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Review Article

The Neuroprotective Effect of Flavonoids in Huntington's Disease: a Systematic Review

Sang Ayu Arta Suryantari[1*], Anak Agung Intan Pramesti[1], I Made Suma Wirawan[1], I Gusti Ngurah Mambal Wirajangsa[1], I Wayan Yudha Wedantha[1], Ni Putu Elisya Nathania Fidela[1]

[1]Faculty of Medicine, Universitas Mahasaraswati Denpasar, Jl. Kamboja, No. 11A, Denpasar, 80233, Indonesia

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Correspondence:
Sang Ayu Arta Suryantari
ayuarta@unmas.ac.id

Abstract

Background: Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by progressive striatal and cortical neuronal loss, resulting in severe motor, cognitive, and psychiatric deficits for which no disease-modifying therapy currently exists. Flavonoids, abundant polyphenolic phytochemicals, are increasingly recognized for their potent neuroprotective properties, specifically acting as antioxidants, anti-inflammatory agents, and modulators of apoptosis and autophagy.

Objective: This systematic literature review was conducted to synthesize and critically evaluate contemporary preclinical evidence regarding the efficacy of flavonoids in animal models of HD.

Methods: A comprehensive search was executed across PubMed, ScienceDirect, and MEDLINE databases (2015–2025) using specific keyword combinations. Studies investigating flavonoid effects in HD animal models with full-text availability were included, whereas publications older than ten years and review studies were excluded. Methodological quality was assessed using the Joanna Briggs Institute (JBI) critical appraisal tool. Twelve eligible animal studies were identified, demonstrating methodological quality ranging from good to very good.

Results: Consistent findings indicated that flavonoid administration significantly enhanced motor coordination and cognitive performance, attenuated oxidative stress and neuroinflammation, and preserved neuronal integrity. These protective outcomes were mediated through the modulation of multiple molecular pathways, encompassing antioxidant defense systems, inflammatory signaling cascades, and apoptosis-related mechanisms.

Conclusion: While current preclinical evidence is promising, underscoring the critical roles of flavonoids as multifaceted neuroprotective agents, further rigorously designed clinical trials are imperative to validate these findings and establish the therapeutic potential and clinical applicability of flavonoids for patients suffering from Huntington's disease.

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INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an abnormal expansion of CAG (Cytosine-Adenine-Guanine) trinucleotide repeats in exon 1 of the HTT (huntingtin) gene. This mutation results in the production of mutant huntingtin protein (mHTT), which carries an extended polyglutamine (polyQ) tract.[1] In normal condition, HTT protein plays various essential roles in neuronal function, including acting as a scaffold for protein complexes, facilitating axonal transport, preserving mitochondrial function, and regulating gene expression.[2] The accumulation of mHTT disrupts neuronal function and homeostasis, leading to progressive neurodegeneration, particularly in the striatum and cerebral cortex.[3,4] Although Huntington's disease is driven by a single genetic mutation, its progression can be influenced by other genetic factors. Variations in DNA repair genes such as FAN1 (Fanconi-Associated Nuclease 1), MSH3 (MutS Homolog 3), and PMS1 (Postmeiotic Segregation Increased 1) have been found to affect the age of symptom onset and the rate of disease progression.[5] These genetic modifiers contribute to the instability of CAG repeats in somatic cells, adding complexity to what is otherwise considered a monogenic disorder. Clinically, HD presents with a triad of motor dysfunction, cognitive decline, and psychiatric symptoms.[6] Although its genetic cause is well established, no current treatment effectively halts or slows disease progression.

Flavonoids are natural polyphenolic compounds widely present in fruits, vegetables, grains, and beverages like tea and wine. Known for their antioxidant, anti-inflammatory, and neuroprotective properties, flavonoids have gained attention as potential therapeutic agents for neurodegenerative diseases, including HD. Recent preclinical studies using animal models of Huntington's disease, have demonstrated that certain flavonoids, including quercetin, epigallocatechin gallate (EGCG), and baicalein, may alleviate HD-related pathology.[7] However, existing reviews often generalize polyphenol effects without dissecting the distinct molecular mechanisms of specific flavonoid subclasses or synthesizing evidence from the last decade of targeted animal studies. Addressing this gap is crucial to identify precise therapeutic candidates beyond general antioxidant claims. These effects are associated with their ability to reduce oxidative stress, enhance mitochondrial biogenesis, suppress inflammation, and modulate pro-survival signaling pathways such as PI3K/Akt and Nrf2/ARE.[8,9] As a systematic literature review, this study aims to summarize and analyze recent experimental evidence on the mechanisms and effectiveness of flavonoids in addressing Huntington's disease pathology in animal models, as well as to evaluate their potential as candidate neuroprotective therapies.

METHODS

Search Strategy

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which include the stages of identification, screening, eligibility assessment, and inclusion. A systematic literature search was performed across major electronic databases, including PubMed, ScienceDirect, and MEDLINE, covering publications from 2015 to 2025. In addition, supplementary searches were conducted using Google Scholar to identify relevant grey literature. Keywords used were a combination of Medical Subject Headings (MeSH) terms and free-text terms. The search string included "Flavonoid" AND "Animal study" AND "Huntington's disease" OR "neurodegenerative disease". Boolean operators (AND, OR) were employed to construct the search strings, which were adapted according to the syntax requirements of each database.

Study Selection

Three researchers initially conducted the study selection process by screening article titles, abstracts, and full texts. Subsequently, two additional reviewers independently assessed the full-text articles for eligibility. Any disagreements regarding article inclusion were resolved through group discussion and consensus with the academic advisor. To ensure methodological rigor and justify the final selection of 12 studies from the initial data pool, precise inclusion and exclusion criteria were strictly applied. Studies were included if they met the following criteria: (1) investigated the effects of flavonoids on Huntington's disease in animal models, and (2) were available in full text. Articles published more than ten years prior and review studies were excluded. Additionally, reference lists of the selected articles were examined to identify and include other relevant studies. This stringent filtering process eliminated 480 records due to irrelevance, duplication, or failure to meet methodological standards, resulting in the final 12 eligible studies.

