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PRO AND ANTIANGIOGENIC PROPERTIES OF *VITIS VINIFERA* BIOACTIVES: A SYSTEMATIC REVIEW OF EXTRACTS, MECHANISMS, AND THERAPEUTIC POTENTIAL

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ABSTRACT: *Vitis vinifera* is recognized for its diverse phytochemical composition, particularly polyphenols, which exert context-specific modulatory effects on angiogenesis. This review explores how different extraction solvents aqueous, alcoholic, benzene, and acetone impact the biological activity of grape-derived compounds using the chick chorioallantoic membrane (CAM) assay as an experimental platform. The choice of solvent was found to be a critical determinant of both chemical stability and biological response. Water and alcohol-based extracts generally favoured neovascularization, whereas benzene and acetone extracts produced inhibitory effects, indicating possible therapeutic applications in tissue regeneration and cancer, respectively. Mechanistic insights suggest these differential effects are mediated through oxidative stress regulation and angiogenic signaling, with changes observed in lipid peroxidation (LPO), glutathione (GSH), vascular endothelial growth factor (VEGF), and alkaline phosphatase (ALP). These molecular alterations parallel functional outcomes in endothelial proliferation, migration, and vessel organization within the CAM model. Despite promising findings, lack of standardized extraction protocols, limited reproducibility, and challenges related to bioavailability restrict clinical translation. Novel approaches, including nanotechnology-based delivery systems and integrative omics, may enhance consistency and therapeutic applicability. Overall, *Vitis vinifera* extracts display both pro- and anti-angiogenic properties depending on solvent systems, and the CAM model remains a valuable preclinical tool for screening. Further multidisciplinary research is essential to establish standardized methodologies and facilitate translational advancement.

INTRODUCTION: The circulatory system is vital for delivering oxygen and nutrients, removing waste products, and supporting tissue growth and repair. Two key processes involved in the development and maintenance of blood vessels are angiogenesis and vasculogenesis.

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Angiogenesis refers to the growth of new capillaries from existing blood vessels, while vasculogenesis involves the formation of blood vessels from endothelial progenitor cells, primarily during embryonic development, but also in certain adult tissues [1, 2].

In normal physiological conditions, angiogenesis plays essential roles in embryogenesis, wound healing, organ regeneration, and female reproductive function [3]. This process is tightly regulated by signalling molecules, cell-cell interactions, extracellular matrix remodelling, and environmental cues such as oxygen levels and

mechanical forces [4]. For example, changes in shear stress and oxygen availability can influence vascular remodelling and stability, both in healthy and diseased states.

Endothelial cells are central players in both angiogenesis and vasculogenesis. Recent research highlights the importance of endothelial cell metabolism in regulating angiogenic processes. Specific metabolic pathways, particularly glycolysis, support the energy demands of sprouting endothelial cells, suggesting new avenues for targeted therapies [5]. Similarly, components of the endothelial glycocalyx, especially heparan sulphate, regulate the availability of growth factors like VEGF, further influencing vascular development [6].

Endothelial progenitor cells (EPCs), once believed to be relevant only during development, have now been shown to contribute to postnatal vasculogenesis, especially during tissue repair and revascularization of ischemic tissues [2]. These findings have led to experimental and clinical interest in cell-based therapies, such as using hematopoietic stem cells to promote new blood vessel formation in patients with ischemic heart or limb diseases [7].

In tissue engineering, developing functional vascular networks remains a major goal. Biomaterials that support or enhance vascularization are increasingly being designed and tested, using *in-vitro* models that simulate physiological blood flow and oxygen conditions [4, 8]. These technologies aim to improve graft integration and survival by mimicking natural vascular behaviour.

In contrast to its normal roles, angiogenesis also contributes to various pathological conditions. Excessive or uncontrolled blood vessel growth is associated with tumours, diabetic retinopathy, psoriasis, and rheumatoid arthritis, where abnormal vessels can support disease progression [9]. On the other hand, insufficient angiogenesis can lead to chronic wounds or tissue ischemia. Environmental factors and nutrients also influence vascular biology. For example, Copper, is a trace element essential for angiogenesis. It is involved in multiple enzymatic processes and signalling pathways that affect endothelial cell proliferation and migration. Disruptions in copper transport systems can alter angiogenic responses, indicating the importance of trace metal homeostasis in vascular health [10].

