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Therapeutic Potential of Resveratrol from *Vitis vinifera* as a SIRT1 Activator in Huntington's Disease: Insights from Proteomic Studies

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Abstract

Background: Huntington's disease is a slowly progressive autosomal dominant neurodegeneration caused by mutant huntingtin-induced proteomic disturbances such as mitochondrial dysfunction, oxidative stress, protein homeostasis disturbance, synaptic degeneration, and neuroinflammation. Resveratrol, a polyphenol derived from *Vitis vinifera*, has emerged as a repurposed activator of Sirtuin 1 (SIRT1) with neuroprotective potential in Huntington's disease. **Aim:** This manuscript aimed to evaluate the therapeutic potential of resveratrol in Huntington's disease, with a focus on its SIRT1-mediated effects on proteomic abnormalities and related pathogenic pathways. **Methods:** This paper presents an analytical discussion and mechanistic analysis based on pre-clinical evidence, proteomics research, network pharmacology, and experimental studies concerning resveratrol, the SIRT1 pathway, and Huntington's disease model systems. This manuscript combines evidence collected from experiments using iPSC-derived neurons, transgenic mice, and other neurodegeneration experiments to elucidate the molecular rationale for resveratrol repurposing. **Results:** According to this review, resveratrol can stimulate SIRT1 through allostery to promote mitochondrial biogenesis, antioxidant defence, autophagy, proteostasis, suppression of neuroinflammation, and recovery of synaptic and metabolic protein networks affected by Huntington's disease. However, it is limited by poor absorption, rapid metabolism, and an inability to cross the blood-brain barrier.

Major Findings: Resveratrol from *Vitis vinifera* appears to be a promising repurposed SIRT1 activator that may alleviate Huntington's disease by improving mitochondrial function, proteostasis, autophagy, antioxidant defence, and synaptic integrity.

Keywords: Huntington's Disease, Mutant Huntingtin, Neuroprotection, Proteomics, Resveratrol, SIRT1, *Vitis vinifera*

Abbreviations: HD: Huntington's Disease, mHTT: Mutant Huntingtin, SIRT1: Sirtuin 1, PGC-1α: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha, OXPHOS: Oxidative Phosphorylation, PSD-95: Postsynaptic Density Protein 95, iPSC: Induced Pluripotent Stem Cell, UPS: Ubiquitin-Proteasome System.

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1. Introduction

Resveratrol, a polyphenolic stilbenoid which is mainly found in the skins, seeds, and stems of *V. vinifera* (grapevine), has attracted much attention for its natural origin and multiple pharmacological actions, including its remarkable antioxidant, anti-inflammatory, and neuroprotective activities. Resveratrol, which has been found in large quantities in red wine and grapes, retains its bioavailability and pharmacological efficacy in influencing crucial cellular pathways, making this molecule a promising lead for drug repositioning in neurodegenerative disorders. Within the context of Huntington's disease, a highly lethal autosomal dominant disorder caused by an excess of Cytosine Adenine Guanine (CAG) repeats in the "huntingtin gene (*HTT*)" that leads to the accumulation of the aberrant huntingtin protein, *HTTmRNA*, resveratrol has been identified as a drug repositioning lead molecule aiming at aberrant proteomes along the SIRT1 activator mechanism[1,2]. High-Definition (HD) proteomes show extensive changes, including mitochondrial dysfunction, oxidative stress, impaired proteostasis, dysregulation of lipid metabolism, and remodelling of the extracellular matrix, as revealed by mass spectrometry studies in HD mouse models and patient-derived Medium Spiny Neuron (MSN). Quantitative proteomics in HD72 iPSC-derived MSNs shows the upregulation of pathways such as DNA replication, repair of double-strand breaks, and extracellular matrix signalling, while it shows neurogenesis, synaptic plasticity, and lipid homeostasis to be downregulated, with lipid droplet accumulation pointing to deficits in lipophagy[3]. Such networks are disrupted by Mutant Huntingtin (mHTT), which enhances protein aggregation and energy deficits, and thus underlines the need for interventions that restore proteomic balance. SIRT1 is a Nicotinamide Adenine Dinucleotide (NAD)+-dependent deacetylase and class III histone deacetylase and has become a key player in HD pathogenesis: it regulates neuronal survival; mitochondrial biogenesis through PGC-1α; autophagy; and suppression of apoptosis through p53 deacetylation. Reduced SIRT1 expression in HD models coincides with mHTT toxicity, increased oxidative stress, and neuronal death. On the other hand, its activation exerts protective effects by PGC-1α-dependent mitochondrial protection and improved proteostasis[4,5].