Data Extraction

One reviewer used standardized forms to extract the data, while a second reviewer independently verified the extracted results to ensure accuracy. The extracted information included flavonoid compound type, dosage and route of administration, experimental model, measured outcomes, and limitation of the study. Following the extraction of data, every journal undergoes quality assessment using the Quasi-Experimental Studies from
Joanna Briggs Institute (JBI). The objective of this assessment is to evaluate the quality of a study's methodology and establish how well the study handled potential bias in its design, implementation, and analysis. The quality evaluation of included studies was performed by two investigators. Any disagreement in study selection or quality assessment was resolved by further discussion.

RESULT AND DISCUSSION

The initial search yielded a total of 492 articles: 231 from PubMed, 259 from ScienceDirect, and 2 from MEDLINE. All retrieved articles were imported into reference manager software, and duplicate records were removed. Articles with irrelevant titles, abstracts, or publication years were excluded during the preliminary screening. Full-text articles were then thoroughly reviewed to assess eligibility based on the inclusion criteria. Additional relevant studies were identified through manual searching of reference lists. After applying all exclusion steps, a total of 12 articles were

included in the final review and discussed further. The study selection process is illustrated in the PRISMA flowchart (**Figure 1**). Study quality was assessed using the Joanna Briggs Institute (JBI) checklist for quasi-experimental studies and presented in **Table 1**. In this assessment, each of the nine critical appraisal items was assigned a score of 1 for 'Yes' and 0 for 'No' or 'Unclear', yielding a maximum total score of 9. Based on the total score, study quality was categorized as poor (0–3), fair (4–5), good (6–7), and very good (8–9). The findings reveal that all included studies were rated as having good to very good methodological quality based on the JBI checklist, with scores ranging from 6 to 9.

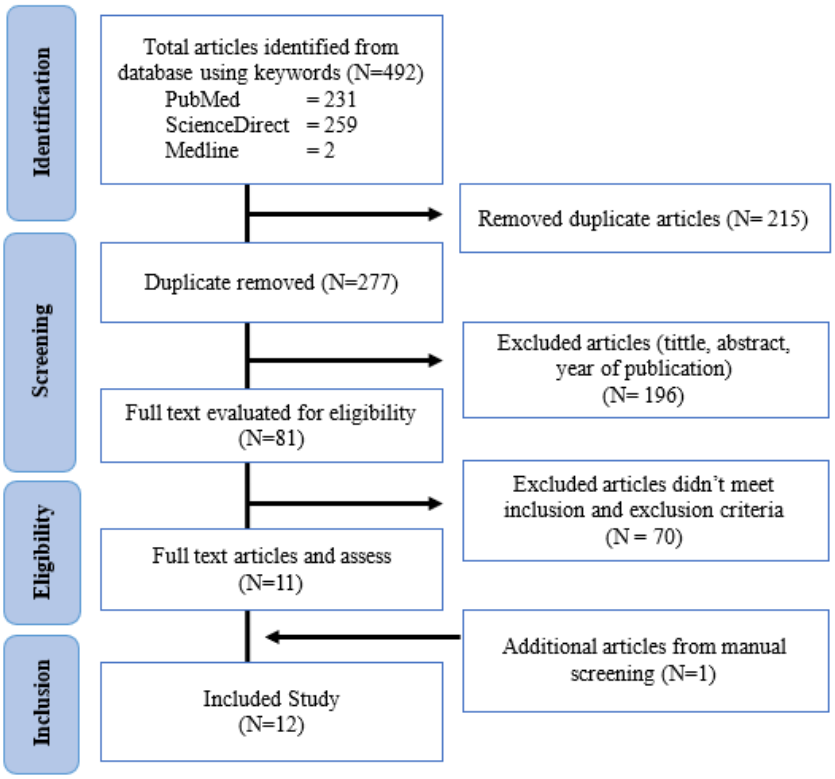

Figure 1. PRISMA Flowchart

We identified 12 animal studies investigating the use of flavonoids in the treatment of Huntington's disease. The most reported effects include enhanced locomotor and behavioral activity, as well as increased antioxidant capacity. Additional observed outcomes comprise anti-inflammatory effects, structural protection of brain regions, cognitive improvement, reduced apoptosis, enhanced autophagy activity, and a decrease in CAG repeat expansion, mutant huntingtin (mHTT), and huntingtin (HTT) aggregates in various brain areas. Moreover, several studies demonstrated improvements in neurotrophic and dopaminergic factors, alongside increased ATP levels, enhanced neuronal function, and improved neurological reflexes. The findings from several reviewed studies on the neuroprotective effects of flavonoids in animal models of Huntington's disease are summarized in **Table 2**. We also summarized the key features of flavonoids that contribute to the improvement of Huntington's disease in **Table 3**.

