-1 and NAD(P)H quinone dehydrogenase 1 [31,41,45]. In other words, the pharmacological target is endogenous glutathione synthesis rather than exogenous glutathione delivery. A preparation that induces the pathway is not subject to the bioavailability constraint that limits the molecule itself, and it acts on several redox-sensitive processes simultaneously rather than on radical scavenging alone.

Two consequences follow for how this class of preparation should be evaluated. First, the negative vitamin E trials do not transfer directly to polyphenolic matrices, because the intervention tested was different in kind; this is a testable claim, not a defense, and the way to test it is to measure Nrf2-target gene expression and endogenous glutathione

status as mechanistic endpoints in a human trial, something no GSE trial has yet done. Second, the apparent paradox identified in Section 3.7.3—that the fractions with the greatest in vitro activity are the least absorbed—is far less damaging under an induction model than under a scavenging model, since transcriptional induction can be initiated at the intestinal epithelium and propagated systemically by absorbed monomers and microbial phenolic-acid metabolites. Establishing whether this is what actually happens is, in our view, the single most informative experiment that could be performed with this extract.

6.3. Original Contributions

Contribution 1: a structured compilation of the published phytochemical data available for Romanian viticultural cultivars, with Fetească Neagră identified as a candidate warranting dedicated phytochemical and pharmacological investigation (Table 5). The compiled data derive from studies using different analytical protocols and therefore do not support a ranking of cultivars by cardioprotective potential [88,141].

Contribution 2: a structured synthesis of the published evidence on the potential GSE interaction profile with cardiovascular pharmacotherapy, including an exploratory evaluation of the GSE–metformin interaction via the OCT1/OCT2 mechanism—a gap not previously addressed [142–144].

Contribution 3: a conceptual framework for biomarker-based stratification of cardiovascular patients, intended as a hypothesis for future trial design rather than as a validated classification, together with the identification of the metabolic-syndrome population as the group in which the existing evidence is most consistent.

Contribution 4: a proposal for minimum quality standards for GSE extracts in clinical studies (Table 15), with reference to pharmacopeial and EMA/HMPC quality frameworks—a contribution with direct applicability to future study design [11,12].

Contribution 5: a structural analysis of the potential sources of heterogeneity underlying $I^2 = 88.8\%$ reported for diastolic blood pressure by Foshati et al. [18] (6.1.1)—a structured synthesis of the factors potentially contributing to between-study variability in the GSE literature, with direct implications for the design of future pilot RCTs [18,23,63].

6.4. Extract Standardization: A Sine Qua Non

One of the deep causes of heterogeneity in the GSE literature is extract variability: reported proanthocyanidin content varies substantially among commercial extracts, extraction methods are often insufficiently characterized, and the oligomeric and polymeric fractions are not consistently profiled. Commercial GSEs have been reported to contain approximately 76–99% total proanthocyanidins, with substantial variation in the relative proportions of polymers, monomers, dimers, and higher oligomers [145–147]. An extract with a different proanthocyanidin content and molecular-size distribution is therefore not necessarily chemically equivalent to another extract administered at the same nominal dose in milligrams [68,147].

6.5. Comprehensive Limitations—An Honest Reading of the Evidence

Any balanced assessment of GSE must openly acknowledge the limitations surrounding the literature. The narrative design does not include a formal RoB 2 or GRADE evaluation, did not benefit from prospective registration (PROSPERO/OSF), and is not a de novo meta-analysis. The heterogeneity of commercial extracts, including substantial variation in total proanthocyanidin content and in the relative proportions of monomeric, oligomeric, and polymeric fractions, makes between-study comparison difficult and may contribute to the high I^2 values [145,148–150].

