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REVIEW ARTICLE

Grape Polyphenols as Multitarget Therapeutic Agents: Decoding Molecular Mechanisms beyond Antioxidant Activity

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Abstract

Grape polyphenols have traditionally been valued for their antioxidant capacity, but growing pharmacological evidence indicates that their therapeutic potential extends well beyond redox activity. Grapes contain structurally diverse bioactive polyphenols, including anthocyanins, flavan-3-ols, flavonols, phenolic acids, and stilbenoids such as resveratrol, each showing tissue-specific distribution and distinct pharmacodynamic profiles. However, extensive intestinal and hepatic metabolism, severely limits systemic bioavailability, raising pharmacokinetic questions that challenge conventional antioxidant-based explanations of efficacy. This review examines the chemical diversity, absorption, metabolic transformation, and pharmacokinetic fate of grape polyphenols, emphasizing molecular mechanisms independent of antioxidant action. As most polyphenols escape small-intestinal absorption and reach the colon, gut microbiota-mediated biotransformation generates smaller, more bioavailable metabolites, notably urolithins, with enhanced pharmacological activity relative to their parent compounds. Both native polyphenols and microbial metabolites modulate key signaling cascades (nuclear factor kappa B, nuclear factor erythroid 2-related factor 2, phosphoinositide 3-kinase/Akt, mitogen-activated protein kinase), influence epigenetic regulation, reshape the gut microbiota, and exert immunomodulatory effects, thereby underpinning cardioprotective, metabolic, neuroprotective, anticancer, and anti-aging benefits. Clinical translation remains constrained by poor bioavailability, interindividual variability and limited robust trial evidence. Grape by-products such as pomace, seeds and skins remain an underutilized source of pharmacologically active polyphenols. Advances in drug delivery systems, bioavailability enhancement and personalized pharmacotherapy may help bridge these translational gaps.

Key words: Anthocyanin, bioavailability, gut microbiota, molecular mechanisms, pharmacokinetics, resveratrol

INTRODUCTION

Grapes (*Vitis vinifera* L.) are a major dietary source of pharmacologically active polyphenols[1] distributed across the skin, seeds, pulp, and pomace, and contributing significantly to the therapeutic and functional value of grapes and grape-derived products.[2] Polyphenol distribution varies markedly across grape tissues, with seeds typically containing the highest total phenolic content (60–70%), followed by skin (28–35%) and pulp (approximately 10%), and total content further modulated by cultivar, ripeness, and viticultural practice.[3] Regular intake of polyphenol-rich foods is linked to reduced chronic disease risk, driving pharmacological interest in grape polyphenols as candidate therapeutic agents.[4] Estimated total dietary polyphenol intake is approximately 1 g/day, although intake varies considerably according to dietary habits and

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preferences.[5] These polyphenols are structurally diverse, spanning flavonoids and non-flavonoids, chiefly anthocyanins, flavan-3-ols, flavonols, phenolic acids and stilbenes (notably resveratrol),[6] with reported roles in cardiovascular protection, metabolic regulation, neuroprotection, cancer prevention and immune modulation.[7] Antioxidant activity, particularly reactive oxygen species scavenging, has long been the primary explanation for these effects.[8] However, their low bioavailability and systemic concentrations increasingly challenge antioxidant activity alone as a sufficient basis for their observed clinical benefits. Emerging evidence indicates grape polyphenols also act through receptor- and pathway-mediated mechanisms, including cell-signaling modulation, gene expression regulation, epigenetic changes, gut microbiota-mediated biotransformation, and inflammatory/metabolic regulation.[9] For instance, resveratrol has been shown to activate Sirtuin 1, adenosine monophosphate-activated protein kinase, and nuclear factor erythroid 2-related factor 2 (Nrf2) while inhibiting nuclear factor kappa B (NF-κB), alongside modulation of phosphoinositide 3-kinase (PI3K)/AKT/mechanistic target of rapamycin, cyclooxygenase-2 and vascular endothelial growth factor signaling, illustrating how a single grape polyphenol can simultaneously engage antioxidant, anti-inflammatory, metabolic and anti-proliferative pathways rather than acting through one mechanism alone.[10] This review therefore surveys the major pharmacological classes of grape polyphenols, emphasizing mechanisms beyond antioxidant activity, alongside their pharmacokinetics, bioavailability-enhancing strategies, and translational potential in pharmacotherapy and functional pharmaceutical product development.

CHEMICAL DIVERSITY AND PHARMACOLOGICAL PROMISE OF GRAPE POLYPHENOLS

Grapes contain diverse secondary metabolites shaping color, flavor, astringency, defense, and pharmacological activity, synthesized via the phenylpropanoid pathway and varying with genotype, environment, developmental stage, and cultivation practices. This chemical diversity underlies their antioxidant, anti-inflammatory, cardioprotective, anticancer, and neuroprotective properties. Indian grapes show total phenolic content of 149–529 mg gallic acid equivalents/100 g fresh fruit, exceeding the typical global range of 62–315 mg/100 g.[11]

Phenolic compounds

Phenolic acids, a major non-flavonoid group, occur mainly as hydroxybenzoic and hydroxycinnamic acids across the skin, seed, pulp, leaf, and stem. Grape seeds contain 5–8% polyphenols, and show the highest antioxidant activity due to gallic, protocatechuic, vanillic, and syringic acids.[12] Gallic acid also serves as a precursor for hydrolyzable tannin biosynthesis. Hydroxycinnamic acids such as caftaric, caffeic, p-coumaric, and ferulic acids, esterified derivatives localized mainly in pulp and skin,[11] contribute pharmacologically relevant antioxidant, antibacterial, and anti-inflammatory activity.

Flavonoids

Flavonoids are the largest, pharmacologically most significant polyphenol class, imparting color, bitterness and astringency, including anthocyanins, flavan-3-ols, proanthocyanidins and flavonols.[13]

Anthocyanins

Anthocyanins, water-soluble flavonoid pigments responsible for red, purple and blue hues, accumulate mainly in outer epidermal cells of red and black cultivars.[14] Malvidin-3-O-glucoside, the most common anthocyanin, reaches up to 164 mg/100 g in wine grapes.[15] Fermentation promotes polymeric pigment formation (pyranoanthocyanins), though only a small fraction transfers to juice.[16] Beyond color, anthocyanins exert potent antioxidant, anti-inflammatory, cardioprotective, and neuroprotective effects, making them among the most therapeutically significant grape bioactives.