Ten flavonoids were identified as having significant protective effects against Huntington's disease, including genistein, luteolin, hesperetin, hibiscetin, naringenin, baicalein, quercetin, tropoflavin (7,8-DHF), rutin, and anthocyanin (**Figure 2**). Each exhibited unique mechanisms of action but generally operated through a combination of antioxidant, anti-inflammatory, and anti-apoptotic effects, enhancement of neurotrophic factors, preservation of mitochondrial function, and repair of neuronal structures. Recent studies have shown that flavonoids can modulate key molecular pathways associated with neuronal survival by reducing oxidative stress and suppressing neuroinflammatory responses, which are major contributors to neuronal damage in neurodegenerative disorders.[10] In addition, flavonoids have been reported to regulate cellular stress responses and intracellular signaling pathways, thereby improving neuronal resilience and promoting neuroprotection in experimental models of neurodegeneration.[11] Furthermore, emerging evidence suggests that flavonoids can cross the blood–brain barrier and interact with multiple molecular targets involved in the pathogenesis of neurodegenerative diseases, including mitochondrial dysfunction, neuroinflammation, and toxic protein aggregation.[12] These compounds have also been reported to inhibit the accumulation of neurotoxic

protein aggregates and enhance neuronal survival, mechanisms that are particularly relevant for disorders such as Alzheimer's disease and Parkinson's disease.[13] Overall, the findings of the present review support these recent observations and further suggest that flavonoids may also reduce mutant huntingtin aggregation and improve neuronal function in Huntington's disease models.

Table 1. Study Quality Assessment.[14]

Study	Questions* Key: O Yes O No O Unclear									Scores
	1	2	3	4	5	6	7	8	9	
Pierzynowska et al. (2024)[15]	O	O	O	O	O	O	O	O	O	8
Mohammed et al. (2024) [16]	O	O	O	O	O	O	O	O	O	7
Etukuri & Avula (2024) [17]	O	O	O	O	O	O	O	O	O	9
Mahdi et al. (2023) [18]	O	O	O	O	O	O	O	O	O	8
Salman et al. (2022)[19]	O	O	O	O	O	O	O	O	O	8
Purushothaman & Sumathi (2022)[20]	O	O	O	O	O	O	O	O	O	6
Moghaddam et al. (2021)[21]	O	O	O	O	O	O	O	O	O	8
Barriga et al. (2017)[22]	O	O	O	O	O	O	O	O	O	6
Suganya & Sumathi (2017)[23]	O	O	O	O	O	O	O	O	O	7
Menze et al. (2016)[24]	O	O	O	O	O	O	O	O	O	7
Kreilaus et al. (2016)[25]	O	O	O	O	O	O	O	O	O	6
Møllersen et al. (2016)[26]	O	O	O	O	O	O	O	O	O	6

***QUESTIONS**

1. Is it clear in the study what is the cause' and what is the 'effect'?
2. Were the participants included in any similar comparisons?
3. Were the participants included in any comparisons receiving similar treatment/care other than the exposure or intervention of interest?
4. Was there a control group?
5. Were there multiple measurements of the outcome both before and after the intervention/exposure?
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?
7. Were the outcomes of participants included in any comparisons measured in the same way?
8. Were outcomes measured in a reliable way?
9. Was appropriate statistical analysis used?

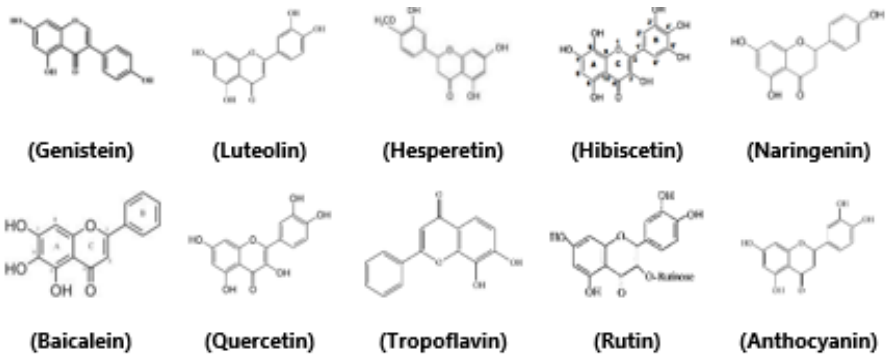

Figure 2. Type of Flavonoids.[27–36]

Genistein

Genistein is a naturally occurring isoflavone from the isoflavone subclass commonly found in soy products, has shown promise as a neuroprotective agent in Huntington's disease (HD). Studies have indicated that genistein can induce autophagy by activating the FOXO3 signaling pathway, which is essential for maintaining cellular homeostasis and managing stress responses. Specifically, genistein enhances FOXO3 expression, thereby promoting the activation of autophagy-related genes that facilitate the clearance of toxic mHTT aggregates and protect neurons from degeneration. Evidence from Pierzynowska et al. (2024) supports the role of genistein in improving cell viability and reducing motor deficits in HD models. These findings suggest that genistein's ability to activate FOXO3-mediated autophagy represents a targeted and potentially effective approach to counteracting the pathological mechanisms of HD, positioning it as a promising candidate for further therapeutic development.[15] In addition, Menze et al. (2016) found that genistein, particularly when combined with 17β-estradiol, enhanced neuroprotection by increasing PPI, ATP levels, and

antioxidant capacity, while reducing inflammation, apoptosis, gliosis, and hemorrhage. These findings reinforce genistein's broad therapeutic potential in HD-like models.[24] Despite these promising findings, notable methodological heterogeneity limits cross-study comparability and reduces confidence in the translational potential of genistein. The included studies employed fundamentally different disease models making it difficult to determine whether the observed benefits reflect true disease modification or model-specific neuroprotection. Additional inconsistencies, including differences in animal sex, substantial variation in dose and administration route, unequal treatment durations, and combination therapy with 17β-estradiol, further complicate interpretation. Moreover, the absence of plasma or brain genistein measurements leaves central nervous system exposure unverified.