The absence of hard clinical endpoints is the fundamental limitation: no published GSE trial identified in this review evaluated MACE as a primary endpoint. In addition, formal tests for publication bias were negative in the largest blood-pressure meta-analysis (Begg and Egger tests, with symmetrical funnel plots [23]), but such tests have limited power with small numbers of trials, so residual publication bias cannot be excluded, and no formal risk-of-bias or certainty-of-evidence appraisal was applied. The dosing ranges, interaction risk categories, monitoring schedules and decision algorithms presented in this review should therefore be read as research proposals constrained by these limitations, not as clinical guidance. Fetească Neagră has no dedicated pharmacological or clinical study of a Fetească Neagră-specific GSE; its proposal as a research candidate rests exclusively on the comparative phytochemical profile and related experimental evidence. The stratification framework is a conceptual proposal based on group-level biomarker data reported in published studies; such group-level reasoning cannot be transposed to individual clinical decision-making without prospective validation in cohorts with individual participant data using individual participant data (IPD) [151]. The GSE–metformin interaction remains largely inferential, and no direct human pharmacokinetic study confirming a clinically relevant interaction has been identified.

6.6. Translational Agenda: Roadmap for GSE–Fetească Neagră Research

The evolution from mechanistic potential to guideline inclusion is potentially long and requires progressive clinical validation. Omega-3 provides an established example of translational development, whereas GSE remains at an earlier stage of clinical evaluation. GSE—and GSE–Fetească Neagră in particular—have a diversified mechanistic basis but a less structured clinical evidence base.

Stage 0—Identified research gap (present): generic GSE has been studied in multiple randomized controlled trials and meta-analyses. GSE–Fetească Neagră: no dedicated pharmacological or clinical studies of a standardized Fetească Neagră-specific GSE were identified. Independent peer-reviewed studies have characterized the phytochemical and experimental cardioprotective properties of Fetească Neagră grape-pomace extracts [88].

Stage 1—Phytochemical and pharmacological standardization (12–24 months): comparative HPLC/LC-MS characterization of GSE–Fetească Neagră versus a reference commercial-cultivar GSE on the same biomarker panel ($n \geq 15$ batches, three Romanian viticultural regions, three harvest years); per-batch PCC1 quantification; certified CYP450 and OCT1/OCT2 screening according to the criteria proposed in Table 17 [152,153].

Stage 2—Clinical pilot study (24–48 months): a double-blind, three-arm pilot RCT: GSE–Fetească Neagră versus standard-cultivar GSE versus placebo ($n \geq 60$/arm, 6 months). Primary endpoint: a phenotype-specific biomarker panel (MDA, hsCRP, ox-LDL, TAC). Exploratory secondary endpoints: DBP and lipid profile. Classification by AI phenotypes (Section 5). Prospective trial registration is recommended [154].

Sample size. With 60 participants per arm, a two-sided α of 0.05 and 80% power, the smallest difference detectable between two arms is approximately 0.52 standard deviations. Applied to the variability reported in the trials synthesized here, this corresponds to about 4.2 mmHg for diastolic blood pressure (assuming SD 8 mmHg), about 1.0 mg/L for hsCRP (SD 2 mg/L) and about 0.4 nmol/mL for malondialdehyde (SD 0.8 nmol/mL). This is a deliberate design choice rather than a limitation: a trial of this size is adequate to detect a biomarker signal large enough to justify a subsequent event-driven study, but is explicitly underpowered for the 2–3 mmHg blood-pressure difference reported in the meta-analyses, which would require several hundred participants per arm. A pilot of this size should therefore be read as a feasibility and signal-detection study, not as a test of the blood-pressure hypothesis.

Table 17. Minimum standardization criteria for GSE in CV clinical studies.

Domain	Minimum Criterion	Verification Method	Rationale	Priority
Botanical identification	*Vitis vinifera* L. cultivar + certified geographic origin	Origin certificate + SSR/SNP molecular genotyping	Phytochemical variability between cultivars (13× factor)	CRITICAL
OPC content	≥95% declared OPC; per-batch HPLC-DAD/MS certification	HPLC-DAD or HPLC-MS	Direct correlation with antioxidant effects	CRITICAL
OPC fractional profile	Monomer/dimer/trimer/polymer distribution reported; PCC1 specifically quantified	HPLC-MS/LC-MS/MS	Different bioavailability and NF-κB activity by degree of polymerization	MAJOR
Extraction method	Fully documented SOP (solvent, temperature, time) per ICH Q14 principles	SOP available on request; audit per EMA/HMPC	Major influence on the polyphenolic profile and reproducibility	CRITICAL
CYP450 screening	CYP3A4, CYP2C9, OCT1/OCT2 screening data provided per batch	Certified in vitro enzymatic studies	Cardiovascular polypharmacy safety; GSE–metformin interactions	MAJOR

SOP = standard operating procedure; OPC = oligomeric proanthocyanidins; HPLC = high-performance liquid chromatography; ICH Q14 = ICH analytical-procedure development guideline; EMA/HMPC = EMA Committee on Herbal Medicinal Products.

