Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

NQO2 Inhibitors

Evidence Summary

Higher NQO2 levels are associated with neurodegenerative diseases. Reduction of NQO2 is associated with learning in mice. NQO2 may have both beneficial or harmful functions depending on the context.

Neuroprotective Benefit: AD and PD appear to be associated with higher levels of NQO2, but the association may be stage-dependent. NQO2-/- mice learn better but NQO2 inhibition has inconsistent effects on cognitive function in a mouse model of AD.

Aging and related health concerns: Higher NQO2 expression is associated with lower risk of breast cancer, suggesting a possibility that NQO2 inhibition may increase risk. The associations between NQO2 activity and other cancers are less established.

Safety: There is theoretical concern that chronic NQO2 inhibition may promote some cancers. No selective NQO2 inhibitors have been tested in humans to date, but natural compounds that inhibit NQO2 have generally been safe (resveratrol, melatonin, etc.).

Availability: not approved for any indication; some inhibitors have been tested in preclinical studies.	**Dose**: No selective NQO2 inhibitors have been tested in humans.	**Chemical formula:** N/A **MW**: N/A
Half-life: N/A	**BBB**: N/A	
Clinical trials: No clinical trials have tested NQO2 inhibitors to date, other than natural products that have inhibitory effects on NQO2 as one of their mechanisms (e.g., resveratrol, melatonin).	**Observational studies**: None with NQO2 inhibitors. Observational studies of NQO2 genetic variants have included over a thousand participants.	

What is it?

Dihydronicotinamide riboside(NRH):quinone oxidoreductase 2 (NQO2), also known as quinone reductase 2 (QR2), is an enzyme that catalyzes two-electron reductions of quinones, pseudoquinones, and other related electron acceptors including a wide range of antitumor drugs (reviewed in Janda et al., 2024). NQO2 has a structural similarity with the more extensively studied NQO1; however, an important difference is that NQO1 utilizes classical electron donors such as NADH or NADPH as a co-substrate, while NQO2 does not and is considered an atypical oxidoreductase, utilizing electron donors such as N-methyldihydronicotinamide (NMH) and N-ribosyldihydronicotinamide (NRH).

NQO2 activity has been associated with both detoxifying and toxifying functions, depending on the substrate, cell type, expression, and activity of other detoxifying enzymes (Janda et al., 2020). NQO2 is involved in the detoxification of quinone derivatives of catecholamines (e.g., dopamine, noradrenaline), catalyzing a two-electron reduction of para-quinones, ortho-quinones, and pseudoquinones. This reaction can be protective or harmful depending on whether the reduced products are safely cleared or reoxidized into reactive oxygen species-generating cycles. For example, quinols (hydroquinones) formed during this reaction can undergo autooxidation to semiquinones, which can transfer their unpaired electron to other oxidants, including molecular oxygen, producing superoxide anion radicals. Another

example of a toxifying function of NQO2 is the binding of acetaminophen and mediation of acetaminophen-induced superoxide production in cultured cells (Miettinen and Bjorklund, 2014).

It is not clear whether the main function of NQO2 is the catalytic reduction of quinones or whether it is a pseudo-enzyme with other roles such as cell signaling (reviewed in Islam et al., 2025). NQO2 binds the FAD cofactor and can exist in either an oxidized or reduced state. It is possible that NQO2 plays a greater role as a redox sensor and regulator rather than reduction of quinones and electrophiles.

There are currently no selective NQO2 inhibitors on the market for any indication. Many drugs and supplements have non-selective (or off-target) inhibitory effects on NQO2, including resveratrol, quercetin, melatonin, hydroxychloroquine, nilotinib, and imatinib. Highly selective NQO2 inhibitors have been developed and tested in animal and cell models of Alzheimer's disease (Gould et al., 2023) and Parkinson's disease (Valluci et al., 2024), but there are no peer-reviewed publications of clinical trial data to date.