Luteolin

Luteolin is a type of flavonoid, has also shown strong therapeutic potential in Huntington's disease (HD). A study by Mohammed et al. (2024) using the N171-82Q transgenic mouse model demonstrated that luteolin administration could extend lifespan, improve motor coordination, and reduce weight loss in HD mice. Notably, luteolin significantly reduced the accumulation of mHTT aggregates in key brain regions such as the cortex, hippocampus, and striatum, which correlated with improved neuronal integrity and motor function. The treatment also lowered serum levels of neurofilament light chain (NfL), further supporting its neuroprotective role.[16] These findings are consistent with previous research on the neuroprotective properties of flavonoids such as genistein and luteolin in Alzheimer's and Parkinson's diseases. The ability of these compounds to cross the blood-brain barrier, along with their multitargeted disease-modifying actions, makes them promising candidates for further development as therapeutic agents for HD.[37] Nevertheless, several limitations restrict translational relevance and cross-study comparability. The N171-82Q model expresses only an N-terminal mHTT fragment rather than the full-length protein, potentially altering aggregation dynamics and toxicity relative to human HD pathology. The exclusive use of male animals prevents assessment of sex-specific effects despite known sex differences in HD progression and luteolin's potential hormonal activity. Moreover, the lack of pharmacokinetic evaluation leaves luteolin's brain exposure uncertain, raising questions about whether the observed effects are centrally or peripherally mediated.

Hesperetin

Hesperetin is a flavanone found in citrus fruits, has shown neuroprotective effects in Huntington's disease (HD). Etukuri et al. (2024) demonstrated that hesperetin improved cognitive, motor, and psychiatric symptoms in 3-NP-induced HD animal models. These effects are linked to reduced oxidative stress, preserved mitochondrial function, and neuronal protection. Comparison of hesperetin with other flavonoids like luteolin, hibiscetin, and genistein reveals a consistent neuroprotective effect via antioxidant and anti-inflammatory mechanism.[17] Significant methodological constraints limit interpretability and generalizability. Reliance on the 3-NP toxin model induces acute striatal damage that does not reflect the progressive neurodegeneration and mHTT aggregation seen in human HD, potentially overstating hesperetin's neuroprotective effects. Male-only animals preclude evaluation of sex-specific responses. The 14-day oral treatment at 50 mg/kg without dose-response analysis or post-treatment follow-up is insufficient to assess long-term disease modification or therapeutic durability. Mechanistic evaluation was also limited, as key HD-related pathways including mitochondrial dysfunction, autophagy, and BDNF signaling were not examined. Furthermore, absence of stereological neuronal quantification and pharmacokinetic assessment of hesperetin weakens the evidence for neuroprotection and obscures whether the effects are centrally mediated.

Hibiscetin

Hibiscetin is a flavonoid derived from Hibiscus sabdariffa, has attracted considerable attention for its neuroprotective properties. In a 3-nitropropionic acid (3-NPA)-induced Huntington's disease (HD) rat model, Mahdi et al. (2023) found that hibiscetin significantly improved motor coordination, restored antioxidant enzyme levels (GSH, SOD, CAT, GPx), and modulated neurotransmitters such as serotonin, norepinephrine, and dopamine.[18] These effects suggest its role in counteracting oxidative stress and supporting neuronal function. Hibiscetin also reduced pro-inflammatory markers and caspase-3 activity, indicating anti-inflammatory and anti-apoptotic actions. These findings suggest its multi-pathway neuroprotection potentially offering therapeutic benefits. Substantial limitations constrain evidence quality and translational relevance. The 3-NP model in male Wistar rats does not reflect the genetic and progressive nature of human HD, limiting confidence in hibiscetin's efficacy. Male-only enrollment prevents evaluation of sex-specific responses. The short 15-day oral treatment at a single dose (10 mg/kg) without dose–response analysis or long-term follow-up precludes assessment of sustained neuroprotection or therapeutic optimization. Small sample size (n=6/group) reduces statistical power. Moreover, absence of behavioral testing, stereological neuronal

quantification, pharmacokinetic evaluation, and comparison with standard HD therapies weakens the functional and translational interpretation of hibiscetin's reported neuroprotective effects.

Naringenin

A citrus flavonoid shown to exert neuroprotective effects in HD-like models by targeting multiple pathological mechanisms. Salman et al. (2022) found that in 3-NP-induced HD rats, naringenin improved motor and behavioral outcomes, restored MAO activity and serotonin levels, and reduced striatal neuronal loss and astrocytic activation. Its effects are attributed to antioxidant, anti-inflammatory, and anti-apoptotic actions that preserve mitochondrial and neuronal function.[19] The use of a 3-NP-induced model in male Wistar rats produces acute striatal toxicity that does not adequately represent the chronic and progressive neurodegeneration observed in genetic Huntington's disease, which may lead to an overestimation of naringenin's therapeutic potential. The exclusive use of male animals also prevents evaluation of possible sex-specific responses. Furthermore, the prophylactic 28-day intervention conducted before and after 3-NP exposure has limited clinical relevance and lacks clear dose. Mechanistic understanding also remains incomplete because several key HD-related pathways, including BDNF signaling, mitochondrial function, and autophagy, were not investigated. In addition, the absence of cognitive assessments, pharmacokinetic profiling, stereological neuronal quantification, and comparison with established HD therapies further weakens the functional and translational interpretation of the reported neuroprotective effects of naringenin.

Baicalein

The study by Purushothaman & Sumathi (2022) highlights baicalein's strong neuroprotective potential against quinolinic acid (QA)-induced Huntington's-like symptoms in rats. QA induced weight loss, motor impairments, and oxidative stress, while baicalein (30 mg/kg) effectively restored body weight, improved motor performance, and reversed oxidative damage by boosting antioxidant enzymes (SOD, CAT, GSH) and reducing oxidative stress markers (MDA, NO). Baicalein also restored mitochondrial function, ATPase activity, and striatal cell integrity. Notably, it upregulated neurotrophic factors (BDNF, GDNF) and preserved TH-positive neurons, supporting its role in neuronal survival and synaptic repair. These findings position baicalein as a promising therapeutic candidate for neurodegenerative diseases like Huntington's.[20]

Important methodological limitations constrain interpretation and generalizability. The QA-induced model in male Wistar rats produces rapid excitotoxic striatal lesions that differ from mHTT-mediated neurodegeneration in genetic Huntington's disease, limiting translational relevance. The exclusive use of male animals prevents evaluation of potential sex-specific responses. Although baicalein was administered intraperitoneally at 10 and 30 mg/kg for 21 days, this route ensures high bioavailability but reduces clinical applicability for long-term HD therapy. In addition, the limited dose exploration, short treatment duration, and immediate post-treatment assessment restrict conclusions regarding sustained neuroprotection, disease modification, and long-term safety. Mechanistic understanding also remains incomplete because pharmacokinetic evaluation, detailed cognitive assessments, and comparison with standard HD therapies were not performed. Furthermore, deeper investigations into receptor targets, signaling pathways, and gene expression were lacking, leaving the mechanistic basis of baicalein's reported neuroprotective effects uncertain.

