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Review

Brain Aging, Neurohormesis and Neuronutrition: Defining Neuroprotective Strategies

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Abstract: Aging is accompanied by a decline in adaptive stress responses, increasing susceptibility to neurodegenerative processes driven by oxidative stress, mitochondrial dysfunction, impaired proteostasis, and chronic inflammation. Hormesis—a biphasic dose–response to low-intensity stressors—has emerged as a central biological strategy for enhancing cellular resilience across multiple systems, including the nervous system. This review highlights neurohormesis as a key mechanism of neuronal protection, wherein subtoxic stimuli activate cytoprotective pathways such as NRF2/ARE, heat shock proteins, and vitagene networks, promoting neuroplasticity and delaying cognitive decline. In parallel, the evolving discipline of neuronutrition offers a complementary strategy by utilizing specific nutrients and bioactive compounds (e.g., polyphenols, magnesium, omega-3 fatty acids) that act as mild stressors or modulators of adaptive signaling. These compounds influence mitochondrial bioenergetics, redox regulation, and neuroinflammatory pathways, often mediated through the gut–brain axis. The synergy between hormesis and neuronutrition provides a systems-level, personalized framework for promoting brain health, enhancing functional longevity, and preventing or attenuating age-related neurodegenerative disorders. In contrast to earlier reviews that have treated neurohormesis and neuronutrition in isolation, the present article offers a novel, systems-level integration of both paradigms under a unified strategy for personalized neuroprotection, with a specific emphasis on the gut-brain axis and microbiota as pivotal regulators of adaptive signaling.

Keywords: aging; hormesis; neuroprotection; neurodegeneration; resilience; neuronutrition

1. Introduction: Brain Aging and Neurodegenerative Disorders

An essential dimension of biogerontology and public health is the concept of healthy brain aging. While much research has explored how lifestyle factors such as physical activity, nutrition, and pharmacological

interventions might extend lifespan, growing attention is being given to enhancing healthspan, particularly in preserving cognitive function and neurological resilience [1]. This includes delaying the onset of neurodegenerative and age-associated diseases, improving recovery from neurological insults, and maintaining the brain's adaptability to psychological, environmental, and medical stressors across the lifespan [2].

According to the World Health Organization (WHO), brain health is defined as "the state of brain functioning across cognitive, sensory, social-emotional, behavioral, and motor domains, allowing a person to realize their full potential over the life course, irrespective of the presence or absence of disorders" [3]. This holistic definition underscores that healthy brain aging is not merely the absence of disease, but the preservation of function and adaptability throughout life [4].

The concepts of life extension and healthy brain aging are deeply interconnected and often inseparable in practical application. Both depend on understanding how the brain and nervous system adapt to cumulative stressors, ranging from oxidative stress and inflammation to trauma and chronic disease [5].

One of the most significant challenges of aging is the increasing risk of neurodegenerative disorders, which can profoundly impact quality of life. As life expectancy increases globally, the incidence of conditions such as Alzheimer's disease (AD) and Parkinson's disease (PD) is also rising [6,7]. As a result, research is intensifying around the factors that drive the development and progression of these diseases and, crucially, how they might be prevented or delayed through modifiable interventions [8].

Age-related changes in the brain reflect a dynamic interaction of genetic, epigenetic, phenotypic and environmental factors that can be temporally restricted or longitudinally present throughout the lifespan [9]. Fundamental to these mechanisms is the capacity for physiological adaptation through modulation of diverse molecular and biochemical signaling occurring from the intracellular to the network-systemic level throughout the brain [10]. In this context, hormesis defines thresholds of adaptive responses that evoke and sustain adaptive plasticity to a range of stimuli and conditions [11,12]. At the center of these adaptive activities is the concept of hormesis, an integrative adaptation strategy that protects against a wide array of endogenous and exogenous stressors by inducing temporarily mediated resilient phenotypes [12–17].