Flavan-3-ols

Flavan-3-ol content in grape seeds reaches ~43–45 g/kg fresh weight at early ripening, and comprises catechin, epicatechin, epigallocatechin, and epicatechin gallate.[17] Their polymerization yields proanthocyanidins (condensed tannins), which are abundant in seeds and skins, and influencing astringency.[18] These display anti-inflammatory, antibacterial, cardioprotective, and anticancer activity alongside potent antioxidant capacity, with benefits for oxidative stress and vascular function.[8]

Flavonols

Flavonols, predominantly in grape skin, include quercetin, kaempferol, myricetin, isorhamnetin, and syringetin, with ultraviolet (UV)-enhanced biosynthesis. Content ranges from 20 to 46 mg/100 g fresh weight, with kaempferol as the major flavonol,[19] functioning as a natural photoprotective agent in the plant.[20] Flavonols show antioxidant, anti-inflammatory, and vasoprotective activity while stabilizing anthocyanin pigmentation via co-pigmentation.[17]

Stilbenes–resveratrol

Stilbenes, induced by biotic and abiotic stress, occur at lower concentrations than flavonoids.[21] Resveratrol (3,5,4'-trihydroxystilbene), the most abundant stilbene, exists as trans- and cis-isomers, with the trans form being pharmacologically more active; produced as a phytoalexin

against fungal infection and UV stress, it accumulates mainly in the skin at trace levels of 11–12 µg/100 g fresh weight.[15,22] Derivatives such as oligomeric viniferins, piceid and piceatannol often show enhanced stability and distinct bioactivity.[23] Acting through pathways governing oxidative stress, inflammation, apoptosis, and cell signaling, resveratrol and its derivatives display antioxidant, anti-inflammatory, cardioprotective, neuroprotective, antidiabetic, and anticancer activity.[21]

BIOAVAILABILITY AND METABOLISM OF GRAPE POLYPHENOLS

Bioavailability denotes the proportion of an ingested compound that crosses the intestinal barrier, enters the bloodstream and reaches target tissues, unchanged or as metabolites, to exert biological effects.[24] Most grape polyphenols show low bioavailability due to extensive metabolic transformation during digestion, absorption, and excretion, with active metabolite levels at target tissues shaped by chemical structure, gut microbiota interactions, and the dietary matrix.[25] Figure 1 outlines the sequential stages of grape polyphenol absorption, metabolism and excretion from the gastrointestinal tract to target tissues.

Absorption and biotransformation

Grape polyphenol absorption reflects a division of labor between the small intestine and colon. Only 5–10% of dietary polyphenols are absorbed in the small intestine,[26] where brush-border enzymes convert them into simpler aglycones that cross the gut lining via passive diffusion and active transport.[27] High-molecular-weight compounds, especially proanthocyanidins and complex flavonoids, largely escape this absorption due to their size and poor lipid solubility; proanthocyanidin bioavailability is roughly 100 times lower than that of monomers.[4] Among grape polyphenols, monomeric flavan-3-ols such as catechin and epicatechin are relatively better absorbed. Quercetin glycosides show variable absorption depending on their sugar moiety and, to a lesser extent, the plant matrix. In humans, quercetin is detected predominantly as glucuronide conjugates rather than as free quercetin, with a terminal elimination half-life of approximately 11 h.[28] Resveratrol is rapidly absorbed (≥70% of an oral dose), but its systemic bioavailability is very low because of extensive intestinal and hepatic first-pass metabolism. Although unchanged resveratrol is detectable only at trace concentrations in plasma, resveratrol-derived material exhibits a plasma half-life of approximately 9.2 h.[29] Anthocyanins show limited systemic availability; in a human ^{13}C-tracer study, cyanidin-3-glucoside showed a minimum relative bioavailability of 12.4%, while its ^{13}C-labelled metabolites exhibited half-lives of approximately 12–52 h.[30] The unabsorbed majority reaches the colon, where gut microbiota enzymes (glycosidases, esterases, decarboxylases) break them down into smaller aromatic metabolites such as urolithins and phenolic acids.[31] In some individuals, absorption of these microbial metabolites approaches nearly 100%, suggesting that polyphenol bioavailability depends largely on microbial derivatives rather than parent compounds. These metabolites also tend to have longer half-lives and broader tissue distribution than the original polyphenols.[25]

Factors affecting bioavailability

Bioavailability of grape polyphenols depends on more than total polyphenol concentration. Intrinsic and extrinsic factors, including host physiology and food matrix interactions, also play a role. Key determinants are the polyphenol's chemical structure, solubility, and membrane permeability,

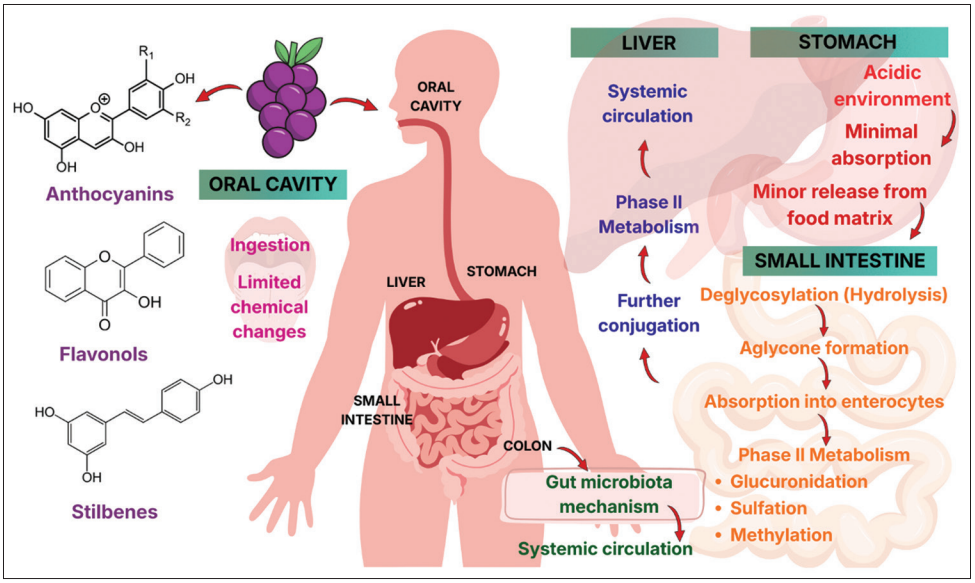


Figure 1: Metabolic pathway of grape polyphenols from ingestion to systemic circulation