Quercetin

Elderberry contains flavonoids like quercetin, known for strong antioxidant and anti-inflammatory properties that help reduce oxidative stress and inflammation in Huntington's disease (HD). Moghaddam et al. (2021) reported that an elderberry-rich diet improved motor coordination, cognitive function, and neuronal density in HD rat models. It also enhanced glutathione (GSH) levels and reduced ROS and caspase 3, supporting neuronal survival.[21] However, several methodological concerns substantially undermine evidence quality and attribution certainty. The 3-NP-induced model in male Wistar rats generates acute striatal toxicity that does not reflect the genetic and progressive pathology of human Huntington's disease, potentially overestimating the therapeutic efficacy of quercetin. The exclusive use of male animals also precludes evaluation of sex-specific responses. Moreover, the dietary administration of a 2% elderberry diet for eight weeks introduces significant confounding because elderberry contains multiple flavonoids and the actual quercetin intake may vary among animals. The lack of pharmacokinetic assessment further obscures quercetin's bioavailability and CNS exposure. Although extensive phenotypic and mechanistic parameters were evaluated, the toxin model prevented assessment of mHTT aggregation, limiting relevance to genetic HD. In addition, the absence of standardized flavonoid content, post-treatment follow-up, and comparison with purified quercetin or standard HD therapies restricts dose–response interpretation and efficacy benchmarking. The lack of validation in genetic HD models further limits confidence in the translational potential of elderberry-derived quercetin.

Tropoflavin (7,8-dihydroxyflavone)

The study from Barriga et al., (2017) provides strong evidence for the therapeutic potential of 7,8-dihydroxyflavone (7,8-DHF) in improving both cognitive and motor impairments in a Huntington's disease (HD) mouse model via a distinctive mechanism of selective TrkB receptor activation. Unlike brain-derived neurotrophic factor (BDNF), which activates TrkB signaling more broadly, 7,8-DHF specifically phosphorylates the Y816 residue of TrkB, thereby engaging the PLCγ1 pathway in a targeted manner. This selective activation leads to marked morphological benefits, including increased neurite complexity and improved striatal network function. In vitro experiments showed that 7,8-DHF induced a distinctive, synchronized neuronal firing pattern, successfully restoring activity in HD cultures. In vivo, long-term administration of 7,8-DHF in R6/1 mice delayed the progression of motor deficits and reversed cognitive decline. Histological analysis revealed partial recovery of striatal architecture, elevated enkephalin expression, and reduced mutant huntingtin aggregates. Importantly, 7,8-DHF also exerted TrkB-independent effects, including modulation of nitric oxide synthase activity and suppression of p75 upregulation, suggesting additional anti-inflammatory and antioxidant properties. These combined actions may work synergistically with its TrkB-mediated effects, enhancing its overall neuroprotective profile.[22]

Reliance on the R6/1 transgenic mouse model restricts generalizability across different HD models, and validation in knock-in or full-length mHTT models would strengthen translational relevance. The exclusive use of male animals also prevents evaluation of potential sex-specific responses. The intervention design further limits interpretability, as single-dose administration of tropoflavin (5 mg/kg/day) from 8 to 20 weeks precludes dose–response analysis and does not reflect the clinical scenario in which treatment begins after symptom onset. Behavioral assessment was also limited to novel object recognition and rotarod tests, without comprehensive evaluation of other HD-related phenotypes. Additionally, unclear sample sizes, lack of pharmacokinetic measurements, and absence of comparisons with standard HD therapies or reference TrkB agonists weaken confidence in efficacy interpretation. Mechanistic understanding also remains incomplete because potential TrkB-independent effects and alternative signaling pathways were not explored, necessitating cautious interpretation of tropoflavin's therapeutic potential.

Rutin

Rutin is a plant-derived flavonoid, protects against 3-nitropropionic acid–induced Huntington's disease–like damage in rats. In the study of Suganya and Sumathi (2017) stated that at 50 mg/kg, rutin improved motor and memory performance, restored antioxidant levels, reduced oxidative/nitrosative stress, and normalized acetylcholinesterase activity. Histology confirmed reduced neuronal loss, inflammation, and astrocyte activation. These benefits likely result from its combined antioxidant, anti-inflammatory, anti-apoptotic, and anticholinesterase actions, making rutin a promising natural therapy for HD-like neurodegeneration caused by mitochondrial toxicity.[23] The 3-NP-induced model in male Wistar rats generates acute striatal excitotoxicity that does not adequately represent the genetic and progressive pathology of human Huntington's disease, potentially overestimating rutin's therapeutic efficacy. The exclusive use of male animals also prevents evaluation of sex-specific responses. Furthermore, the short intervention period (14 days) with only two oral doses limits conclusions regarding long-term neuroprotection, disease modification, and optimal dosing. The absence of pharmacokinetic evaluation further obscures rutin's bioavailability and CNS exposure, particularly given its limited oral absorption. In addition, lack of comparisons with standard HD therapies, absence of exposure–effect correlation, and limited mechanistic exploration beyond oxidative stress and inflammatory markers weaken confidence in the translational potential of rutin without further validation.