2. Hormesis: Background and Perspectives

The concept of hormesis originated over a century ago from the observations of Hugo Schulz, who noted that low concentrations of disinfectants could enhance microbial survival, while high doses were lethal [18–20]. This biphasic dose-response pattern of low-dose stimulation and high-dose inhibition derives from the Greek word meaning "to excite" [15,21]. Subsequent research confirmed that biphasic responses are widespread across biological systems [21].

Despite extensive documentation of hormetic responses [22], traditional toxicology has often relied on high-dose studies and linear extrapolation models. However, recent decades have seen increased investigation into low-dose effects, revealing hormetic relationships and their mechanistic foundations [22]. Hormetic stimulation typically results in a modest increase (30–60% above control) and can arise from direct stimulation or overcompensation after homeostatic disruption [23]. This phenomenon is now recognized as relevant to development, aging, and neuroprotection [12,13,23–25].

Validating hormesis has been methodologically challenging due to the consistently modest amplitude of the response, requiring careful low-dose study design, replication, and consideration of temporal dynamics [26–29]. The advent of in vitro models has facilitated exploration of low-dose effects [30,31], revealing that biological systems are not passive but possess repair and anticipatory (preconditioning) capacities [32,33]. These adaptive hormetic responses can be triggered by diverse stimuli including thermal, chemical, dietary, and psychological stressors [34], each acting as a preconditioning stimulus to enhance resilience [35].

The hormetic dose-response is an evolutionarily conserved strategy mediated by upregulated adaptive mechanisms [22,36]. It reflects a systemic survival principle that delineates the bounds of biological plasticity [22,24] and is linked to regulated resource allocation [37]. Related concepts such as radiation adaptive response, pre/post-conditioning, the repeat bout effect in exercise, and wound healing align with this hormetic framework [16,29], as does the Yerkes-Dodson Law of optimal performance under stress [13].

While well-established, translating hormesis into clinical and public health applications requires further research in several key areas, including:

2.1. Inter-Individual Variation

Recognizing and quantifying the occurrence of inter-individual variation in response to hormetic agents is a very practical challenge for the biomedical community [27]. This would need to be linked to the discovery of

reliable biomarkers of exposure and response that can be used by both normal and high-risk segments of the population so that hormetic-adaptive responses can become integrated within broad strategies utilized for personalized medicine.

2.2. Escaping the Constraints of Biological Plasticity and Increasing the Hormetic Stimulatory Amplitude

The most significant feature of the hormetic dose response is that the amplitude of the stimulatory response is modest, in the percentage range, as noted above [21]. It has been hypothesized that the hormetic maxima is constrained by the limits of biological plasticity. This hormetic maxima is observed throughout the entire plant, microbial and animal kingdoms, and is independent of endpoint, inducing agent as well as mechanism. This strongly suggests that these limited amplitude responses have been highly conserved during the course of evolution [37]. Despite the broad consistency of the hormetic maxima and its strong selection, it would appear of considerable biological, biomedical and clinical relevance if it were possible to redirect underlying hormetic mechanistic patterns, pathways and features such that the stimulatory amplitude could be modulated and increased at least in specific circumstances. For example, it would be important to find ways to increase cognitive functions, especially in those who display compromising neurodegenerative disease. It may also be of importance to enhance the healing of damaged tissue and broken bones. It is possible that there may be negative biological and social consequences if one were to find ways to bypass the bounds of biological plasticity. This question is an important one to raise and to research.

2.3. Hormesis and Synergy

There are relatively few studies which have assessed the capacity of chemical interactions amongst various agents that can induce hormetic dose responses. Limited evidence suggests that chemical interactions can take place and enhance the hormetic response [13]. Such evidence suggests that the maximum stimulatory response remains constrained by the 30–60% ceiling response. However, there are not enough data on this specific issue to draw confident conclusions or generalizations.

2.4. Extending the Duration of Protection within Both Pre- and Postconditioning Protocols

A particularly important area of research involves assessing how the conditioning treatment might be modified to affect significant increases in the duration of resilient phenotypes that significant extend the protection period. While it is uncertain whether and how the amplitude of the stimulatory response may be increased, this is not the case with respect to the duration of the protection period. Research has indicated that the protection duration can be markedly extended when by relatively minor adjustments during the conditioning period(s). For example, Gidday [38] has shown that the duration of protection in rodent models can be extended from a few days out to several months in the case of glaucoma. This is also the case in the mouse studies concerning preconditioning and renal disease [34].