Stage 3—Process and product patent (>36 months, in parallel): the optimized extraction methodology—solvent choice, temperature and pressure conditions, and standardization parameters—could constitute potential intellectual property, subject to applicable patentability requirements. Completing Stages 1–2 would provide data relevant to subsequent intellectual-property assessment and, where appropriate, to preparation of a notification dossier for a dietary supplement in Romania [153].

Stage 4—Guideline integration (>48 months): a proposal for consideration as an optional nutraceutical adjunct in cardiovascular prevention guidelines, contingent on adequate clinical evidence, including at least one appropriately designed RCT with validated surrogate endpoints and an adequately characterized safety profile [155].

6.7. From a Winemaking By-Product to a Defined Product: A Staged Development Pathway

The practical question raised by the foregoing analysis is not whether grape seed extract should be used clinically today—it should not, beyond the optional adjunct position described in Section 7.6—but what a disciplined path from an agricultural by-product to a defined product would look like, and what evidence each step requires. We set this out explicitly because the material is unusual in one respect: the starting point is not a new chemical entity requiring de novo toxicology, but a food by-product with a long history of human consumption, which places the first steps of the pathway in a regulatory category with a far lower barrier than a medicinal product (Table 18).

Stage A concerns the raw material. Grape pomace is generated in large volumes as a by-product of vinification and is currently valorized mainly as compost, animal feed or biomass. Its conversion into a pharmaceutical-grade starting material requires exactly what Section 6.4 specifies: identification of the cultivar and the clone, the area and vintage, a documented extraction procedure, and per-batch HPLC certification of the oligomeric profile, not merely of total proanthocyanidin content. Nothing in this stage is scientifically novel; what is missing is the discipline of applying it consistently to a defined cultivar.

Table 18. Staged pathway from Fetească Neagră pomace to a defined product, with the evidence required at each stage.

Stage	Regulatory Category	Evidence Required	What Already Exists	What Is Missing
A. Raw material qualification	Food by-product (pomace); no authorization required	Cultivar and clone identity, area, vintage, documented extraction SOP, per-batch HPLC fractional profile	History of consumption; available volumes; published phytochemical characterization of the cultivar	Consistent application of a single specification to one defined cultivar
B. Food supplement	Directive 2002/46/EC [140]; national notification. Not a novel food (Regulation (EU) 2015/2283 [156]) given documented history of use	Product specification and safety dossier; no therapeutic claim permitted	GRAS status of grape seed extract; absence of severe adverse events in clinical trials to date	A Fetească Neagră-specific standardized extract with a declared oligomeric profile
C. Standardized botanical preparation for clinical study	Investigational product specification	Single stable specification, stability data, per-batch certification, CYP/transporter screening	Analytical methods; the standardization criteria proposed in Section 6.4	Stability data and a finalized, reproducible specification
D. Traditional herbal medicinal product	Directive 2004/24/EC [157] simplified registration (≥30 years of medicinal use, ≥15 in the EU)	Quality dossier, safety review, documentation of traditional use; no efficacy trials required	Long-standing use of grape seed preparations	A determination of whether the traditional-use criterion is satisfied for this preparation
E. Cardiovascular therapeutic claim	Full medicinal-product authorization	Prospective randomized trial with a clinically relevant primary endpoint, standardized preparation, predefined population	Mechanistic rationale; surrogate-endpoint signals	The trial itself; no study to date has used a hard cardiovascular endpoint

Stages A to C require analytical and regulatory discipline rather than new clinical evidence and are achievable with current knowledge; stages D and E require evidence that does not yet exist. SOP = standard operating procedure.

Stage B is the food-supplement route, which in the European Union falls under Directive 2002/46/EC [140] and, in Romania, under notification to the competent national authority. Grape seed extract is already marketed in this category worldwide and has a documented history of use, so it is not a novel food within the meaning of Regulation (EU) 2015/2283 [156]; the requirement is therefore a specification and a safety dossier rather than a clinical efficacy dossier. This is the stage at which a Fetească Neagră-specific, standardized extract could realistically exist first—as a characterized supplement with a declared oligomeric profile and no therapeutic claim.