shaped largely by glycosylation, methylation, and degree of polymerization.[32] For grape seed proanthocyanidins, absorption declines with increasing polymerization, with monomers and dimers absorbed more readily than larger oligomers.[33] Inter-individual variability is substantial, reflecting both microbial and host factors such as genetics, age, sex, body mass index, health status, diet, physical activity, and biological timing.[34] The dietary matrix also matters, as proteins, minerals, and fiber often reduce flavonoid bioavailability, whereas fats, digestible carbohydrates, and some vitamins can enhance absorption.[27] Interactions with macronutrients, proteins, lipids, and carbohydrates can either increase or inhibit polyphenol bioaccessibility.[31] Bioaccessibility shifts throughout digestion: gastric conditions can release bound polyphenols from the food matrix, whereas small intestinal conditions may destabilize certain classes, particularly anthocyanins.[24] Processing conditions such as fermentation, as used in winemaking, can chemically transform polyphenols before consumption, potentially increasing their stability and bioactivity.[2]

The pivotal role of gut microbiota

Gut microbiota and polyphenols engage in a bidirectional relationship: Microbes metabolize polyphenols, while polyphenols in turn modulate microbial composition, jointly shaping gut ecology and host health.[35] Polyphenols exert prebiotic-like effects, promoting beneficial genera (e.g., *Lactobacillus*, *Bifidobacterium*) while suppressing pathogenic strains, thereby enhancing intestinal barrier integrity, attenuating inflammation, and stimulating short-chain fatty acid production.[36] This microbiota-modulating activity may contribute to the maintenance of microbial homeostasis by promoting beneficial bacterial populations and suppressing potentially harmful microorganisms. In a mouse model of high-fat-diet-induced obesity, grape pomace polyphenol extracts increased the abundance of beneficial taxa such as *Bifidobacterium* and *Blautia*, while reducing potentially harmful bacteria and improving short-chain fatty acid (SCFA) levels.[36] Conversely, the microbiota governs polyphenol metabolic fate, generating bioactive metabolites with systemic effects; for example, gut bacteria convert ellagic acid from grape pomace into urolithins, key mediators of anti-inflammatory and antioxidant activity.[37] This biotransformation capacity varies with individual microbiota composition ("metabotype"), accounting for inter-individual differences in health outcomes, and can be compromised by microbial disruption (e.g., antibiotic exposure), reducing metabolite yield and attenuating polyphenols' protective effects against metabolic disorders.[38] The gut–brain and gut–liver axes further extend these interactions systemically, with microbial metabolites implicated in neuroprotection by modulating neuroinflammation and neurotransmitter regulation, potentially alleviating anxiety and depression.[39] Collectively, this underscores the gut microbiota's role as an active participant, rather than a mere metabolic processor, in the body's response to dietary polyphenols.[35]

Strategies to enhance bioavailability

Given the intrinsically low bioavailability of many grape polyphenols, considerable research has targeted the rate-limiting steps in absorption, with encapsulation emerging as one of the most effective strategies. Beyond enhancing solubility and stability, the most successful methods enable polyphenols to traverse the intestinal mucus layer, a barrier that protects epithelial cells but simultaneously restricts compound access. Cyclodextrin complexation, in which the polyphenol is accommodated within the cyclodextrin ring structure, has been widely used to enhance bioavailability, with techniques such as freeze-drying or ultrasonication further improving incorporation efficiency.[25] Nanostructure-based systems offer complementary approaches: nanoparticles (10–1000 nm) stabilize the compound's environment and enable sustained release, nanomicelles (20–200 nm) encapsulate compounds within a hydrophobic core to improve aqueous solubility, whereas nanoemulsions and nanolipids are more commonly applied for food-quality enhancement.[40] Given their high bioactivity but notoriously poor absorption, resveratrol and quercetin have received particular research attention within this field, reflecting a broader strategic focus on compounds with the largest gap between biological potency and systemic delivery.

MOLECULAR MECHANISMS UNDERLYING THE HEALTH BENEFITS OF GRAPE POLYPHENOLS

Grape polyphenols confer health benefits through interconnected molecular mechanisms extending beyond their antioxidant properties, as illustrated in Table 1. Resveratrol, anthocyanins, proanthocyanidins, and ellagic acid derivatives are the principal bioactive compounds involved.[27] These compounds regulate intracellular signaling pathways, suppress pro-inflammatory mediators, modulate gene expression via epigenetic mechanisms (e.g., DNA methylation, histone acetylation), and interact bidirectionally with the gut microbiota to influence immune function and metabolic homeostasis.[35] Among these, inhibition of the NF-κB and mitogen-activated protein kinase (MAPK) pathways, leading to downregulation of pro-inflammatory cytokines, remains the most well-established mechanism.[41] In contrast, gut microbiota-mediated metabolites and epigenetic regulation represent emerging areas requiring further investigation.