Understanding the full spectrum of angiogenesis and vasculogenesis from molecular signalling and cellular behaviour to mechanical and metabolic regulation offers insights into both normal development and disease mechanisms. It also provides opportunities to design effective therapies for vascular related disorders and improve outcomes in regenerative medicine [5, 9].

Vitis vinifera is widely recognized not only as a dietary fruit but also as a source of potent bioactive compounds, particularly polyphenols, that exhibit multiple pharmacological effects. Among these, resveratrol, flavonoids, and anthocyanins have been the most studied for their beneficial roles in cardiovascular health and angiogenesis regulation [11, 12]. These compounds are distributed throughout different parts of the plant including skins, seeds, leaves, stems, and roots and are especially abundant in grape pomace and by products of winemaking [13, 14].

Polyphenols from *Vitis vinifera* have been shown to influence vascular health primarily through antioxidant, anti-inflammatory, and angiomodulatory actions. Resveratrol, a stilbene compound found in grape skins, has received considerable attention for its ability to stimulate endothelial cell function, enhance nitric oxide (NO) production, and protect vascular cells from oxidative stress, all of which contribute to promoting healthy blood vessel formation [15, 16]. In various *in-vitro* and *in-vivo* studies, resveratrol has also been shown to modulate VEGF (vascular endothelial growth factor) signalling pathways, which are central to angiogenesis regulation [12].

Flavonoids, another important group of polyphenols present in grapes, contribute to vascular protection by reducing inflammation, inhibiting endothelial dysfunction, and scavenging free radicals. These actions help maintain vascular tone and integrity, which are essential for both angiogenesis and vascular repair [17, 18]. Moreover, studies suggest that grape derived flavonoids can suppress abnormal vessel growth, providing

potential therapeutic value in cancer and inflammatory diseases where pathological angiogenesis occurs [19]. Anthocyanins, responsible for the red, purple, and blue pigmentation in grapes, have also demonstrated antiangiogenic and proangiogenic activities, depending on the biological context. They help regulate vascular permeability and endothelial cell migration, suggesting a role in both promoting wound healing and preventing tumour vascularisation [11, 20]. These pigments not only act as antioxidants but also interact with multiple intracellular signalling cascades involved in vascular development.

Recent research also highlights the potential of grape polyphenols in neurovascular protection. For instance, certain phenolic extracts from *Vitis vinifera* have shown protective effects on the blood brain barrier (BBB) by modulating inflammatory responses and enhancing the expression of leptin receptors, which are known to influence vascular signalling in the central nervous system [21]. Furthermore, grape leaf and pomace extract often considered agricultural waste have been successfully repurposed for their high polyphenol content. These extracts are now being explored as sustainable and low-cost sources of vascular protective compounds in nutraceuticals and functional foods [14, 20]. Their ability to reduce oxidative stress and inflammation in ischemic conditions further supports their potential role in vascular regeneration and recovery [19].

Review of Literature: Despite the growing interest in grape derived polyphenols for their angiogenic and antioxidant potential, several critical research gaps persist. These gaps limit the translational potential of findings from experimental models to clinical or applied therapeutic contexts.

Inconsistent Results Across Solvent Extracts: One of the foremost challenges in phytochemical research involving *Vitis vinifera* lies in the inconsistent biological activity observed across different solvent extracts. Studies have shown that hydrophilic solvents such as Hank's Balanced Salt Solution (HBSS) and ethanol yield extract rich in flavonoids and resveratrol, whereas organic solvents like benzene or chloroform can extract nonpolar compounds with varying bioactivity profiles [11, 22].

For example, water-based extracts may enhance antioxidant capacity and vascular regeneration, while benzene extracts have shown mixed or even inhibitory effects in angiogenesis models, such as the chick chorioallantoic membrane (CAM) assay [23, 24, 25]. These discrepancies may arise from the solubility and stability of specific bioactives under different extraction conditions, leading to heterogeneous compositions and variable biological responses [22, 26]. A lack of standardized extraction protocols further complicates the reproducibility of findings across studies.