Anthocyanins

Both study from F. Kreilaus et al., 2016 and Møllersen et al., 2016 indicate that dietary supplementation with anthocyanins, plant-derived flavonoids found in berries, may confer neuroprotective effects in HD models. In female R6/1 mice, anthocyanin supplementation delayed motor deficits, reduced oxidative stress, and decreased CAG repeat instability that could slow disease progression. Benefits were more pronounced in females, possibly due to hormonal influences such as estrogen and BDNF. While molecular and physiological improvements were observed, behavioral gain, such as enhanced cognition or reduced anxiety were limited. Sex-specific responses and study constraints (small sample sizes, varying doses, and treatment durations) highlight the need for personalized therapeutic approaches and further research.[25,26] Although both studies employed the R6/1 transgenic mouse model, their treatment windows differed, capturing distinct stages of disease progression. Kreilaus administered blackcurrant extract in the diet for 20 weeks, whereas Møllersen provided a bilberry–blackcurrant anthocyanin mixture through drinking water for 18 weeks, resulting in differences in anthocyanin composition, dosage, and delivery method that hinder direct comparison. Outcome measures also diverged, with Kreilaus reporting sex-specific motor improvements and delayed clasping, while

Møllersen observed reduced CAG repeat instability but no significant behavioral benefits. These inconsistent findings may reflect differences in dosing, anthocyanin source, treatment timing, or outcome sensitivity. Furthermore, neither study quantified brain anthocyanin concentrations, leaving central nervous system exposure uncertain, and variable intake through diet or drinking water likely introduced additional exposure variability. The absence of standardized anthocyanin composition, mechanistic investigations beyond cholesterol metabolism or CAG instability, and lack of comparison with standard HD therapies further limit interpretation. Collectively, these methodological inconsistencies and gaps necessitate cautious interpretation of anthocyanins' therapeutic potential in HDl.

Table 2. Neuroprotective Effect of Flavonoid in Animal Models of Huntington's disease

Authors, Years	Type of Flavonoids	Animal Model; Ages/BW	Dose; Duration of Treatment	Evaluated Parameters	Outcome	Limitation
Pierzynowska et al., (2024)[15]	Genistein	R6/1 mice; Start at 16 weeks	150 mg/kg/day, oral; Until 24 weeks	Behavioral tests, Inflammation markers, Autophagy markers, Western Blot, and Histology	↑Cognition, ↑motor function, ↓mHTT aggregates, ↓inflammatory cytokines, ↑autophagy markers, ↑lysosome abundance, ↑FOXO3 nuclear translocation	- Only male R6/1 mice were used, limiting applicability to females despite HD affecting both sexes equally.
Mohammed et al., (2024)[16]	Luteolin	N171-82Q HD transgenic mice; Start at 6 weeks	20 mg/kg, i.p.; every other day until 34–36 weeks (~18–20 weeks)	Behavioral tests NfL ELISA, Immunohistochemistry, and Western Blot	↑Motor performance, ↑balance, ↑survival, ↓body weight loss, ↓serum NfL, ↓Htt aggregates in brain regions	- Gender-specific effects of luteolin were not assessed as only male mice were used. - N171-82Q mice express truncated mHTT, limiting its representation of full human HD pathology
Etukuri & Avula, (2024)[17]	Hesperetin	3-nitropropionic acid (3-NP)-induced HD in male Wistar rats; BW 180–220 gr	50 mg/kg/day, oral; 14 days	Behavioral Tests, Biochemical Markers (SOD, CAT, LPO, GSH, SDH, Acetylcholinesterase activity), Neurochemical Analysis (GABA, Glutamate	↑ Behavioral activity, ↓ oxidative stress (↓ MDA), ↑ antioxidant levels (↑ SOD, ↑ CAT, ↑ GSH), ↓ inflammatory markers (↓ TNF-α, ↓ IL-1β), ↓ neuronal damage, and ↑ histological integrity in striatum and cortex.	- No long-term follow-up was conducted to assess the sustained protective effects of hesperetin after treatment cessation. - The study did not include dose-response evaluation beyond the two administered dosages, limiting optimization insights.
Mahdi et al., (2023)[18]	Hibiscetin	Wistar Rats Male; BW 180 ± 20 gram; usually 6-8 weeks	10 mg/kg, oral; 15 days	Oxidative stress markers, Monoamines, BDNF, and Inflammation markers.	↓ LPO, ↑ GSH, SOD, CAT, GR, GPx; ↓ TNF-α, IL-1β, MPO; ↑ BDNF; ↓ caspase-3 activity; normalization of DA, NE, 5-HT, GABA; ↓ Glutamate, DOPAC, HVA, 5-HIAA;	- Small sample size (n = 6) per group may reduce statistical power and generalizability.
Salman et al., (2022)[19]	Naringenin	Male Wistar rats; 200–250 gr (adult)	50 & 100 mg/kg BW/day; 14 days before + 14 days after 3-NP	Motoric Test, Biochemical analysis; Immunohistochemistry analysis.	↑ locomotor activity, ↓ oxidative stress (↑SOD, CAT, GPx), ↓ MDA, ↓ neuroinflammation (↓IL-1β, TNF-α), ↑ neuroprotection, ↑ cognitive and motor functions.	- Short duration of treatment may not represent long-term neuroprotective effects. - No comparison to standard HD therapy or other flavonoids, difficult to benchmark efficacy.