Regulation of cellular signaling pathways

Grape polyphenols exert their biological effects partly through modulation of key intracellular signaling cascades, as summarized in Figure 2. Their metabolites interact with cellular pathways controlling survival, proliferation, and stress responses.[47] A central mechanism is modulation of the NF-κB pathway, a key regulator of inflammation:

Table 1: Molecular mechanisms underlying the therapeutic benefits of grape polyphenols

Mechanism	Pathway	Effect	Polyphenols involved	Downstream outcome	Reference
Cellular signaling regulation	NF-κB	Inhibits phosphorylation/ nuclear translocation	Urolithins, phenolic acids	Suppressed pro-inflammatory cytokine transcription	[42]
	Nrf2	Activation	Resveratrol, anthocyanins	↑ Endogenous antioxidant enzymes (SOD, GPx)	[41]
	PI3K/Akt, MAPK	Modulation	Resveratrol, proanthocyanidins	Regulated cell division and apoptosis	[43]
Anti- inflammatory	COX-2, iNOS	Inhibition	Grape polyphenol extracts	↓ Prostaglandins, leukotrienes, nitric oxide	[35]
	NLRP3 inflammasome	Suppression	Urolithins (from ellagic acid)	↓ TNF-α, IL-6, mature IL-1β/ IL-18	[37]
Epigenetic regulation	HDAC	Inhibition	SCFAs, phenolic compounds	↑ Histone acetylation; activation of anti-inflammatory/ metabolic genes	[36]
	DNA methylation	Modulation	Grape polyphenol metabolites	Restoration of aberrant methylation linked to disease	[44]
Gut microbiota modulation	Microbial ecosystem	Selective enrichment	Whole polyphenol profile	↑ *Lactobacillus*, *Bifidobacterium*, *Akkermansia*, *Faecalibacterium*, *Roseburia*; ↑ SCFAs	[45]
Immunomodulation	Tight junction proteins, Treg differentiation	Upregulation/ promotion	Polyphenol metabolites	↓ LPS translocation; restored immune homeostasis	[46]

NF-κB: Nuclear factor kappa B, Nrf2: Nuclear factor erythroid 2-related factor 2, COX-2: Cyclooxygenase-2, iNOS: Inducible nitric oxide synthase, HDAC: Histone deacetylase, LPS: Lipopolysaccharide, PI3K: Phosphoinositide 3-kinase, MAPK: Mitogen-activated protein kinase, SCFA: Short-chain fatty acids, TNF-α: Tumor necrosis factor alpha, IL: Interleukin, SOD: Superoxide dismutase, GPx: Glutathione peroxidase, NLRP3: NLR family pyrin domain containing 3

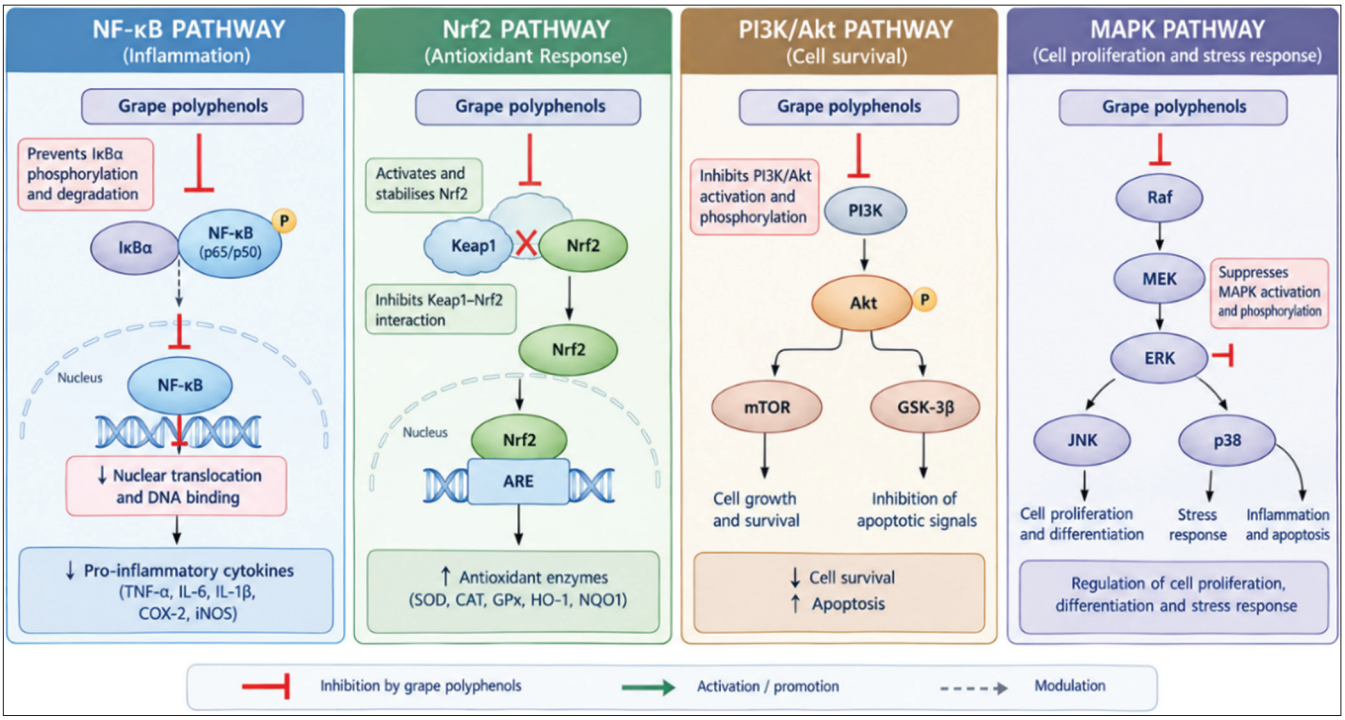


Figure 2: Pharmacological modulation of cellular signaling pathways

Polyphenol-derived metabolites such as urolithins and phenolic acids suppress pro-inflammatory cytokine transcription by preventing NF-κB phosphorylation and nuclear translocation.[42] Grape polyphenols also activate the Nrf2 pathway, upregulating endogenous antioxidant enzymes such as glutathione peroxidase and superoxide dismutase (SOD),[41] thereby strengthening cellular resistance to oxidative stress and helping prevent chronic conditions such as neurodegeneration and cardiovascular disease.[21] Moreover, polyphenols influence the PI3K/Akt and MAPK pathways, which regulate cell division and apoptosis,[43] supporting cellular integrity and helping prevent malignant transformation.