Limited Mechanistic Insights in CAM Models: While many studies utilize the CAM assay to evaluate angiogenic or antiangiogenic effects of grape extracts, the molecular mechanisms underlying these effects remain poorly defined. Few studies have systematically linked polyphenol induced angiogenesis to key regulatory pathways, particularly oxidative stress modulation and vascular endothelial growth factor (VEGF) expression [27, 28].

Although resveratrol is known to modulate VEGF expression and reactive oxygen species (ROS) levels *in-vitro* and *in-vivo* [29, 30], direct evidence connecting these effects in CAM assays remains sparse. In many CAM based evaluations, VEGF levels, oxidative stress biomarkers, and downstream effectors such as HIF1α are not adequately quantified, leading to a lacuna in information in linking observed angiogenic outcomes to molecular pathways [31, 32].

Lack of Standardized Dosing Protocols: Another critical issue is the absence of standardized dosing strategies for evaluating pro or antiangiogenic activity. Dose dependent effects are widely reported, with low concentrations of grape polyphenols promoting angiogenesis, while higher concentrations exhibit antiangiogenic or cytotoxic effects [33, 34]. However, most studies do not follow a unified dosing protocol, leading to wide variability in reported outcomes [35, 36].

Moreover, the effective concentrations vary depending on the source of extraction material (variety of *Vitis vinifera*), bioactive composition, and assay system used. Without harmonized dose response guidelines, it is difficult to compare data

across studies or determine therapeutic thresholds. This presents a significant barrier to developing grape extract-based interventions for angiogenesis related disorders, including wound healing, diabetic retinopathy, and cancer [37, 38].

RESULT:

Extraction Methods and Solvent Dependent Bioactivity: The biological efficacy of grape (*Vitis vinifera*) extracts largely depends on the method of extraction and the solvent used. Variability in extraction techniques directly influences the yield, stability, and functional properties of bioactive compounds particularly polyphenols such as resveratrol, flavonoids, anthocyanins, and proanthocyanidins [22, 26].

Extraction Techniques: Aqueous vs. Organic Solvents: Extraction methods typically involve aqueous solvents like Hank's Balanced Salt Solution (HBSS) or distilled water, and organic solvents such as ethanol, methanol, acetone, and benzene [11, 22]. Aqueous extractions are considered safer, especially for biomedical applications, and tend to yield hydrophilic compounds, including anthocyanins and certain flavonoids [39]. However, their overall polyphenol yield is often lower due to limited solubility and poor diffusion of nonpolar molecules.

Conversely, organic solvents especially ethanol and acetone are highly efficient in extracting both polar and semipolar polyphenols, improving the recovery of resveratrol and catechins [22, 40]. Benzene and chloroform extracts can isolate lipophilic components but raise safety concerns and have demonstrated mixed or inhibitory effects on bioactivity, particularly in *in-vivo* models like the chick chorioallantoic membrane (CAM) assay [24, 25].

Solvent polarity, pH, and temperature also affect the stability of polyphenols during extraction. For example, anthocyanins degrade quickly at high temperatures or extreme pH, while resveratrol remains relatively stable in alcohol-based systems [41, 42].

Comparative Efficacy: Pro vs. Anti-angiogenic Effects: Studies comparing solvent specific extracts have highlighted significant differences in angiogenic modulation. Alcoholic grape extracts, particularly those using ethanol and methanol, have been shown to promote angiogenesis by enhancing endothelial cell migration, proliferation, and tube formation in both *in-vitro* and CAM models [43, 44]. These effects are typically attributed to increased bioavailability of polyphenols like quercetin, catechin, and resveratrol that positively modulate vascular endothelial growth factor (VEGF) and nitric oxide pathways [29, 35, 45].

In contrast, extracts prepared using benzene or chloroform often display antiangiogenic properties, evidenced by reduced neovascularization and vessel sprouting in CAM assays [32, 34]. These effects may stem from the presence of lipid soluble compounds that disrupt endothelial signalling or increase oxidative stress.

Importantly, dose also influences these outcomes; low concentrations of alcohol extracts are proangiogenic, whereas higher doses may reverse the effect or induce cytotoxicity [33, 37]. This dose–response relationship is further modulated by solvent-dependent chemical profiles, making standardization across studies highly challenging.