Authors, Years	Type of Flavonoids	Animal Model; Ages/BW	Dose; Duration of Treatment	Evaluated Parameters	Outcome	Limitation
Purushothaman & Sumathi, (2022)[20]	Baicalein	QA-induced male wistar rats; 3 months/ 200-250 g	10 & 30 mg/kg/day, i.p.; 21 days	Behavioral tests Biochemicals; ELISA; Histology TH-IHC	↓LPO, NO, MDA; ↑SOD, CAT, GSH, BDNF, GDNF; ↓neuroinflammation; ↑motor & cognitive function; ↓neuronal death; ↑TH expression	- Long-term molecular mechanisms are not fully explored. - Sex-based responses not analyzed
Moghaddam et al., 2021[21]	Quercetin (from Elderberry)	3-NP-induced HD in Wistar rats Male; 180–220 g; 8–9 weeks old	2% elderberry diet, oral; 8 weeks	Rotarod, Open field, EMG, Striatal volume, Neuronal & glial cell density, IHC (Iba-1), ROS, GSH, TNF-α, caspase-3, Sholl analysis	↑ Motor coordination; ↑ Locomotion; ↑ Anxiety reduction (open field); ↑ EMG activity; ↑ Striatal volume; ↑ Neuron density; ↓ Glial cell count; ↓ Microgliosis; ↑ Microglial process length & complexity; ↓ ROS; ↑ GSH; ↓ Caspase-3; ↓ TNF-α	- No genetic HD model used (only 3-NP) - Only male rats included (sex-specific effects untested) - No direct measurement of mHTT aggregation - Did not assess long-term persistence after stopping treatment - Dietary intake could vary between rats - Flavonoid content not standardized by concentration per compound
Barriga et al., (2017)[22]	Tropoflavin	R6/1 HD transgenic mice; Starting at 8 weeks (pre-symp)	5 mg/kg/day, oral; Until 20 weeks	NORT; Rota-rod; Primary striatal neuronal cultures; Immunocytochemical staining and branching analysis; Immunohistochemistry; Western blot.	↑Cognition (NORT); ↑Motor (rotarod); ↓mHTT aggregates; ↑enkephalin; ↑TrkB-Y816/PLCc1; ↓iNOS, p75	- Limited model/design – Single mouse model, male-only, no dose–response, unclear sample sizes. - Narrow scope – Few behavioral tests, no long-term safety data. - Mechanistic gaps – TrkB-independent, PLCγ1, and off-target effects unexplored.
Suganya & Sumathi, (2017)[23]	Rutin	Male Wistar rats; 200–250 g	25 & 50 mg/kg BW, oral; 14 days	Body weight, Behavior test, Antioxidant activity test, nitrite, AchE, GFAP (IHC), H&E histology	↑Motor & memory; ↑SOD, CAT, GPx, GR, GST, GSH; ↓LPO, nitrite, AchE; ↓GFAP; ↓striatal damage	- No long-term follow-up for sustained effects or disease progression. - Flavonoid bioavailability variability not addressed.
Menze et al., (2016)[24]	Genistein in combine with 17b-estradiol	Sprague Dawley rats/Crl:CD(SD) Female; 2 months	20 mg/kg, i.p.; 8 days (4 days before + 4 days with 3-NPA) 8 days	Behavior test, ATP levels; Biodiagnostics, El-Doki; PGE2 levels; Western blot, Immunohistochemical.	↑ %PPI, ↑ ATP, ↑ total antioxidant capacity, ↓ PGE2, ↓ Bax/Bcl-2 ratio, ↓ caspase-3 expression, ↓ iNOS & COX-2, ↓ gliosis and hemorrhage;	- Short treatment duration (8 days) may not reflect long-term effects or safety of genistein. - Genistein-only group was not consistently included in all biochemical analyses.
Kreilaus et al., (2016)[25]	Anthocyanin	R6/1 transgenic mice;	Blackcurrant extract 0.48 g anthocyanin/kg	Behavior test, weight, brain mass, GC-MS sterol analysis	↑ motor performance (♀), ↓ onset clasping (♂), no	- Antioxidant action not clear in brain

Authors, Years	Type of Flavonoids	Animal Model; Ages/BW	Dose; Duration of Treatment	Evaluated Parameters	Outcome	Limitation
		6-26 weeks	diet, orally, continuous for 20 weeks		effect on cholesterol metabolism or brain mass	
Møllersen et al., (2016)[26]	Anthocyanin	R6/1 transgenic mice	Medox® capsules (bilberry + blackcurrant), ~300 mg/kg/day orally via drinking water, from week 4 to week 22	CAG repeat length, behavior test, body weight monitoring	↓ CAG repeat instability in cortex and ear; No significant behavioral improvement; ↑latency to fall (trend)	- Anthocyanin levels in brain not measured; possible timing limitations

Abbreviation:
HD: Huntington's disease; BW: body weight; mHTT: mutant huntingtin protein; NfL: neurofilament light chain; ELISA: enzyme-linked immunosorbent assay; 3-NP: 3-nitropropionic acid; SOD: superoxide dismutase; CAT: catalase; LPO: lipid peroxidation; GSH: reduced glutathione; SDH: succinate dehydrogenase; GABA: gamma-aminobutyric acid; MDA: malondialdehyde; TNF-α: tumor necrosis factor alpha; IL-1β: interleukin-1 beta; GR: glutathione reductase; GPx: glutathione peroxidase; MPO: myeloperoxidase; BDNF: brain-derived neurotrophic factor; DA: dopamine; NE: norepinephrine; 5-HT: serotonin; DOPAC: 3,4-dihydroxyphenylacetic acid; HVA: homovanillic acid; 5-HIAA: 5-hydroxyindoleacetic acid; QA: quinolinic acid; NO: nitric oxide; GDNF: glial cell line-derived neurotrophic factor; TH: tyrosine hydroxylase; IHC: immunohistochemistry; NORT: novel object recognition test; TrkB: tropomyosin receptor kinase B; PLCγ1: phospholipase C gamma 1; iNOS: inducible nitric oxide synthase; p75: p75 neurotrophin receptor; AchE: acetylcholinesterase; GFAP: glial fibrillary acidic protein; H&E: hematoxylin and eosin; GST: glutathione S-transferase; PPI: prepulse inhibition; ATP: adenosine triphosphate; PGE2: prostaglandin E2; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; COX-2: cyclooxygenase-2; GC-MS: gas chromatography–mass spectrometry; CAG: cytosine-adenine-guanine trinucleotide repeat.