2.5. Co-Mobidities and Preconditioning Hormesis

It is widely recognized that a range of co-morbidities such as obesity, atherosclerosis, and hypertension can markedly diminish the phenomenon of preconditioning, even in relatively young experimental rodents [39]. For example, while preconditioning works in a very efficient manner in a young adult rodent, it is rapidly lost once these animals become obese [40]. The obesity may be the result of a genetic predisposition or via consumption of a high fat diet. In the case of the fat diet mediated loss of the preconditioning functioning, this process can be reverse when the animal is placed on a normal rodent chow [17]. Recent studies have also indicated that disruption in sleep patterns [41] and cigarette smoking (i.e., equivalent of 20 cigarettes per day for four weeks) [42] blocked preconditioning mediated protection in animal models. These activities are so common that follow up research is needed to confirm and extend the findings.

2.6. Aging, the Loss of Preconditioning and Its Restoration

Numerous experimental studies have established that the striking occurrence of preconditioning in young adult rodents is lost when the animals become old and especially so when they are elderly [16]. In human terms this is precisely the time of life when the capacity to have resilience against acutely life-threatening heart attacks and strokes is particularly important [43]. Given the potential importance of preconditioning in the elderly considerable research has been directed to determine whether the loss of such functions may be restored, partially or fully. Within this context, research by multiple groups have shown that dietary interventions as well as the

adoption of a relatively modest but consistent exercise programs can fully restore the preconditioning capacity as was present during early adulthood in experimental rodent models [44]. Furthermore, it is important to note that most lifetime rodent experimental studies occurred with the animal in a small cage, with ad libitum access to food and essentially no exercise. This results in a very high probability that the rodents will become very fat during the course of their captive lives. In fact, it is not uncommon for a rodent to triple or quadruple its weight during the course of its two-year caged captivity. Such a massive relative increase in body weight far exceeds that observed for humans even those considered by medical standards as being obese [45]. Such observations strongly suggest that researchers undertaking chronic studies with animal models try to make their experimental protocols as directly relevant to the human condition as possible to enhance reliable extrapolation.

2.7. Caenorhabditis Elegans (C. elegans) as a Model for Aging Studies

The elucidation of biological mechanisms underlying human aging represents a central aim in biomedical research [46]. However, studies in humans and other vertebrate models are often constrained by long lifespans and complex maintenance requirements. In this context, *C. elegans* has emerged as a well-established model organism for aging studies, owing to its short lifespan, fully annotated genome, and compatibility with high-throughput experimental approaches. This nematode is extensively employed to investigate the impact of genetic mutations, pharmacological compounds, and environmental factors on lifespan and age-associated functional decline [47]. Commonly assessed aging phenotypes include pharyngeal pumping rate, which peaks at the L4/young adult stage and decreases with age [48], and locomotion, which transitions from coordinated sinusoidal movement in young adults to reduced or absent mobility in aged individuals [47,49,50]. Mobility can be quantified manually or through automated systems [51], with classifications ranging from fully mobile (Class A) to minimally responsive (Class C). Chemotaxis, or the ability to respond to olfactory cues, also deteriorates with age and can be quantified by measuring directional movement toward attractants [47,52]. Lifespan remains a primary endpoint in aging studies, typically assessed by daily monitoring under standard (25 °C) or elevated (37 °C) temperature conditions [53,54], or via fluorescent viability assays using SYTOX green, which is a fluorescent dye that binds to DNA only if the cell's membrane has been compromised [55].