Anti-inflammatory mechanisms

Grape polyphenols mitigate inflammation through multiple interconnected mechanisms, as depicted in Figure 3. Chronic low-grade inflammation underlies many metabolic and degenerative disorders, and grape polyphenols exert strong anti-inflammatory effects via several molecular pathways.[48] By inhibiting cyclooxygenase-2 and inducible nitric oxide synthase, these compounds reduce the synthesis of inflammatory mediators such as prostaglandins, leukotrienes, and nitric oxide.[35] Their biotransformation into microbial metabolites, which possess greater bioavailability and tissue penetration, further enhances anti-inflammatory activity.[49] For example, urolithins produced from microbial degradation of ellagic acid in grape by-products suppress tumor necrosis factor alpha (TNF-α) and interleukin (IL)-6 release in intestinal epithelial cells and macrophages,[37] thereby limiting cytokine-driven tissue damage and systemic inflammation. Grape polyphenols also modulate the inflammasome complex, particularly NLR family pyrin domain containing 3, reducing release of mature IL-1β and IL-18, key drivers of inflammatory disease.[47]

Modulation of gene expression and epigenetic regulation

As shown in Figure 4, grape polyphenols regulate gene expression through epigenetic mechanisms, thereby modulating pathways involved in cell proliferation, apoptosis, and oxidative stress response. Growing evidence indicates that grape polyphenols and their microbiota-derived metabolites act as epigenetic modulators, influencing host gene expression without altering the underlying DNA sequence.[44] They affect three principal epigenetic processes: DNA methylation, histone modification, and non-coding RNA regulation. SCFAs and phenolic compounds generated by the gut microbiota inhibit histone deacetylases,[36] increasing histone acetylation and activating genes involved in metabolic and anti-inflammatory processes. Grape polyphenols can also alter DNA methylation patterns, potentially reversing aberrant methylation associated with disease states.[44] These epigenetic changes are thought to underlie polyphenols' long-term health effects, producing durable alterations in gene expression profiles linked to immune response, lipid metabolism, and insulin sensitivity.[42] As individual genetic and microbial profiles influence the effectiveness of such interventions, the interaction between dietary polyphenols and the epigenome represents a promising avenue for precision health solutions.[50]

Modulation of gut microbiota

Beyond direct effects on host cells, grape polyphenols influence gut microbiota ecology, acting as ecosystem