This review highlights the strong neuroprotective potential of flavonoids in the context of Huntington's disease (HD), as demonstrated across multiple animal models. In the 12 studies analyzed, flavonoids consistently improved both behavioral symptoms and molecular markers of HD. Enhancements in motor coordination, cognitive function, and behavioral stability were accompanied by biochemical changes, including reduced oxidative stress, decreased neuroinflammation, inhibition of apoptosis, and restoration of mitochondrial function. Several flavonoids also promoted neurotrophic factor activity and increased autophagy, aiding in the clearance of mutant huntingtin aggregates. The variety of mechanisms includes antioxidant and anti-inflammatory actions (e.g., rutin, quercetin, naringenin) as well as specific molecular targets such as FOXO3 activation by genistein or selective TrkB receptor activation by 7,8-dihydroxyflavone.

Table 3. The Roles of Flavonoids in the Improvement of Huntington's Disease (HD)

Roles of Flavonoids	Study
↓ CAG	Møllersen et al., 2016
↑Autophagy activity/↓mHTT /Htt aggregate	Pierzynowska et al., 2024; Mohammed et al., 2024; Barriga et al., 2017
↓ Apoptosis	Mohammed et al., 2024; Purushothaman & Sumathi, 2022; Moghaddam et al., 2021; Menze et al., 2016
↑ Neurotropic/ dopaminergic	Mahdi et al., 2023; Purushothaman & Sumathi, 2022; Barriga et al., 2017
Protection structural of the brain (↑ striatal volume, neuron density; ↓ gliosis, glial cell)	Etukuri & Avula, 2024; Salman et al., 2022; Moghaddam et al., 2021; Suganya & Sumathi, 2017; Menze et al., 2016
↑Motor function/behavioral activity	Pierzynowska et al., 2024; Mohammed et al., 2024; Etukuri & Avula, 2024; Salman et al., 2022; Purushothaman & Sumathi, 2022; Moghaddam et al., 2021; Barriga et al., 2017; Suganya & Sumathi, 2017; Kreilaus et al., 2016; Møllersen et al., 2016
↑Cognitive	Pierzynowska et al., 2024; Salman et al., 2022; Purushothaman & Sumathi, 2022; Barriga et al., 2017; Suganya & Sumathi, 2017
↑ ATP/ reflex and neuronal complexity	Moghaddam et al., 2021; Menze et al., 2016
↓ Oxidative stress/↑Antioxidant	Mahdi et al., 2023; Etukuri & Avula, 2024; Salman et al., 2022; Purushothaman & Sumathi, 2022; Moghaddam et al., 2021; Barriga et al., 2017; Suganya & Sumathi, 2017; Menze et al., 2016
↓Inflammatory cytokines	Pierzynowska et al., 2024; Mahdi et al., 2023; Etukuri & Avula, 2024; Moghaddam et al., 2021; Salman et al., 2022; Purushothaman & Sumathi, 2022

Limitation

Despite these promising outcomes, several limitations remain. All included studies were conducted in animal models, which, while critical for mechanistic insights, cannot fully replicate the complexity of HD in humans. Variations in study design, flavonoid dosage, treatment duration, and disease induction methods complicate direct comparisons. Furthermore, sex-specific responses, long-term effects after treatment cessation, and possible interactions with standard HD therapies have not been extensively explored. Overall, the evidence positions flavonoids as promising candidates for further HD therapy development. However, translation into clinical applications will require rigorous human trials to determine pharmacokinetics, optimal delivery methods, dosage safety, and long-term therapeutic potential.

CONCLUSION

Huntington's disease (HD) is a progressive neurodegenerative disorder with limited therapeutic options, resulting in substantial health and socioeconomic burdens. The current therapeutic landscape remains characterized by a critical lack of disease-modifying agents, highlighting the need for strategies that target multiple pathogenic pathways simultaneously. Evidence synthesized from animal studies indicates that flavonoids may represent such a multi-target approach. Preclinical findings demonstrate that flavonoids can improve motor and cognitive functions, enhance antioxidant defenses, reduce oxidative stress and neuroinflammation, and preserve neuronal integrity. These neuroprotective effects are largely attributed to their antioxidant, anti-inflammatory, anti-apoptotic, and neurotrophic properties, suggesting that flavonoids may act on upstream pathological mechanisms rather than merely alleviating downstream symptoms. These findings provide a critical foundation for future translational studies and clinical trials aimed at validating efficacy, optimizing dosing strategies, and ensuring long-term safety, ultimately contributing to the development of more effective and comprehensive therapeutic interventions for HD.

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AUTHOR CONTRIBUTION STATEMENT

Sang Ayu Arta Suryantari: Conceptualization, Methodology, Literature Search, Data Curation, Writing—Original Draft; **Anak Agung Intan Pramesti**: Literature Search, Data Curation, Writing—Reviewing and Editing; **I Made Suma Wirawan**: Methodology, Study Selection, Quality Assessment, Writing—Reviewing and Editing; **I Gusti Ngurah Mambal Wirajangsa**: Quality Assessment, Data Interpretation, Writing—Reviewing and Editing; **I Wayan Yudha Wedantha**: Supervision, Methodological Review, Validation; **Ni Putu Elisya Nathania Fidela**: Literature Search, Data Interpretation, Writing—Reviewing and Editing.

CONFLICT OF INTEREST DECLARATION

The authors declare no conflict of interest.

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