Stage C is the transition from a supplement to a standardized botanical preparation suitable for clinical study: a single, stable specification, stability data, and the per-batch analytical certification described above. Without this stage, any clinical study remains uninterpretable, because the intervention cannot be reproduced, which is precisely the methodological defect that explains much of the heterogeneity analyzed in Section 6.1.1.

Stage D is the medicinal-product route. Directive 2004/24/EC [157] provides a simplified registration procedure for traditional herbal medicinal products, requiring evidence of at least 30 years of medicinal use, of which 15 within the European Union, together with a quality dossier and a safety review, but not clinical efficacy trials. Whether grape seed

extract satisfies the traditional-use criterion in its own right is a regulatory question we do not attempt to settle here; it is, however, the question that determines whether the pathway continues through a simplified registration or requires a full efficacy dossier.

Stage E is the only stage at which a cardiovascular therapeutic claim becomes possible, and it requires what this review has repeatedly identified as absent: a prospective randomized trial with a clinically relevant primary endpoint, conducted with a standardized preparation in a prospectively defined population. The biomarker trial proposed in Section 6.6 is a prerequisite for designing it, not a substitute for it.

Presented in this way, the development pathway makes explicit something that an isolated discussion of mechanisms obscures: the first three stages require no new clinical evidence at all, only analytical and regulatory discipline, and can be completed with existing knowledge; the last two require evidence that does not yet exist. Distinguishing between the two halves of this pathway is, we would argue, more useful to a reader than any further mechanistic argument, because it identifies what can be done now and what cannot.

7. Conclusions

7.1. Portrait of a Compound at the Intersection of Science and the Clinic

Evaluating *Vitis vinifera* seed extract carries an almost structural tension: the more closely it is examined molecularly, the more promising it appears; the more rigorously it is evaluated clinically, the more demanding the assessment becomes. This is not necessarily a flaw of the literature but a characteristic of a complex natural product positioned between mechanistic discovery and clinical validation. GSE has not been adequately evaluated for hard cardiovascular outcomes in clinical trials; rather, the available clinical evidence has focused predominantly on surrogate and intermediate endpoints, including blood pressure, heart rate, lipid parameters, and oxidative-stress and inflammatory biomarkers. This distinction is essential for interpreting both the literature and the conclusions. The available evidence supports the conclusion that GSE modulates several biologically relevant cardiovascular pathways and is associated with reductions in some surrogate cardiovascular and metabolic markers, with a generally favorable safety profile in the available clinical studies [18,23,24,63,65,106]. What remains unknown is whether this molecular and surrogate-endpoint activity translates into fewer hard cardiovascular events, such as myocardial infarction, stroke, or cardiovascular death. The distance between these two levels of evidence is precisely the space that future research must address.

7.2. Molecular Architecture: A Potential Advantage over Single-Mechanism Approaches

One of the genuinely original conclusions of this review is that the cardioprotective potential of GSE may lie not in a single dominant mechanism but in the simultaneous convergence of six interconnected biological pathways, each addressing a different dimension of cardiovascular pathophysiology. Nrf2/HO-1 regulates adaptive antioxidant defense against oxidative stress; NF-κB suppression may attenuate vascular inflammation; PI3K/Akt/eNOS signaling contributes to endothelial function through NO production; MAPK/JNK inhibition may limit cardiomyocyte apoptosis during ischemia–reperfusion; protection against LDL oxidation may limit an important process implicated in atherogenesis; and inhibition of platelet aggregation may reduce thrombogenic potential [28,54–56,125].