In addition to environmental cues, genetic determinants are fundamental regulators of lifespan in *C. elegans* [47]. Numerous conserved genes and signaling cascades implicated in mammalian aging have been identified in this model organism [47]. Among these, the transcription factor SKN-1 serves as the functional ortholog of the mammalian Nrf/CNC family. Under oxidative stress conditions, SKN-1 translocates to the nucleus and activates the transcription of genes involved in detoxification and cellular stress responses [56]. Loss-of-function mutations in skn-1 result in heightened sensitivity to oxidative stress and reduced lifespan, while constitutive activation of SKN-1 enhances stress resistance and extends longevity [57,58]. Similarly, sirtuins—an evolutionarily conserved family of NAD^+-dependent deacetylases—play a key role in modulating stress responses and lifespan. In low-energy states, elevated NAD^+/NADH ratios activate sirtuins, leading to transcriptional repression of pro-apoptotic genes such as p53 and enhanced cellular resistance to stress. In *C. elegans*, the sirtuin sir-2.1 responds to metabolic and environmental signals, and its overexpression promotes longevity through a DAF-16/FOXO-dependent mechanism. This interaction links sirtuins to the insulin/IGF-1 signaling pathway, which regulates the expression of antioxidant enzymes such as superoxide dismutase (SOD). Reduced insulin/IGF-1 signaling or increased sirtuin activity enhances oxidative stress resistance and contributes to lifespan extension. Together, these findings underscore the role of conserved genetic pathways in the regulation of aging and stress resilience [59].

Mitochondrial function also exerts a profound influence on aging in *C. elegans*. The clk-1 gene, the first mitochondrial gene linked to longevity in this species, encodes a demethoxyubiquinone hydroxylase required for ubiquinone (CoQ10) biosynthesis, a crucial component of the mitochondrial electron transport chain [60,61]. Clk-1 mutants display extended lifespan and delayed physiological processes, including locomotion and pharyngeal pumping [62]. Similarly, mutations in mev-1, which encodes a subunit of succinate–coenzyme Q oxidoreductase (complex II), lead to increased mitochondrial ROS production, oxidative stress sensitivity, and shortened lifespan [63]. Conversely, mutations in isp-1, encoding an iron–sulfur protein within complex III, result in increased oxidative stress resistance and significant lifespan extension [64]. Collectively, these findings emphasize the critical role of detoxification pathways and mitochondrial bioenergetics in the genetic regulation of aging in *C. elegans*.

2.7.1. Enhancing Medical Interventions Success Via Hormesis

Hormesis has the potential to significantly improve patient treatment and success. Many of the ideas for how this could happen is based on a plethora of experimental studies, awaiting their potential translation into human activities. The area of pre-and post-conditioning is seen as one that may have enormous potential, affecting a vast

array of concerns. For example, studies have demonstrated clearly that pre-and post-conditioning markedly reduces multi-organ damage from shock [65]. This is an important issue for people involved in traumatic accidents, a factor that affects the lives of a relatively high proportion of young adults. Preconditioning of the skin via various commercial and other preparations could reduce the risks of skin cancer and affect the appearance of the skin, reducing wrinkling with age, both factors related to healthy aging [66]. Preconditioning patients prior to surgery, chemo-and radiation therapy are now hotly researched areas, showing strong potential [67].

2.7.2. Finding the Hormetic Optima

An important key to a healthy life is the adoption of hormetic activities within the optimal dose range. This challenge will be one that the public health and medical communities will need to address via research and public educational programs. Many hormetic concepts and prescriptions have been widely discussed in the scientific literature, including issues related to optimal diets, exercise, use of anti-aging cosmetics, consumption of phytochemicals, consumption of ethanol beverages such as wine and beer, the use of mental exercises and many others [68]. While scientific-based cases can be made for how such activities can enhance the public health, all have an optimal dose range (i.e., hormetic-adaptive zone) and all may have the potential to be counter-productive and harmful to one's health if experienced in sufficient excess [69]. The challenge of knowing, identifying, optimizing and integrating hormetic optima into a lifestyle will be an important and ongoing challenge.