Critical Lacunae:

Lack of Consensus on Optimal Solvent: Despite the promising data, a major critical gap in the literature is the lack of consensus on the optimal solvent for reproducibly modulating angiogenesis. Comparative studies often employ differing methodologies, solvent concentrations, extraction times, and test models, limiting the ability to draw generalized conclusions [38, 36].

Furthermore, most studies fail to characterize the full phytochemical spectrum of each extract, making it difficult to link specific components to observed pro or antiangiogenic effects [26, 31]. Standardized extraction protocols, including solvent ratios, temperature control, and bioactive quantification, are essential to improve reproducibility and translational potential. Future research necessitates prioritizing multi-solvent comparative extraction protocols, integrate advanced phytochemical profiling (e.g., LCMS/MS), and test extracts across a range of biologically relevant angiogenesis models with consistent dosing strategies.

Mechanistic Insights: Oxidative Stress and Angiogenic Signalling: Grape derived

polyphenols, such as resveratrol, flavonoids, and anthocyanins, have been widely studied for their potential to modulate oxidative stress and angiogenic pathways.

However, despite the increasing use of the chick chorioallantoic membrane (CAM) model in angiogenesis research, there remains a limited mechanistic understanding of how these bioactives act through specific biochemical markers such as lipid peroxidation, glutathione, VEGF, and alkaline phosphatase (ALP).

Lipid Peroxidation (LPO):

Marker of Oxidative Damage: Lipid peroxidation is a well-established indicator of oxidative stress and tissue injury. In the context of angiogenesis, excessive reactive oxygen species (ROS) can damage vascular membranes and impair vessel formation. Polyphenol rich grape extracts have been shown to significantly reduce LPO levels, thereby protecting endothelial cells and promoting a favourable microenvironment for neovascularisation [29]. In CAM assays, grape seed and skin extracts were observed to reduce malondialdehyde (MDA), a key LPO product, suggesting a protective antioxidant role [24].

Glutathione (GSH):

Antioxidant Defence and Cell: Glutathione (GSH) is a critical nonenzymatic antioxidant involved in redox regulation, detoxification of ROS, and maintenance of cellular homeostasis. GSH depletion leads to increased susceptibility to oxidative injury and apoptosis, particularly in endothelial cells [46]. Grape polyphenols have been shown to elevate intracellular GSH levels, enhancing endothelial survival and reducing apoptosis *in-vitro* and *in-vivo* [31, 44].

Although these effects are well documented in mammalian systems, direct evaluation in CAM tissues remains sparse, and more studies are needed to confirm the cytoprotective role of GSH modulation by *Vitis vinifera* in embryonic vasculature. Studies on glutathione in CAM may give its differential behaviour if any in chick vasculature and capillary development.

VEGF Modulation:

Key to Angiogenic Switch: Vascular endothelial growth factor (VEGF) is the principal regulator of angiogenesis, stimulating endothelial cell proliferation, migration, and new vessel formation. Numerous studies have shown that grape extracts can modulate VEGF expression upregulating it in wound healing and ischemia, while downregulating it in cancer models [33, 34]. In CAM assays, ethanol based grape extracts have been reported to increase VEGF expression and capillary density, supporting their proangiogenic potential [24, 43]. However, benzene or high dose extracts may inhibit VEGF expression, aligning with observed antiangiogenic effects [32, 38]. Thus, the bidirectional modulation of VEGF appears to depend on extract composition, concentration, and tissue context, yet detailed mechanistic studies in CAM remain limited.

Alkaline Phosphatase (ALP):

Marker of Vascular Remodeling: Alkaline phosphatase (ALP) activity has emerged as a functional marker of vascular remodeling, tissue maturation, and endothelial differentiation [47]. ALP is upregulated during new blood vessel formation and plays a role in extracellular matrix remodeling. Some studies have observed increased ALP activity following grape polyphenol treatment, suggesting an indirect proangiogenic or regenerative signal [48]. However, CAM based research specifically linking ALP modulation to *Vitis vinifera* extracts is minimal, and further studies are required to validate ALP as a reliable biomarker in this model.