Neuroprotective Benefit: AD and PD appear to be associated with higher levels of NQO2, but the association may be stage-dependent. NQO2-/- mice learn better but NQO2 inhibition has inconsistent effects on cognitive function in a mouse model of AD.

Types of evidence:

- 0 clinical trials
- 7 observational studies linking NQO2 protein levels or genetic variants with disease
- Numerous laboratory studies
- Numerous reviews

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No studies have tested the efficacy of selective NQO2 inhibitors for the prevention of dementia or age-related cognitive decline.

In a cohort study of 722 Caucasian community-dwelling non-demented older people over the age of 50, a functional non-synonymous coding single nucleotide polymorphism (SNP; rs1143684) within the NQO2 gene exon 3 was nominally associated with decline in delayed memory (p=0.029)(Payton et al., 2010).

There were no associations between this SNP and fluid intelligence or processing speed. It is not clear how this SNP affects NQO2 function.

Human research to suggest benefits to patients with dementia:

Selective NQO2 inhibitors have not been tested in dementia patients.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Across species including humans, NQO2 is expressed abundantly in the brain, particularly in the cortex and hippocampus (Benoit et al., 2010).

Studies in humans: In a postmortem study of 20 Alzheimer's disease and 13 age-matched control brains, NQO2 protein levels were significantly higher in the hippocampus of Alzheimer's disease brains compared to controls ($p<0.001$)(Hashimoto and Nakai, 2011). No significant differences in NQO2 protein levels between Alzheimer's disease and control brains were found for two other brain regions: the superior frontal gyrus and amygdala. There were no significant sex differences in the levels of NQO2 protein.

In a postmortem study of 27 Alzheimer's disease and 11 control brains, NQO2 mRNA levels in the frontal cortex (Brodmann area 8) were more than two-fold in Alzheimer's disease compared to controls ($p=0.034$)(Rappaport et al., 2015).

In an observational study of 111 Parkinson's disease and 100 healthy controls, polymorphism in the form of an insertion or deletion of 29 base pairs in the promotor region of the NQO2 gene was associated with Parkinson's disease (Harada et al., 2001). The frequency of the 29-base pair deletion, which results in higher NQO2 gene expression, was significantly higher in Parkinson's disease patients than in controls (OR=3.463; $p<0.0001$). Other NQO2 polymorphisms, including nucleotide substitutions (747A→G, 938A→C, and 11094T→C), missense mutation (Phe47Leu), and silent mutation (Pro110Pro) showed no differences in genotype/allele frequencies between Parkinson's disease and controls. In a case-control study of 118 Parkinson's disease patients and 80 age-matched control individuals, the same 29-base pair deletion of the NQO2 promotor occurred at a higher frequency in Parkinson's disease than in age-matched control individuals (Wang et al., 2008). However, in a larger population-based case-control study of 190 idiopathic Parkinson's disease patients and 305 unrelated controls, no associations with Parkinson's disease were detected for NQO2 polymorphisms (Okada et al., 2005).

Analyses of the Gene Expression Omnibus (GEO) datasets of Affymetrix Human Genome arrays revealed relationships between NQO2 expression and Parkinson's disease that appeared to depend on the stage of illness (Janda et al., 2023). In an analysis of whole blood of 50 early-stage Parkinson's disease patients compared to 22 healthy donors, NQO2 expression was highly variable and non-normally distributed in early Parkinson's disease with most cases (73%) showing a higher NQO2 expression than the healthy patients. In a smaller dataset of 10 Parkinson's cases and 9 controls, a higher median NQO2 expression was observed in white blood cells of Parkinson's disease patients compared to controls, though the difference was not statistically significant. In a postmortem brain specimen analysis of 24 late-stage Parkinson's disease cases and 16 controls, NQO2 expression was significantly lower in the lateral and medial substantial nigra in Parkinson's brains compared to healthy donor brains ($p=0.04$). In this study, 71% of Parkinson's cases showed lower NQO2 expression compared to the mean of control cases.