3. Neurohormesis and Neuronutrition

Neurohormesis represents a fundamental adaptive mechanism by which the brain responds to subtoxic, low-intensity stressors through the activation of conserved cytoprotective pathways [70]. These responses serve to enhance neuronal resilience, promote cellular homeostasis, and support long-term brain function [11,71]. Within the context of neurodegenerative disorders, neurohormesis offers an alternative and mechanistically grounded therapeutic framework, particularly in light of the limited efficacy of conventional pharmacological interventions, which are often constrained by single-target actions and inadequate neuronal bioavailability [72,73].

Following the hormetic dose-response model, numerous bioactive compounds—particularly polyphenols—have demonstrated the ability to elicit adaptive neuroprotective effects at low concentrations [74]. Compounds such as sulforaphane and hydroxytyrosol upregulate transcriptional programs associated with the KEAP1/NRF2/ARE axis, heat shock response, and vitagene networks, promoting antioxidant defense, redox regulation, protein homeostasis, and xenobiotic detoxification [75]. These molecular cascades contribute to the maintenance of mitochondrial integrity, suppression of neuroinflammation, activation of cytoprotective proteins and prevention of neuronal apoptosis, core mechanisms implicated in the pathogenesis of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Figure 1).

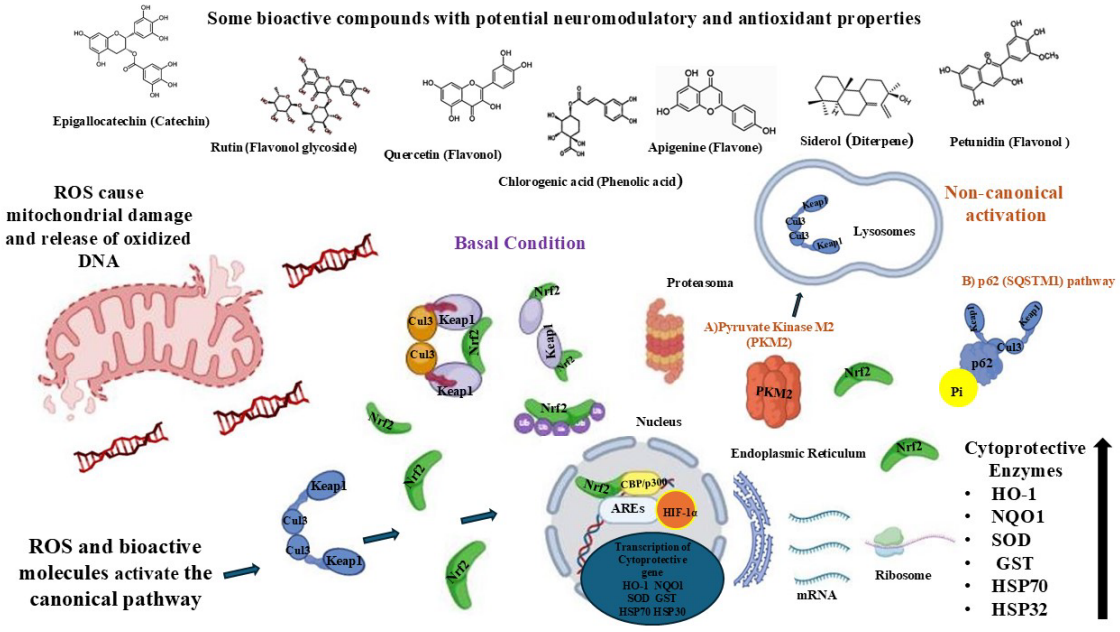

Figure 1. NRF2 activation pathways and neurohormetic resilience.

The activation of Nuclear Factor Erythroid 2–Related Factor 2 (NRF2) constitutes a central cytoprotective mechanism that coordinates cellular defense against oxidative, electrophilic, and metabolic stress. NRF2 activation occurs through canonical (KEAP1-dependent), ROS-driven hormetic, non-canonical, and Pyruvate Kinase M2–mediated pathways. Together, these converge on the upregulation of the vitagene network—an adaptive program critical for neurohormetic resilience.