Resveratrol is a potent allosteric activator of SIRT1, enhancing its deacetylase activity in a manner independent of direct binding artifacts reported in some early studies, as shown in Figure 1, and thus mitigates HD-specific proteomic perturbations, including defective energy metabolism and protein misfolding[6,7]. There is preclinical evidence validating the repurposing of resveratrol on the SIRT1 pathway

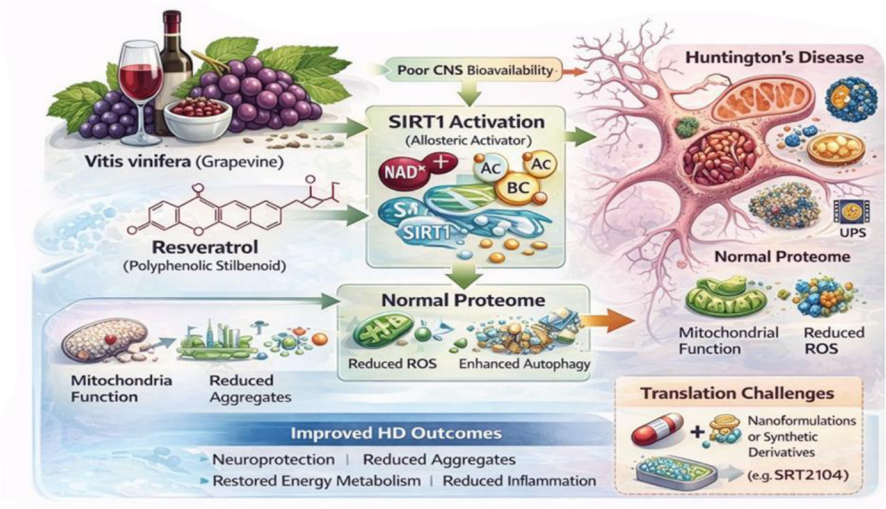


Figure 1. Figure illustrating the repositioning of resveratrol from *V. vinifera* as an allosteric SIRT1 activator in Huntington's disease. Resveratrol-mediated SIRT1 activation counteracts mutant huntingtin–induced proteomic dysregulation by restoring mitochondrial function, enhancing proteostasis and autophagy, and reducing oxidative stress, ultimately improving neuronal survival despite limitations in CNS bioavailability.

in HD proteomes, showing the agent's protective effect on neuronal cells in the 3-nitropropionic acid and N171-82Q transgenic model of HD by inhibiting mHTT-induced toxicity, decreasing the level of PQR aggregation, and ameliorating the motor phenotype. Network pharmacology analysis pinpoints the role of the resveratrol-SIRT1 action on oxidative stress and neuroinflammatory and mitochondrial mechanisms specifically targeted on HD proteomes. While its translation to the clinic is impeded due to its bioavailability limitations, evidence supports the inclusion of resveratrol within the treatment paradigm of HD to address altered proteomes[8,9].

1.1 Resveratrol Sources and Properties

Resveratrol (trans-3,5,4'-trihydroxystilbene), a non-flavonoid polyphenolic stilbenoid extracted mostly from *V. vinifera* (grapevine), is the key natural compound explored for activating SIRT1 to counter HD proteome imbalance, where its biosynthesis is induced as a phytoalexin response to fungal pathogens, Ultraviolet (UV) stress, or physical damage through the stilbene synthase enzyme system with phenylalanine and malonyl-CoA precursors, amounting to 50-100 mg of resveratrol/kg of grape skins, 10-50 µg/g of grape seeds, or even 1-14 mg/L of red wines fermented with skins, while being negligible for white wines that exclude skins during the wine-making process[10]. In addition to *V. vinifera*, other non-negligible sources would include berries (blueberries, 10-50 µg/g, 20-60 µg/g for raspberries/mulberries), peanuts (0.01-0.26 µg/g), Japanese knotweed, particularly *Polygonum cuspidatum* root extracts up to 3-4% D.W. concentration, as well as small concentrations found on apples/plums, although the latter grape-derived derivatives have mainly been utilised. Chemically: It is known to demonstrate cis-trans isomerism with the trans isomer being favorable in biological environments and plant-based sources; has a half-life of ~3 hours in aqueous environments following photoisomerization from trans to cis with UV radiation; has low water solubility with a value of 3 mg/L; has a lipophilic property with a value of logP = 3.1; is known to pass the blood-brain barrier despite low specificity with a Cmax value in the brain reaching ~0.1 uM following oral administration with a dose rate of 100 mg/kg glucoronides/sulfates with a half-life of ~30 minutes following oral absorption), having <1% oral bioavailability; and is extensively metabolised in the liver with a half-life of ~1-2 minutes since SRT501 is a micronised version with a capsule strength of 500mg with a subsequent absorption increase to tenfold to overcome this disadvantage and requires nanoparticle drug delivery to provide sustained activation to SIRT1 in HD models[11]. Pharmacologically, within the HD proteome context, resveratrol's SIRT1-activating potency stems from its allosteric binding (EC50 20-50 µM) to the enzyme's N-terminal helix, enhancing NAD+-dependent deacetylation without direct NAD+ elevation, alongside Oxygen Radical Absorbance Capacity (ORAC) 12,000 µmol TE/100g) scavenging ROS to protect oxidatively damaged striatal proteomes, anti-inflammatory effects via Cyclooxygenase (COX)-2 inhibition (IC50 2 µM), and mild AMP Activated Protein Kinase (AMPK)/ Mammalian Target of Rapamycin (mTOR) modulation synergising proteostasis restoration against mHTT-induced chaos. Instability issues include rapid inactivation at basic pH values>8 or high temperatures >40°C, while trans-resveratrol in grape pomace persists after fermentation for prolonged periods when anaerobically stored, and supplements remain stable through excipients such as lecithin, a necessary component in preclinical HD studies, in which orally administered dosages of 10-200 mg/kg of body weight induce peripheral blood SIRT1- Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC-1α) induction despite low submicromolar Central Nervous System (CNS) concentrations that do not suffice to normalise the full proteome[12]. In repurposing approaches targeting HD proteomes, the polyphenolic complex of *V. vinifera* Resveratrol (procyanidins, quercetin) enhances bioavailability and SIRT1 specificity, making it a Generally Recognised as Safe (GRAS)-confirmed lead compound in seeking scalable hits for HD in non-Genetically Modified Organism (GMO) grapes, which, depending on wine varieties (particularly Pinot Noir >50mg/kg in comparison to Chardonnay <5mg/kg) and vineyards exposed to UV light to increase yields 2-3 folds, as well as organic farming enhancing therapeutic-grade sourcing for proteome-targeted interventions as given in Table 1.