Studies of normal rodents: In mice, novel contextual stimuli results in dopamine D1 receptor-activation that leads to upregulation of miR-182, which suppresses QR2 locally (e.g., in the CA1), leading to enhanced memory observed with novelty (Gould et al., 2020). Performance on the novel object recognition in mice is improved by reduced QR2 expression in inhibitory interneurons, without affecting excitatory neurons, with a net effect of lessening inhibition. In aged mice, QR2 mRNA levels are slightly increased in the hippocampal CA1, while miR-182 is significantly decreased compared to young mice (Gould et al., 2020).

In mice, trace fear conditioning (which relies on the dorsal hippocampus for memory formation) significantly reduced QR2 expression in the hippocampal CA1 region 3 hours later (Gould et al., 2020).

Moving mice from their home cages into a novel context cage also significantly reduced QR2 mRNA in the CA1 (Gould et al., 2020).

In rats, conditioned taste aversion learning leads to a ~50% reduction in QR2 mRNA in the insular cortex compared to the control group (Rappaport et al., 2015). Novel taste learning also led to a ~50% reduction in QR2 mRNA expression compared to rats exposed to a familiar taste. Reduction of QR2 expression associated with better learning and memory required the activation of muscarinic acetylcholine receptors (mAChR).

Studies of NQO2 deletion or knockdown: Mice deficient in QR2 (QR2-/- mice) showed better learning abilities on the Morris water maze (measured by shorter latency to locate the hidden platform)

compared to wild-type littermates (Benoit et al., 2010). QR2-/- mice exhibited similar learning performance as the wild-type littermates in the probe test of the water maze, measured by the time spent in the target quadrant and the amount of time they crossed the platform location. QR2-/- mice performed significantly better than their wild-type littermates on the novel object recognition test and rotarod test (measuring motor function). There were no differences between QR2-/- and wild-type littermates in measures of sensorimotor gating (prepulse inhibition), anxiety (elevated plus maze), or depression (forced swim test).

When QR2 expression was reduced using a lentiviral vector expression of QR2 shRNA stereotaxically injected in the rat insular cortex, novel taste learning was significantly enhanced (Rappaport et al., 2015).

In mice injected a QR2 shRNA into the hippocampal CA1, greater freezing was seen in response to the context, tone, and trace in the trace fear conditioning paradigm, indicating improved memory of the learned experience (Gould et al., 2020).

In human cell culture (HCT116 cells), deletion of NQO2 produced a shift in the proteome that opposed that found in Alzheimer's disease (Gould et al., 2023). Specifically, deletion of NQO2 increased the expression of mitochondrial mRNA translation and oxidative phosphorylation proteins, while decreasing levels of reactive oxygen species and proteins involved in glycolysis and the pentose phosphate pathway. Other proteins down-regulated by the deletion of NQO2 were involved in cell-cell junction and cell-matrix interactions. In HCT116 cells, treatment with 20 µM of an NQO2 inhibitor (YB-800) significantly reduced reactive oxygen species 3 hours later, while no effect was seen in HCT116 cells with NQO2 deleted.

Studies of NQO2 inhibitors: In a rat model of cognitive dysfunction (induced by scopolamine), chronic intracerebroventricular injection of an QR2 inhibitor (S26695; 8 mg/kg via osmotic minipumps) significantly reversed scopolamine-induced impairment in spatial memory, measured by the Morris water maze task (Benoit et al., 2010).

In mice with a QR2 inhibitor (S29434) infused into the hippocampal CA1 via an implanted cannula 20 minutes before trace fear conditioning, greater freezing was seen in response to the context, tone, and trace, suggesting improved hippocampal memory (Gould et al., 2020). S29434 treatment also significantly reduced the oxidation ratio of a potassium channel, Kv2.1, suggesting a slight reduction in reactive oxygen species in the CA1.

Treatment with synthetic QR2 inhibitors, S29434 and S26695, significantly improved novel taste learning in rats (Rappaport et al., 2015).

In wild-type mice, administration of S29434 (i.p.) 30 minutes before acquisition of the object recognition test led to improved performance on the test, measured by an increase in time of exploration of the unfamiliar object (Boutin et al., 2019).