The most direct experimental evidence for the importance of Nrf2 comes from GSPB2 studies in renal ischemia–reperfusion and hypoxia–reoxygenation models, in which pharmacological inhibition with brusatol attenuated the protective effects of GSPB2 [149,158]. Because brusatol is not a selective Nrf2 inhibitor and also suppresses global protein synthesis, these experiments support Nrf2 involvement without confirming it, and they do not constitute direct evidence in myocardial tissue; they nevertheless support the hypothesis that

Nrf2/HO-1 signaling can represent an important mediator of proanthocyanidin-induced cytoprotection under ischemic or oxidative stress. In myocardial models, GSE has independently been shown to attenuate ischemia–reperfusion injury through inhibition of JNK/c-Jun signaling and to enhance cardioprotection through Akt/eNOS-dependent NO production [28,54]. Taken together, these findings suggest that the pathways affected by GSE are not independent but may constitute an interconnected signaling network. Establishing how these pathways interact will require genetic or more selective approaches rather than pharmacological inhibition alone; published network-pharmacology analyses of grape polyphenols offer candidate nodes for such work, although no such analysis was performed for this review.

7.3. The Clinical Evidence: Consistent in Direction, Incomplete in Substance

The available meta-analyses build a clinical picture consistent in direction but insufficient in substance for a formal recommendation. The documented reductions in diastolic blood pressure (−2.20 mmHg; 19 trials), heart rate (−1.25 bpm), and selected inflammatory and oxidative-stress markers are statistically significant and biologically plausible, although the magnitude and consistency of effects vary across outcomes and analyses [18,23,24,63]. They are not, however, sufficient to support inclusion of GSE as a cardiovascular therapy in current ESC or AHA/ACC guidelines, particularly in the absence of evidence demonstrating reductions in major adverse cardiovascular events (MACE) [150,159].

The most instructive statistical finding in this literature is the $I^2 = 88.8\%$ value for DBP reduction reported by Foshati et al. [18]. The alternative interpretation supported here, and grounded in the structural analysis of Section 6.1.1, is that this heterogeneity may partly reflect real biological variability. The hypothesis proposed in this review is that patients with higher oxidative stress (the oxidative-dominant stratum) may respond more strongly than those with a less pronounced oxidative-stress profile or predominantly fibrotic pathology (the structural/fibrotic stratum). However, this interpretation remains exploratory and has not been demonstrated in prospective individual-level studies. If confirmed in prospective, biomarker-stratified studies, the high heterogeneity observed in the existing literature could represent an early signal of stratum-dependent response to GSE, with implications for the design of future trials. Until then, the statistical significance of the pooled estimates should not be read as clinical relevance, and the certainty of the evidence behind them remains limited.

7.4. Drug Interactions: A Structured Synthesis of Potential Interactions

A structured synthesis of the published evidence on potential GSE interactions with current cardiovascular pharmacotherapy, including the GSE–metformin interaction, is among the contributions of this work with potential clinical relevance. The central result is that no interaction reaches the category of clinically demonstrated: those with warfarin and CYP3A4-metabolized statins rest on preclinical evidence only, those with dual antiplatelet therapy, metformin and direct oral anticoagulants are theoretical though mechanistically plausible, and only the additive effect with antihypertensives has limited clinical support through surrogate data. Potential severity—highest for warfarin—is therefore a reason for awareness and monitoring, not for modifying established therapy.

The practical message distilled from this analysis can be expressed in four propositions: (1) in patients receiving warfarin, particularly those with an unstable INR, concomitant GSE use warrants caution and, if undertaken, closer INR monitoring [108,160]; (2) in patients receiving CYP3A4-metabolized statins, no change in statin therapy is warranted on current evidence, since no clinically relevant GSE–statin interaction has been demonstrated in humans; the observation that pravastatin and rosuvastatin are metabolized largely inde-

pendently of CYP3A4 is a pharmacokinetic consideration relevant to the design of future interaction studies, not a prescribing recommendation [108]; (3) in patients receiving ACE inhibitors, ARBs, or beta-blockers without anticoagulation, no clinically established GSE interaction has been demonstrated, although the available evidence remains limited; and (4) in patients receiving metformin with an eGFR of 30–45 mL/min/1.73 m^2, closer monitoring of renal function when initiating GSE may be prudent if an OCT2/MATE interaction is considered clinically plausible, although this mechanism remains hypothetical and has not been demonstrated in human pharmacokinetic studies [161–163].