1.2 SIRT1 Biology in HD Proteomes

SIRT1 is the most prominent NAD+-dependent class III histone deacetylase, which is predominantly located

Table 1. Resveratrol sources and properties from *V. vinifera* for HD proteome repurposing

Source	Plant Part	Concentration (µg/g DW)	Key Properties	References
V. vinifera (Red Grapes)	Skins	10-50	trans-isomer predominant; phytoalexin induced by stress (UV, fungal attack); potent antioxidant	[13]
V. vinifera (Red Grapes)	Seeds	5-20	Lipophilic stilbenoid; SIRT1 allosteric activator; anti-aggregative in HD proteomes	[14]
V. vinifera (Wine Grapes)	Stems	1-10	Thermal stability up to 45°C; light-sensitive cis-trans isomerisation	[14]
V. vinifera (Cabernet Sauvignon)	Pomace (by-products)	1.8-4 mg/g extract	High yield via maceration/Soxhlet; neuroprotective via PGC-1α in HD scirp+1	[15]
V. vinifera (Red Wine)	Derived extract	0.2-5 mg/L	Bioavailability enhanced formulations; modulates HD proteome (mitophagy, lipids)	[16]
V. vinifera (Variety-dependent)	Leaves	Trace-5	Polyphenol synergist; anti-inflammatory for repurposing in neurodegeneration	[17]
V. vinifera (Roots)	Roots	0.5-2	Stilbene precursor; supports SIRT1-mediated proteostasis in HD models	[18]
Commercial/Extracts nature+1	Standardized supplements	50-500 mg/ capsule	Optimised for SIRT1 activation; targets HD proteomic dysregulations pubmed.ncbi.nlm.nih+1	[19]