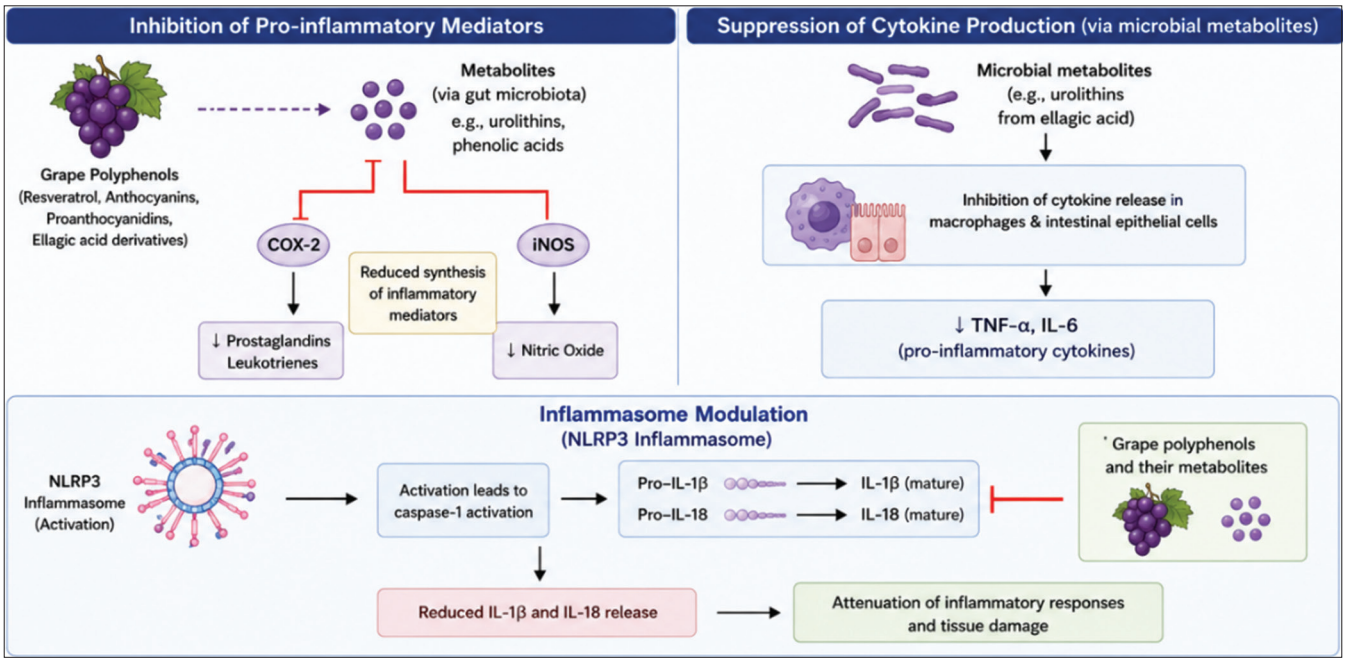


Figure 3: Anti-inflammatory mechanisms of grape polyphenols

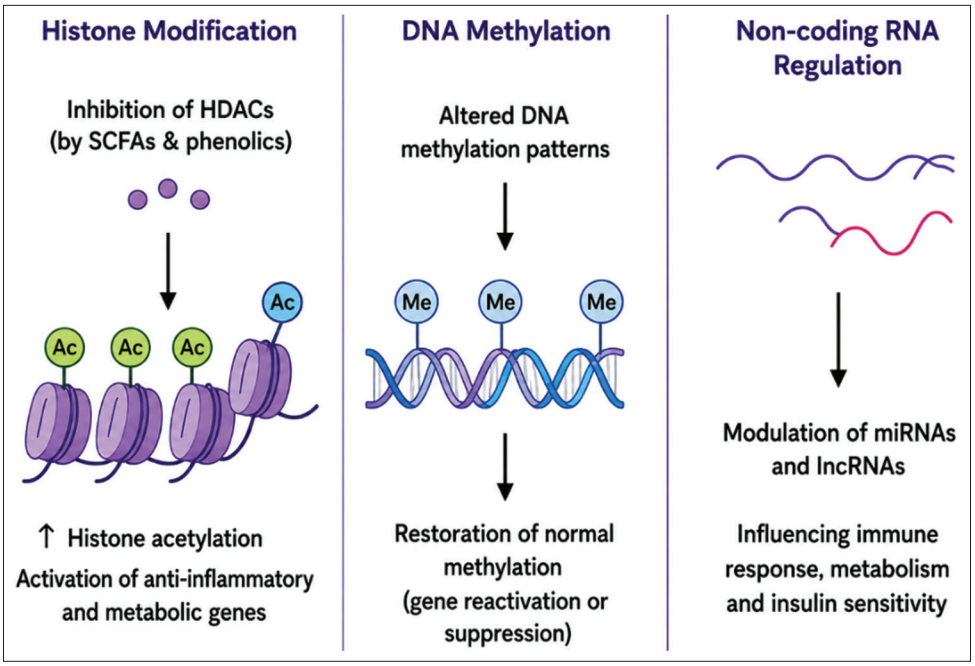


Figure 4: Epigenetic and transcriptional modulation

modulators rather than simple substrates.[51] This selective regulation supports intestinal homeostasis and microbial diversity, increasing production of beneficial metabolites, particularly SCFAs, critical for barrier integrity, immune regulation, and reduced inflammation.[45] Improved barrier integrity also limits bacterial endotoxin translocation, lowering metabolic dysfunction and systemic inflammation.[32] Grape polyphenols actively restore microbial diversity in dysbiotic states induced by high-fat diets, aging, or metabolic disease, reversing taxonomic richness loss and enhancing gut ecosystem resilience,[52] partly through selective enrichment of beneficial taxa including *Lactobacillus*, *Bifidobacterium,* and the mucin-associated, butyrate-producing genera *Akkermansia*, *Faecalibacterium,* and *Roseburia*.[38] Microbiota-derived metabolites exert pharmacological effects via the gut–liver, gut–brain, and gut–immune axes and local intestinal effects,[53] enhancing immune function, neuroprotection, and metabolic regulation by modulating oxidative stress, inflammatory signaling, and neurotransmitter balance. Gut microbiota modulation thus represents a key indirect mechanism of grape polyphenols, alongside their direct effects on cellular signaling and gene regulation [Figure 5].

Immunomodulatory effects

Grape polyphenols exert significant immunomodulatory effects by regulating both innate and adaptive immune responses. They enhance intestinal immune cell function, including macrophages and dendritic cells, by promoting polarisation toward anti-inflammatory phenotypes.[42] By upregulating tight junction proteins and strengthening intestinal barrier integrity, these compounds prevent bacterial lipopolysaccharide translocation into systemic circulation, thereby reducing systemic immune activation.[46] Polyphenol metabolites also influence T lymphocyte development, promoting regulatory T cell expansion to limit excessive immune responses.[35] This immunomodulatory capacity is particularly relevant to autoimmune and chronic inflammatory conditions, where grape polyphenols may help restore immunological homeostasis.[54] The integration of these immune effects with metabolic and neurological signaling, mediated through complex gut–immune–distant organ interactions, underscores the systemic nature of grape polyphenol benefits. Figure 6 depicts the effects of grape polyphenols on immune cell function, cytokine production, and immune signaling pathways relevant to health and disease prevention.

EMERGING THERAPEUTIC POTENTIAL OF GRAPE POLYPHENOLS

Grape polyphenols such as flavonoids, phenolic acids, stilbenes, and tannins act synergistically as multitarget agents, modulating gene expression, signaling, and gut microbiota beyond their antioxidant role. By attenuating oxidative stress and inflammation, they confer broad therapeutic effects spanning cardiovascular, metabolic, neuroprotective, and anticancer domains. Table 2 summarizes these system-wise effects.

Cardiovascular health

Grape polyphenols exert cardioprotective effects primarily through improved endothelial function, enhanced nitric oxide synthesis, and reduced oxidative stress, lowering