In rats, microinjection of an NQO2 inhibitor (YB-808; 1 µL of 20 µM) into the anterior insular cortex (the primary gustatory cortex) resulted in a stronger memory of taste than the vehicle-injected group (Gould et al., 2023). In mice, microinjection of an NQO2 inhibitor (YB-537; 1 µL of 5 µM) to the hippocampal CA1 region showed significantly increased freezing in the fear conditioning test, indicating enhanced hippocampal-dependent memory. YB-537 shows greater than 6,000-fold higher binding affinity to NQO2 than to NQO1. YB-537 is water-soluble, 82% orally bioavailable, and crosses the blood-brain barrier in mice. The clearance half-life in mice is approximately 1 hour after acute oral dosing.

5-Methoxy-3-(5-methoxyindolin-2-yl)-1H-indole, referred to as 'compound 3', is a low nanomolar inhibitor of QR2 (IC50 = 7.7 nM), with greater potency than melatonin and comparable efficacy to other potent QR2 inhibitors tested to date (Herrera-Aronzamena et al., 2024). Compound 3 also inhibits monoamine oxidase A and B (MAO-A and MAO-B) and LOX-5 in the low micromolar range. In the oxygen radical absorbance capacity assay, compound 3 had the same radical scavenging potency as melatonin and more than double that of Trolox. In a cell culture model of Alzheimer's disease (SH-SY5Y cells exposed to rotenone and oligomycin A), compound 3 showed a slightly higher neuroprotective capacity (50% protection) compared to melatonin (43% protection) at the same concentration. Cells treated with compound 3 also showed a significant increase in neurogenesis (measured by TuJ-1) and cell maturation (measured by MAP-2). Using the in vitro blood-brain barrier permeation assay (PAMPA-BBB), compound 3 exhibited a value that indicated it could cross the blood-brain barrier by passive diffusion.

In a cellular damage model (HT-22 cells exposed to NQO2 endogenous substrate adrenochrome and co-substrate BNAH), treatment with an NQO2 inhibitor (2-[2-(3-oxomorpholin-4-il)-ethylthio]-5-ethoxybenzimidazole hydrochloride or M11) significantly reduced production of reactive oxygen species (Voronin et al., 2021). M-11 interacts with the NQO2 regulatory site with a Ki of 0.39 µM, with no influence on the NQO1. Preincubation of HT-22 cells with M-11 or a different NQO2 inhibitor (S29434) resulted in reduced DNA damage and proportion of late apoptotic cells.

In human leukemic cells (K562 cells) that naturally express NQO2, as well as in NQO2-transduced neuronal cells (SHSY5Y cells), treatment with the NQO2 inhibitor (S29434) suppressed production of reactive oxygen species (Cassagnes et al., 2018).

Mouse models of Alzheimer's disease: In a mouse model of Alzheimer's disease (9-month-old 5xFAD mice), treatment with YB-537 (50 mg/kg in drinking water) for 1 month resulted in a trend for faster escape latency on the Morris water maze than the control group, though the difference between treatment groups was not statistically significant (Gould et al., 2023). Similarly, a 1-month YB-537 treatment (in drinking water) did not significantly improve novel object recognition in the overall cohort of 9-month-old 5xFAD mice, but significantly higher discrimination index was observed exclusively in female mice. With regards to the delayed fear conditioning test, a 1-month YB-537 treatment significantly improved contextual fear memory, and this improvement was driven by female mice, with no treatment effects seen in male mice. With regards to Alzheimer's disease-related biomarkers in the hippocampal CA1, a 1-month YB-537 treatment in 9-month-old 5xFAD mice had no significant effects on Aβ, phospho-tau (AT8), microglial activation (Iba1), astrocytic activation (GFAP), or oxidative stress (4-HNE). However, in female 5xFAD mice, YB-537 treatment significantly reduced Aβ, p-tau, and Iba1. In the cortex, neither male nor female 5xFAD mice showed any effects of YB-537 treatment on Aβ, p-tau, or 4-HNE, but Iba1 was reduced in female mice and GFAP was reduced in male mice.