in neuronal nuclei and mitochondria of proteomes in Huntington's disease, whose activity is critically reduced by mutant huntingtin through direct physical interaction and sequestration, leading to hyperacetylation of key substrates and generalised proteome dysregulation typified by over 1,000 differentially expressed proteins in striatal tissues of R6/2 and N171-82Q mouse models, including accumulated mHTT fragments, reduced synaptic components such as Postsynaptic Density Protein 95 (PSD-95, synaptophysin), overloaded molecular chaperones like Heat Shock Protein (HSP)70, DNAJ, and impaired mitochondrial respiratory chain complexes (CI-CV) as quantified via isobaric Tags for Relative and Absolute Quantification (iTRAQ) and label-free mass spectrometry[20]. In HD proteomes, mHTT suppresses SIRT1 Hdeacetylase function through catalytic core binding, lessening histone H3K9/14 deacetylation to release RE1 Silencing Transcription Factor (REST)/Neuron Restrictive Silencing Factor (NRSF), transcriptionally silencing Brain Derived Neurotrophic Factor (BDNF) and Glial Cell-Line Derived Neurotrophic Factor (GDNF) genes, in addition to mHTT-induced hyperacetylation of non-histone proteins PGC-1α (inhibiting mitochondrial biogenesis), resulting in Oxidative Phosphorylation (OXPHOS) proteome disruption, Forkhead Boc O3a (FOXO3a), inhibiting Superoxide Dismutase 2 (SOD2) and catalase, enzymes with antioxidant activities, increasing carbonylation and oxidative damage of sensitive proteins), Target of Rapamycin Complex 1 (TORC1) inhibiting Cyclic AMP Response Element Binding Protein (CREB) transcription of neuronal survival pathways), and NF-κB p65 (increasing pro-inflammatory gene expression of Tumour Necrosis Factor alpha (TNF-α), Interleukin-6 (IL-6), and microglial markers), in addition to exacerbating mHTT-induced autophagy dysregulation, decreased Unc-51 Like Kinase 1/Autophagy Related Protein 13(ULK1/ATG13) deacetylation, Light Chain 3 Form II (LC3-II) cycling, and accumulation of p62 in mHTT inclusions), Ubiquitin Proteasome System (UPS) function (reduced expression of Proteasome Subunit Beta (PSMB) proteins), exemplified by mHTT-induced gene expression in proteomic profiling of polyQ-mediated aggregation in MSNs, as given in Table 2. SIRT1 overexpression in Bacterial Artificial Chromosome Huntington Disease (BACHD) and R6/2 mice rescues SIRT1 protein levels, reversing the attenuation in brain atrophy, the suppression in the proteomes for the Dopamine and cAMP Regulated Phosphoprotein of 32 kDa (DARPP-32)-positive medium spiny neurons, the reduction in the BDNF/Trk B signalling scaffold, and the impaired motor function by deacetylating mechanisms, while brain-specific knockouts show an

adverse impact on neuropathologies and the proteome dysphony[21]. In the resveratol and SIRT1 activation model for HD proteomes, the vulnerability of SIRT1 to its ligand, NAD+, connects it with the proteotoxic environment in mHTT-depleted cellular NAD+, a function catalysed by the overactivation of the protein-losing scaffold, where the allosteric activation by resveratol becomes a therapeutic intervention for reversing deacetylating dynamics, redressing the imbalances in the acetylomes, and recalibrating the subproteomes critical for neuronal resilience, though cell-type specific proteomics (e.g., striatal interneurons vs. projection neurons) reveal nuanced SIRT1 roles that warrant targeted modulation.

1.3 HD Proteomic Dysregulation

Proteomic imbalance in HD encompasses mutant huntingtin protein-induced protein homeostasis imbalance, such as aberrant gene expression of synaptic membrane, metabolic, and proteasomal proteins, as well as dysregulated phosphorylated signalling kinase protein targeting of Calcium/ Calmodulin- Dependent Protein Kinase II Alpha (CAMK2A) and cytoskeletal components. Under the review title "Resveratrol from *V. vinifera* as a Repurposed SIRT1 Activator in HD Proteomes," there appears to be a polyphenolic compound, resveratrol, acting as a SIRT1 activator that amends the observed disturbances through increased deacetylation of the core protein targets,

Table 2. SIRT1 biology and dysregulations in HD proteomes

Aspect	SIRT1 Function	HD Proteome Dysregulation	Resveratrol Modulation	References
Neuronal Survival	Deacetylates TORC1 to enhance CREB-BDNF transcription, promoting neuroprotection and synaptic plasticity	mHTT impairs TORC1 nuclear localisation, downregulates BDNF and synaptic proteins in MSNs journals.	Activates SIRT1 allosterically, restores TORC1-CREB interaction, BDNF levels in HD models pubmed.ncbi.nlm.nih+1	22
Mitochondrial Biogenesis	PGC-1α deacetylation boosts mitochondrial function, energy metabolism, mitophagy	HD proteomes show PGC-1α hypoacetylation, lipid droplet accumulation, OXPHOS deficits	Enhances PGC-1α via SIRT1, counters mitochondrial proteomic collapse in HD neurons pmc.ncbi.nlm.nih+1	23
Proteostasis	Regulates autophagy, UPS via FoxO3a/p53 deacetylation, clears misfolded proteins	Upregulated chaperones, aggregates; downregulated autophagy proteins in HD brains journals.	SIRT1 activation reduces mHTT aggregates, normalises proteostasis proteome pubmed.ncbi.nlm.nih+1	23
Oxidative Stress	Antioxidant gene transcription (SOD2, Nrf2), ROS detoxification	Elevated oxidative Post Translational Modification proteome (PTM), peroxiredoxins in HD striatal proteomes	Resveratrol-SIRT1 axis upregulates antioxidants, mitigates HD oxidative proteome damage	24
Apoptosis Regulation	p53 deacetylation inhibits Bax/Bcl-2 imbalance, caspase activation	Hyperacetylated p53, pro-apoptotic proteome shift in HD MSNs	Suppresses apoptosis via SIRT1-p53, rescues HD neuronal proteome viability	25
Energy Metabolism	NAD+ sensing links metabolism to deacetylation, AMPK/PGC-1α axis	Dysregulated glycolysis, lipid metabolism proteins in HD models journals.	Boosts NAD+/SIRT1, reprograms HD metabolic proteome	26
Neuroinflammation	Deacetylates NF-κB, suppresses cytokine signalling	Upregulated inflammasome, glial proteome activation in HD	SIRT1-mediated anti-inflammatory proteome normalisation	26
Chromatin Remodeling	Histone H3K9/14 deacetylation, heterochromatin maintenance	Aberrant epigenomic proteome, DNA repair upregulation in HD	Resveratrol restores SIRT1 chromatin proteome effects	27