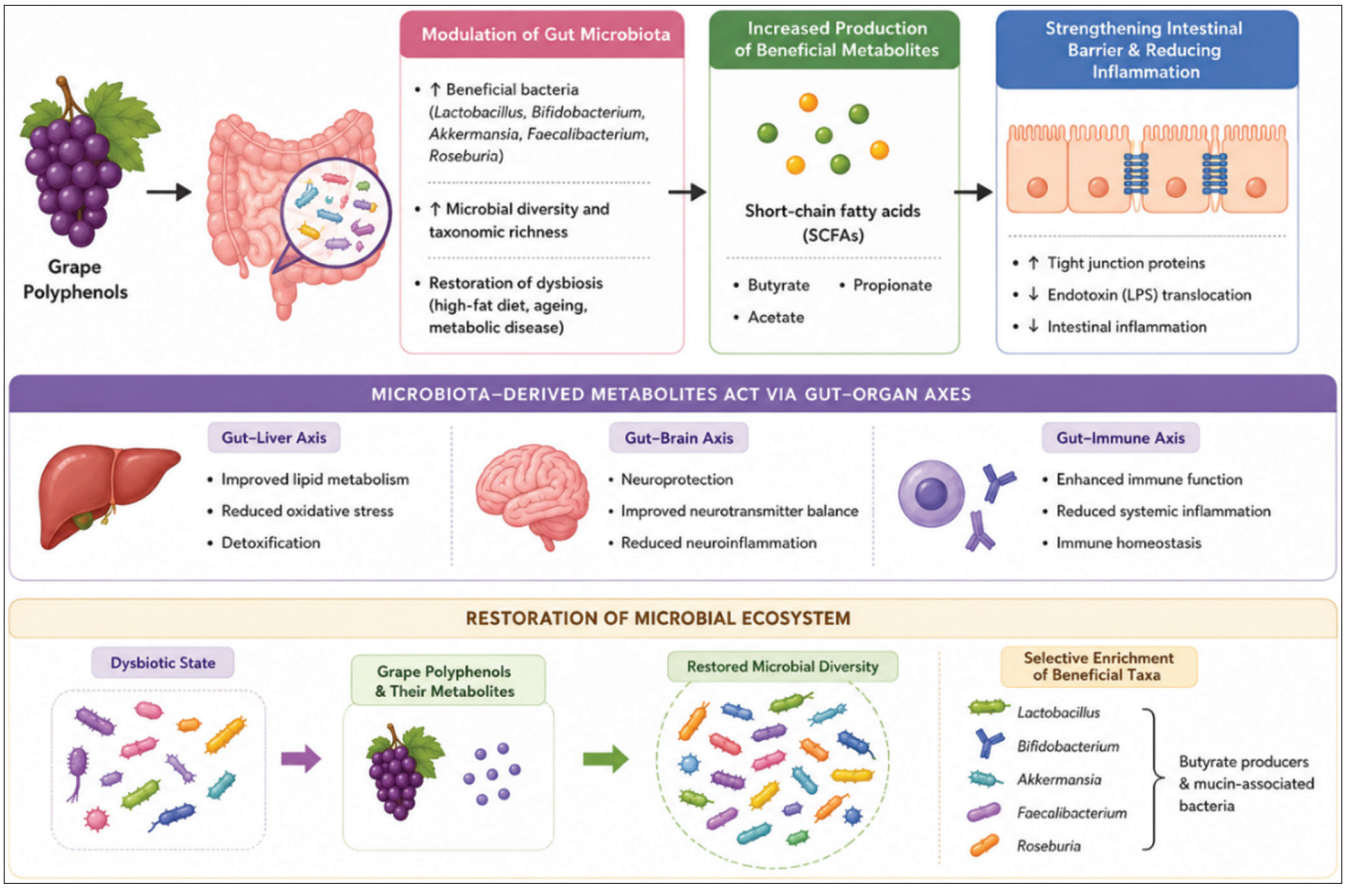


Figure 5: Schematic representation of the polyphenol-gut microbiota axis and its pharmacokinetic implications

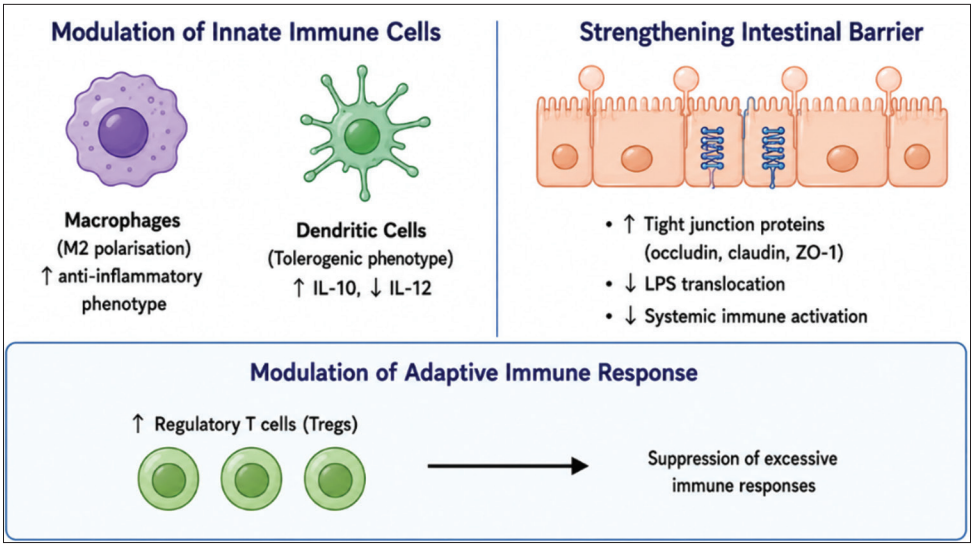


Figure 6: Immunomodulatory effects of grape polyphenols

hypertension and low-density lipoprotein (LDL) oxidation risk.[59] Grape pomace polyphenols act directly via free radical scavenging and indirectly by suppressing pro-inflammatory/oxidative mediators (ROS, malondialdehyde, TNF-α, IL-6, and NF-κB) while upregulating SOD and catalase, preserving ventricular function and limiting infarct size.[60] Resveratrol, flavonoids, and catechins further regulate lipid metabolism and protect LDL from oxidation. In contrast, muscadine skin/seed extracts prevented diastolic dysfunction in hypertension-induced cardiac damage,[61] positioning grape polyphenols as promising cardiovascular therapeutic candidates.

Metabolic health and diabetes

Grape polyphenols play a pivotal role in managing metabolic syndrome – hypertension, hyperlipidemia, and insulin

Table 2: Emerging pharmacological benefits of grape polyphenols

Health benefit	Polyphenol compounds	Primary mechanism	Outcome	Reference
Cardiovascular	Resveratrol, flavonoids, catechins	↑ NO synthesis; ↓ ROS/ NF-κB; LDL protection	↓ Blood pressure, LDL oxidation, infarct size	[55]
Metabolic/ Diabetes	Whole polyphenol profile	Inhibition of α-amylase/ α-glucosidase; ↑ insulin sensitivity	↓ Postprandial hyperglycemia; conflicting insulin-sensitivity data	[56]
Neuroprotection	Anthocyanins, proanthocyanidins, resveratrol	Cross BBB; ↓ neuroinflammation, amyloid-β	Delayed cognitive decline; protection in Alzheimer's/ Parkinson's models	[57]
Anticancer	Grape seed extract, anthocyanins	↑ ROS in cancer cells; modulation of MAPK/PI3K/ NF-κB	↓ Proliferation; ↑ apoptosis	[22]
Healthy aging/ Longevity	Whole polyphenol profile	↓ Oxidative stress/ inflammation; muscle preservation	↓ Age-related muscle loss; improved functional outcomes in older adults	[58]

NO: Nitric oxide, ROS: Reactive oxygen species, NF-κB: Nuclear Factor kappa-B, LDL: Low-density lipoprotein, BBB: Blood–brain barrier, MAPK: Mitogen-activated protein kinase, PI3K: Phosphoinositide 3-kinase

resistance – by inhibiting α-amylase and α-glucosidase and enhancing peripheral insulin sensitivity to attenuate postprandial hyperglycemia.[62] Clinical evidence suggests polyphenol-rich interventions can improve diabetes-related cognitive and metabolic impairments, though excessive intake may cause adverse effects, underscoring the need for dose optimization.[56] Evidence remains heterogeneous: some trials show no short-term change in insulin sensitivity or fat deposition, whereas systematic reviews confirm reduced insulin resistance and beta-cell preservation.[63] Grape polyphenols also exert antiglycative effects and coordinate lipid/glucose metabolism while preserving mitochondrial homeostasis, representing a promising adjunctive therapy for metabolic disorders.