The authors ran an additional study to probe whether male 5xFAD mice require earlier intervention and/or a longer dosing regimen to achieve therapeutic benefits. In 5-month-old 5xFAD male mice, YB-537 treatment (50 mg/kg in drinking water) for 4 months resulted in a trend for better contextual memory (p=0.0504) compared to vehicle-treated 5xFAD mice (Gould et al., 2023). With regards to Alzheimer's disease-related biomarkers in the hippocampal CA1, a 4-month YB-537 treatment in 5-month-old male 5xFAD mice resulted in a trend for decreased Aβ (p=0.0535) and Iba1 (p=0.0512), but no differences were seen for p-tau, 4HNE, and GFAP. In the cortex, a 4-month YB-537 treatment in the same mice resulted in significantly reduced Aβ, 4HNE, Iba1, and GFAP, with no changes in p-tau.

Models of Parkinson's disease: In the MPTP mouse model of Parkinson's disease, treatment with an NQO2 inhibitor (S29434; 1.5, 3.0, or 4.5 mg/kg) given 12 hours after the final MPTP injection and twice daily subsequently for 7 days did not significantly protect dopaminergic neurons in the substantia nigra, even though NQO2 was abundantly expressed in that brain region (Valluci et al., 2024). The 1.5 or 3 mg/kg dose of S29434 showed a slight increase of dopaminergic cell survival on day 7 and 21 following MPTP; only one time point (day 7) had a statistically significant difference compared to control. Protective effects did not persist at later time points. S29434 treatment did not have any effects on

microglial activation. The authors noted that the general lack of protective benefits with S29434 in the MPTP model may be attributed to the stimulation of autophagic flux with S29434 at the level of LC3-II production (a measure of autophagosome formation) without enhancing lysosomal function, which may have been counterproductive in the MPTP model that already has excessive upregulation of LC3-II.

In human U373 cells (glioblastoma-astrocytoma cells), administration of the parkinsonian neurotoxin, 6OHDA, enhanced NQO2 expression and activity (Janda et al., 2023). In human U373 cells and mouse astrocytes exposed to 6OHDA, administration of an NQO2 inhibitor (S29434) restored autophagic flux and partially reduced oxidative stress. NQO2 inhibition also protected dopaminergic SHSY5Y cells from 6OHDA-induced cell death when cocultured with astrocytes.

In human U373 cells, administration of the parkinsonian toxin, paraquat, decreased the basal levels of LC3-II-positive vesicles, suggesting downregulation of autophagy (Janda et al., 2015). Administration of an NQO2 inhibitor (S29434) in these cells potently enhanced LC3-II processing and restored the normal percentage of LC3-LAMP1-positive autolysosomes, suggesting restored autophagic flux. S29434 treatment also reduced the paraquat-induced increase in oxidative stress and percentage of dead cells.

APOE4 interactions: Unknown

Aging and related health concerns: Higher NQO2 expression is associated with lower risk of breast cancer, suggesting a possibility that NQO2 inhibition may increase risk. The associations between NQO2 activity and other cancers are less established.

Types of evidence:

- Numerous observational studies evaluating the NQO2 polymorphisms and expression as they relate to cancer
- Several review articles

Breast cancer: HIGHER NQO2 EXPRESSION ASSOCIATED WITH LOWER RISK

Estrogen metabolism generates quinones and NQO2 may influence how quinone metabolites are processed. In a hospital-based case-control study of 1,604 people, the 29 base-pair deletion and the +237C-allele of rs2071002, both located on the NQO2 promotor region and associated with gain of function, were associated with a lower risk of breast cancer (OR=0.76, p=0.0027 for the 29bp deletion;

OR=0.80, p=0.0031 for the 237C-allele)(Yu et al., 2009). These associations were replicated in a different population of familial/early-onset breast cancer cases and community-based controls (n=1,442). The combined p-values were $3.8x10^{-7}$ for the 29 bp deletion and $2.3x10^{-6}$ for rs2071002. In an *ex vivo* study, normal breast tissues with the protective genotypes expressed significantly higher levels of NQO2 mRNA than those with the risk genotypes.