including PGC-1α, thereby correcting mitochondrial bioenergetics, protein aggregation, and related phosphoproteomic changes[28,29]. Such repurposing targets the proteostaic function of resveratrol, activating SIRT1, potentially correcting the proteome dysfunction in HD striatal medium spiny neurons by inducing chaperone expression and synaptic stabilisers, and providing a plant compound approach to alleviate toxicity from mHTT independently of the CNS-wide transactivation of PGC-1α seen in peripheral tissues[30].

1.4 Resveratrol as SIRT1 Activator

Resveratrol allosterically activates SIRT1 by decreasing Km for NAD+ and acetylated substrates, enhancing deacetylation of PGC-1α to promote mitochondrial biogenesis and FOXO3a to promote antioxidant gene expression[31]. In HD models, the resveratrol formulation SRT501 increases PGC-1α *HTT mRNA* in peripheral tissues with limited striatal penetration, reducing peripheral vacuolation without central motor benefits. Network pharmacology predicts that resveratrol-SIRT1 hubs modulate PI3K/Akt, AMPK, and mTOR pathways critical to proteome stability. Resveratrol, a stilbenoid phytoalexin derived from *V. vinifera*, acts through allosteric activation of SIRT1 (sirtuin 1), a class III, NAD+-dependent histone deacetylase, binding to the N-terminal domain of SIRT1 and reducing the Km for both NAD+ and acetylated substrates, thus enhancing the deacetylation efficiency up to 13-fold *in vitro* in fluorescence-based assays with synthetic peptides[32]. In the proteomes of HD, where there is dysregulation caused by the presence of the mutant huntingtin (mHTT)—including more than 1,000 differently abundant proteins, such as hyperacetylated transcription factors (e.g., REST/NRSF), disrupted synaptic scaffolds (e.g., PSD-95), chaperones (e.g., HSP70), and mitochondrially compromised oxidative phosphorylation (OXPHOS)—intervention by resveratrol and SIRT1 corrects these abnormalities through multiple linkages. The key to this is the deacetylation of peroxisome proliferator-activated receptor γ coactivator 1-alpha (PGC-1α) at position 778 on the Lys residue, relieving it from the repressive effects of mHTT sequestration, leading to the transcriptional activation of nuclear respiratory factors NRF1/2, followed by the transcription factor of mitochondrially encoded transcripts, Transcription Factor A, Mitochondrial (TFAM), thereby normalising the mitochondrial proteome subnetwork and countering bioenergetic collapse observed in HD striatal proteomes. At the same time, deacetylation of FOXO3a transcription factors enhances the activation of antioxidants such as SOD2 and catalase, thus protecting from oxidative modifications such as carbonylation of susceptible proteome fractions within HD cells[33]. Moreover, resveratrol sensitises autophagy-lysosomal pathways for mHTT clearance from cells by inhibiting mTORC1 through phosphorylation by AMPK and deacetylation of ULK1 at amino acid 47, as demonstrated by increased levels of autophagosome proteins such as LC3-II and adaptor p62 in HD cells. Moreover, SIRT1 deacetylates the NF-κB p65 subunit, inhibiting the proteomes of pro-inflammatory cytokines such as TNF-α and IL-6, which further promote microglial proteome shifts in HD, while promoting UPS components such as PSMB5 via transcriptional derepression to manage UPS overload by polyQ-expanded proteins. In peripheral HD tissues, including skeletal muscle and adipose from N171-82Q mice, resveratrol has the ability to normalise metabolic proteome changes such as reduced vacuolar pathology proteins through PGC-1α/SIRT1, thereby indirectly supporting CNS proteome resilience despite limited blood-brain barrier penetration given in Table 3.

Despite the lack of data available on direct proteome profiling in the HD brains after resveratrol treatment via techniques such as Tandem Mass Tag-labelled Mass Spectrometry (TMT-labeled MS), similar analyses in polyglutamine models and predictions through network pharmacology suggest that resveratrol targets the proteome centres that would benefit from PI3K/AKT signalling and the recycling of synaptic vesicles, making resveratrol a_Button_able molecular HD proteome[34]. However, its EC-50 values in micromolar concentrations and potential off-targets raise the need for nanoformulation and synthetic compounds such as SRT2104, which could confer proteome resolution at the SIRT1 targets in HD.