(1) Canonical Activation: Electrophile-Mediated KEAP1 Cysteine Modification

The canonical pathway is initiated by electrophilic and polyphenolic bioactive compounds that disrupt the KEAP1–NRF2 interaction. Under basal conditions, KEAP1—an adaptor for the CUL3 ubiquitin ligase complex—targets NRF2 for continuous ubiquitination and proteasomal degradation.

A variety of dietary phytochemicals—such as Epigallocatechin (a catechin), Chlorogenic acid (a phenolic acid), Rutin (a flavonol glycoside), Apigenin (a flavone), Petunidin (a flavonol), Siderol (a diterpene), and Quercetin (a flavonol)—possess reactive chemical groups capable of forming covalent adducts with key cysteine residues on KEAP1 (notably Cys151, Cys273, and Cys288).

This modification inactivates KEAP1, preventing NRF2 ubiquitination. Stabilized NRF2 accumulates in the cytosol and subsequently translocates to the nucleus.

(2) ROS-Dependent Activation (Hormesis)

Mild to moderate increases in intracellular Reactive Oxygen Species (ROS) produce a hormetic response—an adaptive cellular benefit triggered by low-dose stress.

ROS oxidize KEAP1 cysteine thiols, inducing conformational changes that inhibit its ability to bind and degrade NRF2. This oxidation mimics the action of electrophilic phytochemicals. As a result, NRF2 escapes degradation, accumulates, and migrates to the nucleus.

This ROS-dependent activation represents a core mechanism of cellular hormesis, enabling cells to strengthen antioxidant capacity in response to mild stress.

(3) Non-Canonical and PKM2-Mediated NRF2 Activation

NRF2 activation is also regulated through mechanisms independent of direct KEAP1 inhibition.

a. Pyruvate Kinase M2 (PKM2)

Under metabolic stress, PKM2 shifts from its tetrameric to dimeric form and translocates to the nucleus. Nuclear PKM2 promotes NRF2 transcription by cooperating with cofactors such as Hypoxia-Inducible Factor 1α (HIF-1α).

Additionally, PKM2 supports redox balance by stimulating the pentose phosphate pathway, thereby increasing NADPH production—an essential cofactor for antioxidant defenses.

b. p62/Sequestosome 1 (SQSTM1)

Phosphorylated p62 (notably at residues S351 and S403) binds KEAP1 via its STGE motif with high affinity. This interaction sequesters KEAP1 into autophagosomes, which are then degraded through lysosomal autophagy.

The resulting depletion of cytosolic KEAP1 stabilizes NRF2. This non-canonical mechanism is particularly relevant in conditions with impaired autophagy, including cancer and neurodegenerative disorders.

(4) Activation of the Vitagene Network

Once inside the nucleus, NRF2 binds to Antioxidant Response Elements (AREs) located in the promoters of its target genes. NRF2 then recruits coactivators such as CREB-binding protein (CBP) and p300 (E1A-binding protein p300), forming a transcriptional complex that drives the expression of a broad cytoprotective program.

This NRF2-dependent gene network—commonly called the vitagene network—includes:

- Phase II detoxification enzymes: NQO1, HO-1, GSTs
- Antioxidant enzymes: SODs, GPXs, PRDXs
- Thioredoxin and glutathione systems
- Proteostatic and chaperone proteins: HSP70, HSP32
- Metabolic regulators that restore redox homeostasis

Collectively, activation of the vitagene network enhances neurohormetic resilience, protecting neurons and glial cells from oxidative, metabolic, and proteotoxic challenges.