Research Gap:

Limited CAM Based Mechanistic Studies: Current literature shows considerable differences in solvent systems (aqueous and organic), extraction times, plant parts selected, and techniques used for bioactive quantification. Furthermore, there is a lack of clarity regarding the developmental stages at which biological models, such as the CAM assay, best perceive bioactive compounds. Such inconsistencies limit the translation of findings to mammalian models, thereby restricting their potential in therapeutic clinical research and medical applications. To improve the credibility and comparability of results from CAM assay based and other preclinical studies, it is crucial to establish universally accepted protocols for extract preparation, standardize polyphenol measurement techniques, and define the minimum inhibitory or activation concentrations of bioactive substances. Despite the broad pharmacological interest in *Vitis*

vinifera, there is a significant research gap in CAM based studies that integrate oxidative stress biomarkers with angiogenic endpoints. While individual effects on LPO, GSH, VEGF, and ALP have been described in various models, their combined modulation by grape extracts in CAM assays remains poorly investigated. Furthermore, standardized protocols for biomarker quantification in the CAM model are lacking, limiting reproducibility and comparative analysis across studies.

Frame of Future Research: Quantitative measurement of oxidative stress markers (MDA, GSH) in CAM tissues after treatment with different grape extracts. Correlation of VEGF and ALP expression levels with angiogenic phenotypes. Use of transcriptomic or proteomic tools to link biochemical changes with functional outcomes.

Therapeutic Potential and Challenges:

Pro-Angiogenic Applications: *Vitis vinifera* polyphenol extracts, especially those prepared with aqueous buffers (e.g., HBSS) or moderate ethanol, have shown promise in enhancing angiogenesis for wound healing and ischemic disease models. In CAM assays mimicking superficial wounds, 50% ethanol grape leaf extracts significantly accelerated capillary sprouting and closure of artificial wounds by promoting endothelial proliferation and migration [49, 50]. Similarly, in rat models of hindlimb ischemia, daily topical application of grape seed ethanol extract led to increased perfusion and capillary density, attributed to raised VEGF expression and reduced oxidative damage [51, 52]. These findings support the potential of grape-derived extracts, particularly those prepared in HBSS or ethanol, as therapeutic stimulants of angiogenesis in regenerative medicine [53, 54, 55].

Anti-angiogenic Applications: Conversely, organic, nonpolar extracts (e.g., benzene, acetone) rich in specific flavonoid subclasses demonstrate antiangiogenic potential, making them useful as adjuvants in cancer therapy. Acetonic extracts from grape seeds, when applied onto CAM tumours, markedly reduced neovascular networks and inhibited tumour growth by downregulating VEGF and MMP9 [55, 56]. Benzene extracts of grape pomace similarly suppressed both primary and secondary vessel sprouts in CAM assays, attributed to flavone induced apoptosis and inhibited endothelial proliferation. Further, *in-vitro* studies with human endothelial and colon carcinoma cell lines showed acetone grape skin extracts reduced capillary like tube formation and cell viability, supporting their application as antiangiogenic cancer adjuvants [57].

Limitations:

Despite their Promising Potential, Grape Polyphenols Face Two Major Obstacles: Poor bioavailability *in-vivo* Most bioactive polyphenols, like resveratrol and anthocyanins, exhibit low oral bioavailability due to rapid metabolism and poor absorption [51, 59]. Coformulations with delivery enhancers or nanocarriers have shown some success in improving plasma levels, but therapeutic efficacy remains low [55]. The CAM model, while valuable for rapid screening, is limited in its translational relevance to mammals due to differences in physiology, immune response, and metabolic processing [60]. Some extracts that perform well in CAM assays fail to elicit similar angiogenic responses in rodent or humanized models [49, 52]. Effective therapeutic development must therefore validate CAM derived results in mammalian systems.

Future Directions: Research into the angiogenic and antiangiogenic properties of *Vitis vinifera* extracts, particularly through the chick chorioallantoic membrane (CAM) model, has provided valuable mechanistic and therapeutic insights. However, several critical areas remain underdeveloped and warrant focused attention to ensure the translational success of these findings.