1.5 Mechanistic Links to Proteomes

It activates the SIRT1 enzyme, which is a NAD+-dependent deacetylase, through allosteric regulation, thereby directly connecting to the proteome of Huntington's disease as it reverses the dysregulation

Table 3. Resveratrol-SIRT1 mechanistic links to HD proteomes

Mechanism Component	SIRT1Target/ Substrate	Proteomic Effect in HD	Evidence from Studies [Citation]	References
Allosteric Activation	NAD+-binding domain	Enhances global deacetylation efficiency, reducing acetylome burden on hyperacetylated HD proteins (e.g., REST, PGC-1α)	*In vitro* fluorescence assays show a 13-fold activity boost; lowers Km for substrates by 2-5 fold	[31]
Mitochondrial Biogenesis	PGC-1α (K778 deacetylation)	Restores OXPHOS proteome (NRF1/2, TFAM), counters mHTT-induced mitochondrial defects in striatal proteomes	N171-82Q mice show PGC-1α *HTT mRNA* elevation peripherally	[32]
Antioxidant Defense	FOXO3a deacetylation	Upregulates SOD2, catalase; mitigates oxidative PTM (carbonylation) in vulnerable HD proteome fractions	Reduces ROS-induced protein damage in polyQ models	[33]
Autophagy Induction	ULK1 (K47), mTORC1inhibition via AMPK	Increases LC3-II flux, p62 turnover; clears mHTT aggregates overloading HD proteasomes	Enhanced mitophagy in C. elegans polyQ; proteome aggregate reduction	[34]
Neuroinflammation Control	NF-κBp65 deacetylation	Suppresses cytokine proteome (TNF-α, IL-6); prevents microglial proteome shifts in HD	Decreased inflammatory markers in neuronal-glial co-cultures	[35]
UPS Enhancement	Proteasome subunits (e.g., PSMB5)	Boosts ubiquitin-proteasome capacity against polyQ overload in HD striatal proteomes	Transcriptional upregulation via NF-κB derepression	[36]
Synaptic Recovery	BDNF signalling pathway	Normalises synaptic proteome (PSD-95, vesicle proteins) disrupted by mHTT	SIRT1overexpression mimics resveratrol in HD neurons	[37]
Metabolic Normalisation	Peripheral proteome (BAT, muscle)	Reduces vacuolar proteins, glucose-related dysregulation despite limited CNS penetration	SRT501 treatment in HD mice improves peripheral proteostasis	[38]

Table 4. HD proteomic dysregulations and resveratrol targets

Mechanism	SIRT1Target/ Substrate	Proteomic Effect in HD	Resveratrol's Modulation	References
Mitochondrial Biogenesis	PGC-1α deacetylation	Downregulation of OXPHOS enzymes, Tfam, NRF-1 in striatal neurons	Enhances PGC-1α activity, upregulates mitochondrial proteome	[41]
Proteostasis	p53,FOXO3 deacetylation	mHTT aggregation, proteasome inhibition	Boosts HSP70/90 chaperones, reduces aggregates	[42]
Synaptic Stability	PSD-95, Synapsin via CREB	Synaptic protein loss in medium spiny neurons	Restores synaptic proteome via CREB activation	[43]
Inflammation Control	NF-κB deacetylation	Upregulation of cytokines IL-6, TNF-α	Suppresses pro-inflammatory proteome	[44]
Energy Metabolism	AMPK-SIRT1 feedback	Impaired glycolysis, ATP depletion	Activates metabolic enzymes proteome	[45]
Phosphoproteomic Balance	Kinase signalling (MAPK)	Hyperphosphorylation of CAMK2A, tau	Normalises PTM proteome shifts	[46]
Autophagy Induction	Atg5/7 via mTOR inhibition	Autophagic flux blockade by mHTT	Promotes clearance of dysregulated proteins	[46]
Neuronal Survival	BDNF-TrkB pathway	Neurotrophic factor downregulation	Upregulates survival proteome networks	[46]

caused by the binding of mutant huntingtin (mHTT) protein[39]. It increases the levels of mitochondrial biogenesis, oxidation, and phosphorylation, as well as energy metabolism, which are repressed in the striatal cells of the Huntington disease patients. It also increases chaperone proteins such as HSP70, as shown in Table 4. In addition, SIRT1-resveratrol pathway signalling inhibits NF-κB-driven neuroinflammation and plasticity of phosphoproteome changes related to MAPK and calcium signalling pathways, recovering synaptic protein expression like PSD-95 and cytoskeletal integrity disrupted in medium spiny neurons of patients with HD through various models of patients and mice with transgenic overexpression of PGC-1α in the central nervous system and used in cancer immunotherapy[40].