Neuroprotection and cognitive function

Grape polyphenols cross the blood–brain barrier and accumulate in brain tissue, exerting neuroprotective effects by modulating signaling pathways and redox balance.[39] Long-term consumption is linked to delayed cognitive decline and reduced Alzheimer's and Parkinson's risk via reduced neuroinflammation, oxidative stress, and amyloid-beta deposition.[23] Multitargeting strategies preserve neuronal viability in Alzheimer's models.[64] In contrast, anthocyanin- and proanthocyanidin-enriched extracts inhibit dopaminergic neuronal death in Parkinson's models[57] and demonstrate preventive effects in neonatal hypoxia-ischemia models via enhanced neurogenesis and synaptic plasticity.[65]

Anticancer pharmacology and chemoprevention

Grape polyphenols exhibit substantial anticancer activity through antioxidant, anti-inflammatory, and antimutagenic mechanisms, reducing malignant cell proliferation and offering chemopreventive potential across multiple cancer types.[66] Table grape consumption alters circulating microRNA levels, potentially impacting gastrointestinal cancer pathways.[67] Grape seed extract shows anti-tumoral activity across lung, colon, breast, bladder, leukemia, and prostate cancers, primarily by increasing ROS and modulating MAPK, PI3K/ Akt, and NF-κB pathways to inhibit proliferation and promote apoptosis.[68] Grape pomace phenolics exhibit antibacterial and antiviral activity against carcinogenesis-linked pathogens.[18] High-anthocyanin "Vintinto" lines showed strong antiproliferative activity against Michigan Cancer Foundation-7 (MCF-7) cells despite variable antioxidant efficiency,[69] and encapsulation technologies are improving phenolic bioaccessibility and anticancer efficacy.

Healthy aging and longevity

Grape polyphenols contribute to healthy aging primarily by mitigating oxidative stress and chronic inflammation, the principal drivers of cellular senescence, thereby attenuating age-related neurodegeneration and preserving skeletal muscle integrity against obesity- and aging-related insults.[58] At the systemic level, grape bioactives modulate immune function and enhance endogenous antioxidant capacity, mechanisms linked to extended lifespan.[19] Dietary incorporation improves physiological, cognitive, and functional outcomes in older adults, supporting their inclusion in healthy-aging strategies.

POST-HARVEST PROCESSING, VALORIZATION OF GRAPE POLYPHENOLS

Post-harvest handling, storage and processing critically influence the concentration, stability and bioaccessibility of grape polyphenols.[70] Temperature, storage duration

and polyphenol oxidase activity affect phenolic stability, with anthocyanins and flavonols particularly susceptible to degradation.[71] Controlled-atmosphere storage and low temperatures can minimize these losses, whereas moderate stresses such as dehydration and UV exposure may stimulate polyphenol biosynthesis through hormetic responses; excessive stress, however, can accelerate oxidative degradation.[72]

Processing technologies further determine polyphenol recovery and stability. Conventional winemaking facilitates the extraction of phenolics from grape skins and seeds, although prolonged thermal and oxygen exposure may promote degradation.[73] Emerging approaches, including high-pressure processing, pulsed electric fields, ultrasound- and microwave-assisted extraction, and subcritical water extraction, offer opportunities to improve the recovery and preservation of labile compounds such as resveratrol and proanthocyanidins.[14] Encapsulation and freeze-drying can additionally enhance the stability and bioaccessibility of grape polyphenols.[74]

Grape pomace represents an important source of flavonoids, phenolic acids, and stilbenes with antioxidant, anti-inflammatory, and antimicrobial potential, making it a promising raw material for nutraceutical and functional-food applications.[1] Microbial biotransformation can further generate bioactive metabolites from these compounds, contributing to their biological effects.[75] Thus, optimized post-harvest handling, processing, and by-product valorization provide complementary strategies for preserving grape polyphenols and facilitating their incorporation into value-added products.

CURRENT CHALLENGES AND FUTURE PERSPECTIVES IN PHARMACEUTICAL TRANSLATION

Despite robust pre-clinical and epidemiological evidence for their pharmacological benefits, clinical translation of grape polyphenols faces substantial barriers. Low oral bioavailability, driven by extensive first-pass intestinal and hepatic metabolism, restricts systemic concentrations, though nanoencapsulation and lipid-based delivery systems show promise for improving pharmacokinetic performance. Marked inter-individual variability – arising from gut microbiota composition, genetic polymorphisms, age and diet – likely underlies inconsistent trial outcomes. In contrast, the evidence base remains constrained by small sample sizes, short durations and heterogeneous dosing, underscoring the need for large-scale, long-term trials of pharmaceutical-grade rigor. Advances in omics technologies (genomics, metabolomics, and metagenomics) offer powerful tools to unravel individualized metabolic mechanisms and identify response biomarkers, enabling personalized pharmacotherapy tailored to genetic, metabolic, and microbial profiles. Pharmaceutical formulations and nutraceuticals – standardized extracts, fortified products, and novel delivery systems – offer a viable route from laboratory findings to clinical application, provided formulation stability, bioavailability, and regulatory approval are addressed. Overcoming these barriers through advanced delivery systems, rigorous trials, and omics-driven innovation will be essential to realize the full therapeutic potential of grape polyphenols in clinical practice.

CONCLUSION

Grape polyphenols demonstrate significant pharmacological and therapeutic potential across cardiovascular, metabolic, neurological, and anticancer domains, extending well beyond their traditional antioxidant classification. However, translation of these promising bioactivities into clinically relevant applications remains constrained by low and variable bioavailability, extensive metabolism, and inter-individual differences in pharmacokinetic and pharmacodynamic responses. Advances in formulation and drug-delivery strategies, including encapsulation, may improve polyphenol stability, bioavailability, and tissue exposure. At the same time, standardized extraction and chemical characterization are essential for ensuring reproducible composition and efficacy. Future research should prioritize dose–response relationships, long-term safety, potential drug interactions, pharmacokinetic/pharmacodynamic validation, and regulatory requirements, supported by well-designed clinical studies. Integration of metabolomics and gut-microbiome profiling with personalized pharmacology may further clarify inter-individual responses and facilitate the development of grape polyphenols as evidence-based nutraceuticals and candidates for pharmaceutical development.

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