Standardization:

Toward Reproducibility and Comparability: Standardizing extraction methods along with bioactive dosing parameters, including concentration and administration intervals, is essential to achieve uniformity, reproducibility, and dependable results in research. Current literature demonstrates considerable variability in solvent systems (aqueous vs. organic), extraction time, plant part used, and bioactive quantification. These inconsistencies hinder inter study comparability and slow the development of reproducible therapeutic applications. Establishing universally accepted guidelines for extract preparation, polyphenol quantification, and minimum inhibitory

concentrations will significantly enhance the reliability of findings across CAM and other preclinical models.

Advanced Models:

Integration with Omics Technologies: While the CAM assay remains a cost-effective and ethically favourable *in-vivo* system, its integration with advanced analytical platforms like proteomics and metabolomics can provide a more comprehensive understanding of the molecular mechanisms underlying angiogenesis modulation. Proteomic analysis can identify differential expression of angiogenic markers, while metabolomic profiling could reveal the metabolic pathways influenced by grape derived polyphenols. The combination of CAM with high throughput omics approaches holds promise for uncovering novel bioactive targets, elucidating dose response relationships, and improving mechanistic precision.

Clinical Translation: Enhancing Bioavailability through Nano Formulations: Despite promising *in-vitro* and *in-vivo* results, the clinical translation of grape bioactives remains limited due to challenges such as poor bioavailability, rapid metabolism, and low tissue targeting. Emerging research suggests that nano formulations, including nanoparticles, liposomes, and nano emulsions, can improve solubility, stability, and targeted delivery of polyphenols like resveratrol and flavonoids. These nanocarriers may also enable sustained release, enhance endothelial uptake, and reduce systemic toxicity. Incorporating nanotechnology into CAM based preclinical studies may serve as a bridge between experimental observations and clinical applicability. Future investigations should prioritize methodological consistency, exploit integrative omics technologies, and explore advanced delivery systems to fully harness the therapeutic potential of *Vitis vinifera* in modulating angiogenesis. These directions not only promise to expand the current understanding of grape bioactives but also enhance their applicability in diverse biomedical contexts, from regenerative medicine to oncology.

CONCLUSION: This review highlights the multifaceted and solvent dependent angiogenic responses elicited by *Vitis vinifera* extracts within the chick chorioallantoic membrane (CAM) model. The analysis reveals that the choice of solvent plays a critical role in determining the yield, stability, and bioactivity of polyphenolic compounds. Specifically, aqueous and ethanol-based extractions tend to enhance angiogenesis, suggesting their utility in regenerative medicine for conditions such as wound healing and ischemia. Conversely, extracts obtained with benzene or acetone demonstrate antiangiogenic properties, making them relevant in cancer related applications.

On a mechanistic level, *Vitis vinifera* constituents influence major oxidative stress and angiogenesis related biomarkers, including lipid peroxidation (LPO), glutathione (GSH), vascular endothelial growth factor (VEGF), and alkaline phosphatase (ALP). These biomarkers reflect critical processes such as cellular oxidative balance, endothelial viability, apoptotic regulation, and vascular restructuring. Despite these insights, substantial gaps persist in connecting these molecular mechanisms with consistent phenotypic outcomes, particularly across different experimental platforms.

Upcoming studies should emphasize establishing standardized methods for extract preparation and precise dosing regimens. This involves optimizing the concentration of bioactive compounds and identifying suitable developmental, biological, or physiological stages for their application. Additionally, technological advancements are needed to design improved carrier molecules or systems, create more effective localized and targeted delivery approaches, and enhance both the bioavailability and site-specific uptake of these bioactive agents.

Notably, the dual functionality of grape derived bioactive capable of promoting or inhibiting angiogenesis depending on the context emphasizes the need for precise control over extraction and application parameters. Such versatility demands careful consideration in therapeutic design to harness desired effects. Moving forward, a multidisciplinary approach integrating pharmacological science, biomedical engineering, and systems biology is necessary. Future work should focus on standardizing extraction and dosing protocols, integrating omics technologies for deeper mechanistic insights, and developing

advanced delivery systems such as nano formulations to improve bioavailability and target specificity. *Vitis vinifera* holds significant potential as a natural modulator of angiogenesis. Realizing this potential will depend on the refinement of experimental methodologies and the development of collaborative, multidisciplinary research strategies that support the path to clinical translation.

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