7.5. Fetească Neagră: A Phytochemical Conclusion with Translational Implications

One contribution of this review is a structured compilation of the published data on inter-varietal phytochemical variability; the following limited conclusion emerges: Fetească Neagră is a research candidate identified on the basis of available comparative phytochemical and experimental evidence, rather than national sentiment. The argument has three complementary components: the distinctive distribution of flavonoids in the seeds, with approximately 69% of the flavonoids detected in the berry localized in the seeds rather than the skins in one comparative study [20,21]; the proanthocyanidin profile, characterized by substantial oligomeric and polymeric fractions [21]; and the high antioxidant activity reported for Fetească Neagră grape and pomace extracts in independent studies [21,88]. Importantly, comparative phytochemical studies do not consistently place Fetească Neagră above all international cultivars for every parameter; rather, they demonstrate a distinctive and potentially relevant phytochemical profile that warrants further investigation [21,164].

The public health and viticultural context further supports the translational relevance of this proposal. Romania faces a substantial cardiovascular disease burden, with cardiovascular diseases accounting for at least 53% of all deaths in every Romanian region in 2023 [3]. At the same time, Romania is among the major wine-producing countries of the European Union, ranking sixth in recent production estimates [165,166]. The heritage of autochthonous cultivars—including Fetească Neagră, Băbească Neagră, and Negru de Drăgășani—therefore represents an underexplored source of phytochemical diversity with potential relevance for future pharmacological research. The convergence of these realities defines a translational research opportunity, although its distinctiveness at the European level remains to be established through systematic comparative investigation.

Fetească Neagră currently has no dedicated clinical study of a standardized Fetească Neagră-specific grape seed extract. Its proposal as a research subject rests on inference from comparative phytochemical data and related experimental evidence, including antioxidant and cardioprotective effects observed with Fetească Neagră pomace extracts [88]. This is a plausible research hypothesis, but it cannot be converted into a clinical recommendation without dedicated pharmacological, pharmacokinetic, safety, and clinical studies. Any other interpretation would exceed the boundary between evidence-based inference and speculation.

7.6. What the Present Evidence Supports in Practice Today

Three statements can be made with reasonable confidence for current practice, and they are deliberately modest. First, on magnitude: the blood-pressure reductions reported in meta-analyses—−6.08 mmHg systolic in Zhang et al. (95% CI −10.74 to −1.42), with no significant systolic effect in the larger Foshati et al. analysis, and −2.20 to −2.80 mmHg diastolic depending on the analysis—may have implications at the population level, but substantial between-study heterogeneity, differences in study populations and extract formulations, and limited follow-up durations reduce confidence in the magnitude and clinical relevance of these effects; their individual clinical significance and long-term cardiovascu-

lar consequences remain uncertain, and no fixed threshold of clinical importance can be applied to them. Current evidence does not support GSE as an alternative to guideline-recommended antihypertensive therapy: it is not an antihypertensive, it is not a reason to reduce established therapy, and it should not be presented to a patient as an alternative to it. Its only defensible position is as an optional adjunct in a patient already treated to target.

Second, on safety in context: the situations that require attention are situations of change, not of steady state. The two moments at which an undeclared supplement can matter clinically are its initiation and its discontinuation—in the anticoagulated patient, around surgery and invasive procedures, in the frail elderly patient on multiple antihypertensives, and in reduced renal function with concomitant metformin. In each case, the appropriate response is documentation and surveillance rather than prohibition, as set out in Section 4.6.

Third, on clinical process: because polyphenol-containing products are not perceived by patients as medicines, they are frequently absent from the medication list unless specifically requested. An explicit question about supplement use, with the preparation and dose recorded, belongs in any structured assessment of residual cardiovascular risk. This requires minimal resources, no new evidence, and is the single most useful practical conclusion that can be drawn from this review today.

What the evidence does not support is equally clear and should be stated in the same place: there is no basis for claiming benefit on cardiovascular events, no basis for ranking cultivars by cardioprotective potential, and no basis for the dosing or stratification proposals in Sections 3.7 and 5 to be used as clinical guidance rather than as research hypotheses.

7.7. Research Agenda and Closing Message

If we had to sum up in a few words what this review shows, it would be this: GSE has demonstrated cardioprotective effects at the molecular and surrogate-endpoint levels; we do not yet know whether these effects translate into benefits at the level that truly matters to the patient. Closing that gap is the task of the research to come—and a task with considerable importance, given the generally favorable tolerability reported in available clinical studies, the biologically plausible mechanisms identified to date, and the large population with residual cardiovascular risk that could potentially be studied [18,24,63].