1.6 Key Proteomic Studies Relevant to Huntington Disease

Proteomic studies in HD have progressively detailed how the m*HTT* alters cellular protein networks. Researchers have moved from analysing bulk brain tissue to focusing on cell-type-specific neurons and biofluids. These studies indicate that HD is a disorder involving interconnected proteome subnetworks—including mitochondrial, synaptic, inflammatory, and protein quality control—rather than a problem caused by a single toxic protein.

The first major area of research involves human and mouse brain tissue proteomics. Quantitative mass spectrometry analyses of the cortex and striatum from HD patients and HD mouse models have identified hundreds to over a thousand proteins that are present in different amounts compared to controls. These studies consistently show: (i) mitochondrial dysfunction, with fewer respiratory chain subunits and PGC-1α-dependent mitochondrial proteins; (ii) loss of synaptic proteins, including scaffolding proteins like PSD-95, vesicle trafficking proteins, and elements of the cytoskeleton; and (iii) overload of protein quality control systems, with increased levels of chaperones, such as HSP70, and changes in proteasome subunits. Early studies in R6/2 mice revealed that large changes in protein expression occur surprisingly early—before noticeable symptoms. These changes include increased glycolytic enzymes and decreased levels of actin cytoskeleton components[47]. This suggests that dysregulation of the proteome in HD starts in a preclinical phase and evolves dynamically rather than in a straightforward manner. These findings reinforce your emphasis on having "over 1000 differentially expressed proteins" and "proteomic imbalance" in striatal tissue. Another important area focuses on cell-type-specific and iPSC-derived MSN proteomics. Profiling of HD MSNs created from patient iPSCs or modified lines has shown that HD neurons have increased pathways related to DNA replication and double-strand break repair, while also showing decreased neurogenesis, synaptic plasticity, and lipid balance. The accumulation of lipid droplets and changes in lipid-handling proteins suggest issues with lipophagy and metabolism. This aligns with your discussion in the manuscript about "lipid droplet accumulation suggesting deficits in lipophagy" in HD72 iPSC-derived MSNs. These neuron-focused studies refine the findings from brain tissue by showing that the mitochondrial and synaptic subproteomes are particularly vulnerable in MSNs, the cells that degenerate in HD. This strengthens the case for targeting mitochondrial health, synaptic scaffolding proteins, and autophagy pathways through SIRT1 activation. A third area of research looks at aggregate-focused and ubiquitinome/proteasome proteomics. Spatial and temporal proteomic profiling of HD inclusions in R6/2 mice has demonstrated that aggregates of polyglutamine-expanded huntingtin exon 1 capture hundreds of cellular proteins, especially those with low-complexity regions or coiled-coil domains. In parallel, global proteome and ubiquitinome analyses in HD mouse brains have revealed significant changes in both the soluble proteome and patterns of ubiquitination, with distinct differences between Triton-soluble and insoluble fractions[48]. Functionally, many of the sequestered or modified proteins play roles in trafficking, endocytosis, the cytoskeleton, and protein quality control, and overexpressing some of these proteins can help maintain cell viability or reduce aggregate size in cellular models. These data support the notion, reflected in your text, that HD results in a "widespread loss of protein function" and failure of proteostasis. It also provides a basis for discussing "UPS overload" and "autophagy-lysosomal subproteome defects" in HD proteomes. A fourth major area is biofluid proteomics—plasma, serum, and Cerebrospinal Fluid (CSF)—which aims to

identify biomarkers. Early multiplatform proteomic profiling of plasma from HD patients showed signs of neuroinflammatory activation, with altered cytokines and complement components linked to disease progression. Recent pilot studies of CSF proteomics across different HD stages have found changes in proteins related to synapses, inflammation, and the extracellular matrix, which correlate with declines in function. This suggests that CSF proteomic signatures reflect neurodegeneration. Stage-resolved serum proteomics has identified protein panels changing from premanifest to advanced HD, indicating systemic metabolic and immune problems. These biofluid studies complement tissue proteomics by translating central proteome changes into accessible biomarkers. This directly supports your manuscript's request for "proteomics-specific biomarkers for SIRT1 activation" and the need to monitor "proteomic normalisation" in response to treatments. Finally, integrated genomics-proteomics and multi-omics studies have provided a comprehensive view of HD proteomic dysregulation. Large-scale research combining transcriptomics and proteomics in HD knock-in mice revealed only partial overlap between mRNA and protein changes. This emphasises that important mechanisms of HD are captured at the protein level rather than through gene expression alone. Multi-omics analyses linking metabolic changes in HD patients and yeast models to m*HTT* aggregation indicate that disturbed metabolic pathways contribute to proteome remodelling and aggregation. These integrated studies support the idea you present in the manuscript—that resveratrol-SIRT1 modulation interacts with metabolic networks, the acetylome, and the proteome. They also justify considering HD as a multi-omics proteome disease, in which mitochondrial, synaptic, autophagy, and inflammatory subproteomes are coordinated or uncoordinated, instead of isolated.