Other cancers: NQO2 ACTIVITY MAY BE PROTECTIVE OR HARMFUL BASED ON THE TYPE AND STAGE

Some studies have suggested that NQO2 may play a role in other cancers, such as colorectal, ovarian, prostate, gastric, pancreatic, bladder, and thyroid cancers, based on genetic association studies (reviewed in Janda et al., 2024). For example, a significant downregulation of NQO2 mRNA levels was observed in colorectal cancer that has metastasized to liver compared to colorectal cancer without metastasis (Chen et al., 2016). It appears that depending on the tissue, tumor type, stage of cancer, and context, NQO2 may either inhibit or promote tumors.

Safety: There is theoretical concern that chronic NQO2 inhibition may promote some cancers. No selective NQO2 inhibitors have been tested in humans to date, but natural compounds that inhibit NQO2 have generally been safe (resveratrol, melatonin, etc.).

Types of evidence:

- Some observational studies examining the links between NQO2 genetics and cancer risk
- Some laboratory studies

No selective NQO2 inhibitors have been tested for safety in humans to date.

In a mouse model of Alzheimer's disease (5xFAD mice), YB-537 treatment was well tolerated at 50 mg/kg orally or 10 mg/kg, intravenously, with no discernable adverse symptoms at any time up to 24 hours following administration (Gould et al., 2023).

There is theoretical concern that chronic NQO2 inhibition may promote some cancers based on genetic association studies (reviewed in Janda et al., 2024).

Drug interactions: No studies of selective NQO2 inhibitors have assessed drug-drug or drug-supplement interactions. NQO2 itself binds to over 30 kinase inhibitors (with a submicromolar affinity for 10 kinase

inhibitors), other drugs, and natural products such as resveratrol (reviewed in Islam et al., 2025). Resveratrol has a high affinity with NQO2 (Kd=35 nM)(Britton et al., 2015).

Sources and dosing:

No selective NQO2 inhibitor has been approved for any indication as of May 2026. Many drugs and supplements have non-selective (or off-target) inhibitory effects on NQO2, including resveratrol, quercetin, melatonin, hydroxychloroquine, nilotinib, and imatinib. Gould et al., 2023 has described a set of highly selective NQO2 inhibitors. For example, YB-537 shows greater than 6,000-fold higher binding affinity to NQO2 than to NQO1; it is 82% orally bioavailable and crosses the blood-brain barrier in mice. Dosage has not been established for any indication.

Research underway:

There are no ongoing clinical trials of selective NQO2 inhibitors, based on ClinicalTrials.gov.

An NQO2 inhibitor, M11, significantly reduced production of reactive oxygen species in a cellular damage model and the authors noted there is rationale for further development of the M11 compound as a potential neuroprotective agent (Voronin et al., 2021).

5-Methoxy-3-(5-methoxyindolin-2-yl)-1H-indole, referred to as 'compound 3' in the publication, is a low nanomolar inhibitor of NQO2 (IC50 = 7.7 nM), with greater potency than melatonin and comparable efficacy to other potent NQO2 inhibitors tested to date (Herrera-Aronzamena et al., 2024). It also inhibits MAO-A, MAO-B, and LOX-5, which are associated with oxidative stress and inflammation. The authors noted that based on *in vitro* and *in silico* studies, compound 3 has excellent drug-like profile, neurogenic properties, negligible toxicity, and likelihood of blood-brain barrier penetrance, making this compound a potentially promising candidate for treatment of neurodegenerative diseases.

Search terms:

Pubmed, Google: NQO2 inhibitor, NQO2 inhibition, QR2 inhibitor, QR2 inhibition, S29434, NMDPEF

Websites visited for NQO2 inhibitor, QR2 inhibitor:

- Clinicaltrials.gov (0)

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