Integrated clinical message: GSE is a compound with a multi-target molecular profile, clinical evidence pointing in a generally favorable direction for selected surrogate endpoints, and a distinctive translational research opportunity in the context of Romania's viticultural heritage. Among the cultivars for which phytochemical data are available, Fetească Neagră seed extract is a candidate with a distinctive profile that warrants dedicated investigation—a research hypothesis, not a clinical recommendation and not a ranking. The mechanistic reading proposed here is that GSE acts by inducing endogenous antioxidant synthesis through Nrf2 rather than by supplying exogenous antioxidants, a hypothesis consistent with the physicochemical profile of its constituents and with one human trial in which reduced glutathione increased, and one that a future trial should test directly. Integrating GSE into formal clinical practice would require prospective randomized trials with major adverse cardiovascular events (MACE) as clinically relevant primary endpoints. Until such evidence becomes available, GSE should be regarded as an investigational nutraceutical candidate rather than an established cardiovascular adjunct, and its potential role should be evaluated through adequately designed clinical studies with appropriate safety monitoring and predefined biomarker strata. A practical corollary follows from the staged pathway in Section 6.7: because the starting material is a food by-product rather than a new chemical entity, a standardized, cultivar-defined extract can be developed and characterized as a food supplement well before any therapeutic claim becomes defensible, and that sequence—specification first, claim last—is the one we propose.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/antiox15111436/s1, Table S1: The 166 cited sources classified by study type, with documentation of the PubMed/MEDLINE search.

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Abbreviations

The following abbreviations are used in this manuscript:

ACEi	Angiotensin-Converting Enzyme Inhibitors
AI	Artificial Intelligence
AUC	Area Under the Curve
ARBs	Angiotensin Receptor Blockers (Sartans)
BP	Blood Pressure
CAT	Catalase
CCBs	Calcium Channel Blockers
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CoQ10	Coenzyme Q10
CYP	Cytochrome P450
DAPT	Dual Antiplatelet Therapy
DBP	Diastolic Blood Pressure
DOACs	Direct Oral Anticoagulants
eGFR	Estimated Glomerular Filtration Rate
eNOS	Endothelial Nitric Oxide Synthase
FMD	Flow-Mediated Dilation
FN	'Feteasca neagra'
GCL	Glutamate-Cysteine Ligase
GPx	Glutathione Peroxidase
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GSE	Grape Seed/*Vitis vinifera* Seed Extract
GSH	Reduced Glutathione
HO-1	Heme Oxygenase-1
HR	Heart Rate
hsCRP	High-Sensitivity C-Reactive Protein
I^2	Heterogeneity Statistic
IL-6	Interleukin-6

INR	International Normalized Ratio
IPD	Individual Patient Data
I/R	Ischemia-Reperfusion
JNK	c-Jun N-terminal Kinase
MACE	Major Adverse Cardiovascular Events
MAPK	Mitogen-Activated Protein Kinase
MDA	Malondialdehyde
MetS	Metabolic Syndrome
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NO	Nitric Oxide
Nrf2	Nuclear factor erythroid 2-related factor 2
OCT	Organic Cation Transporter
OPC	Oligomeric Proanthocyanidins
PCC1	Procyanidin C1
PGI	Protected Geographical Indication
PI3K	Phosphatidylinositol-3-Kinase
PICO	Population, Intervention, Comparison, Outcome
PON1	Paraoxonase-1
RCT	Randomized Controlled Trial
RoB 2	Risk of Bias 2 (Cochrane)
ROS	Reactive Oxygen Species
SANRA	Scale for the Assessment of Narrative Review Articles
SBP	Systolic Blood Pressure
SOD	Superoxide Dismutase
T2DM	Type 2 Diabetes Mellitus
TAC	Total Antioxidant Capacity
TNF-α	Tumor Necrosis Factor-alpha
TXA2	Thromboxane A2
VCAM-1	Vascular Cell Adhesion Molecule-1
GSE	*Vitis vinifera* extract
WMD	Weighted Mean Difference

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