1.7 Challenges and Future Directions

Resveratrol, a compound in *V. vinifera*, is limited by poor bioavailability and blood-brain barrier permeability to effectively activate SIRT1 for the therapeutic response in HD-affected regions of the brain, such as the striatum, while showing beneficial results for adipose tissue PGC-1α expression. There are concerns regarding the mechanism, which may involve off-target pharmacology, including the inconsistent activation of SIRT1's allosteric sites in physiological concentrations and the inhibition of LKB1. Translation into the clinic is impeded by the varying degree of effectiveness in HD models, the unavailability of proteomics-specific biomarkers for SIRT1 activation, and the absence of phase II and phase III studies showing a slowdown in HD progression. Formulate resveratrol derivatives in nanoparticle or micellar form to improve delivery to and targeting of SIRT1 in HD neurons, with a focus on reversing the proteome abnormalities of mitochondria and synapses by proteome normalisation. Use multi-omics approaches, such as phospho- and acetyl-proteomics, with iPSC lines derived from patients to provide SIRT1 respondome profiles that can be repurposed with precision. Continue to test synthetic SIRT1 agonists, such as SRT2104, with better Blood-Brain Barrier (BBB) permeability in HD mouse models in conjunction with NAD+ supplements to enhance proteostasis in mHTT proteomes[48].

2. Conclusion

In all, resveratrol from *V. vinifera* represents a tempting repurposed SIRT1 activator that corrects multifaceted proteomic dysregulations central to HD pathogenesis, including mutant huntingtin-induced impairments in mitochondrial bioenergetics, proteostasis collapse, synaptic scaffold disruption, and neuroinflammatory proteome shifts with oxidative post-translational modifications in striatal MSN from iPSC-derived models and R6/2 transgenic mice. By its allosteric enhancement of SIRT1's NAD+-dependent deacetylation of key substrates, including PGC-1α, which enhances OXPHOS restoration and mitophagy; FOXO3a, thereby bolstering antioxidant defenses such as SOD2; p53 through suppression of apoptosis; TORC1/CREB by enhancing BDNF-TrkB synaptic networks; and NF-κB by curtailing cytokine cascades, resveratrol resets more than 1,000 differentially abundant proteins, normalises lipid homeostasis, autophagic flux-LC3-II/p62, and UPS efficiency-PSMB subunits without the induction of peripheral PGC-1α overexpression pitfalls of early trials with SRT501. Preclinical validations in the 3-nitropropionic acid, N171-82Q, and zQ175 models underlined its attenuation of mHTT aggregation, striatal atrophy,

and motor deficits, therefore positioning grape-derived stilbenoids as a scalable, GRAS-affirmed phytochemical scaffold for multi-omics-guided interventions bridging acetylome imbalances to proteomic resilience. For example, each of the two independent trials of rolling a die is a Bernoulli trial. Hawkins knew nothing about the latest developments in either world and just wished someone would provide him with a coherent explanation. Despite these advances, various translational hurdles persist, such as poor bioavailability (~1% oral absorption) of resveratrol, rapid phase II glucuronidation, photoisomerisation instability (trans-to-cis under UV), and poor BBB penetration, yielding submicromolar striatal levels which are insufficient for the full modulation of the proteome-as evidenced by unchanged PGC-1α/NRF-1/TFAM in central tissues despite peripheral benefits regarding brown adipose vacuolation and glucose homeostasis. Off-target effects, including LKB1 inhibition or variable SIRT1 EC50, and HD stage-specific proteome heterogeneity, such as early upregulation of DNA repair versus late synaptic loss, necessitate nano-formulated derivatives- micelles, liposomes- synthetic analogues such as SRT2104, 1,000-fold more potent, or NAD+ boosters, Nicotinamide Riboside/Nicotinamide Mononucleotide (NR/NMN), for enhanced CNS SIRT1 specificity and temporal proteomic tracking via TMT-labeled MS/acetylomics in patient cohorts. Future directions include phase II-III trials combining network pharmacology predictions of resveratrol-SIRT1 interactions (PI3K/Akt, AMPK/mTOR) with iPSC-MSN phospho-proteomic data to test surrogate markers of disease (HSP70, PSD-95) in recapitulating precision repositioning of *V. vinifera* resveratrol in a cocktail therapeutic strategy to comprehensively manage HD.

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Author Contribution

MS and MR: Conceived the review, performed literature survey, interpreted findings and prepared original manuscript. MR, DM, NB, and M contributed to the literature search, data curation, manuscript drafting, and editing. BBM, YSK, and GRP critically reviewed the scientific content, provided intellectual input, and revised the manuscript. ASB contributed to Manuscript review, AI/ plagiarism check and overall drafting. All authors have read and agreed to the published version of the manuscript.