Abbreviations:

- NRF2: Nuclear Factor Erythroid 2–Related Factor 2
- KEAP1: Kelch-like ECH-associated protein 1
- ROS: Reactive Oxygen Species

- Cul3: Cullin 3
- PKM2: Pyruvate Kinase M2
- HIF-1α: Hypoxia-Inducible Factor 1-alpha
- p62/SQSTM1: p62/Sequestosome 1
- STGE: Serine-Threonine-Glycine-Glutamate motif
- ARE: Antioxidant Response Element
- CBP: CREB-binding protein
- p300: E1A-binding protein p300
- HO-1: Heme Oxygenase-1
- NQO1: NAD(P)H:quinone oxidoreductase 1
- SOD: Superoxide Dismutase
- HSP: Heat Shock Protein

Despite these advances, the amplitude of hormetic stimulation typically remains within a constrained range (30–60% above baseline), prompting ongoing inquiry into strategies that might safely enhance or sustain these effects [76]. Chronic or long-term activation of neurohormetic mechanisms may induce trade-offs related to energy allocation, proteostasis, or immune modulation, and thus require finely tuned interventions [77]. In this regard, the controlled induction of neurohormesis through lifestyle and dietary strategies such as moderate physical exercise, intermittent fasting, and nutraceutical supplementation has gained recognition as a viable and low-risk approach to induce mild stress responses with neuroprotective outcomes [78].

This is where the emerging discipline of neuronutrition intersects with neurohormesis. Neuronutrition encompasses the study of how specific dietary compounds, nutrients, and nutritional patterns influence brain structure and function across the lifespan, with particular relevance to cognitive aging and neurodegenerative disease prevention [79]. Unlike conventional nutritional paradigms focused on adequacy and deficiency, neuronutrition emphasizes the targeted use of neuroactive nutrients—including polyphenols, carotenoids, vitamin D, B-vitamins, magnesium, zinc, and omega-3 fatty acids—to modulate signaling pathways involved in mitochondrial bioenergetics, neurotransmission, oxidative metabolism, and neuroinflammation [80].

An integral component of neuronutritional intervention is the modulation of the gut–brain axis, which serves as a key interface for neuroimmune and neuroendocrine signaling [81]. Dietary polyphenols and fibers, once metabolized by the intestinal microbiota, yield bioactive metabolites with enhanced neuroprotective potential and bioavailability [82]. These metabolites, capable of crossing the blood–brain barrier, exert antioxidant and anti-inflammatory effects that contribute to the maintenance of synaptic function and neuronal viability [83]. Conversely, intestinal dysbiosis and increased gut permeability have been associated with neuroinflammatory processes that may exacerbate neurodegenerative pathophysiology [84]. Therefore, microbiota-targeted interventions such as prebiotics, probiotics, and fermentable dietary fibers represent promising adjunct strategies to support neurohormetic pathways and mitigate degenerative cascades [85].

The integration of neurohormesis and neuronutrition constitutes a promising systems-level approach to neurodegenerative disease prevention and management. By leveraging evolutionarily conserved adaptive mechanisms through precision dietary interventions, it is possible to enhance cellular resilience, delay functional decline, and modulate key molecular determinants of brain aging. While preclinical data are encouraging, the therapeutic application of mentioned neuronutritional supplements faces significant challenges, including poor bioavailability, inter-individual metabolic variability, and the absence of established dosing regimens. An additional consideration is the potential for some dietary interventions to act as pro-oxidants when administered at elevated doses. Future research should aim to elucidate optimal combinations, dosing regimens, and temporal dynamics of neuroactive nutrients in hormetic contexts, with the ultimate goal of developing translational strategies that harness endogenous protective pathways for sustainable neurological health.

4. Conclusions

The current paper reinforces the centrality of hormesis as a unifying biological principle and its growing relevance in the context of neurodegeneration and healthy aging. Hormesis, understood as a biphasic dose–response characterized by low-dose stimulation and high-dose inhibition, reflects an evolutionarily conserved survival strategy [86]. This mechanism enables biological systems to mount adaptive responses when confronted with mild stressors, thereby fostering resilience and optimizing functionality across cellular, tissue, and organismal levels.

A critical insight from recent studies is the temporal dynamics of hormetic adaptation. These responses appear to be structured in at least two temporally distinct phases: an early phase beginning within an hour of the stimulus, and a broader, delayed window between 12 and 72 h [16]. The duration of protection varies by system and stimulus

but may range from days to several months, as demonstrated in various rodent models [33,38]. Notably, Flurin Cathomas et al. [87] reported that the induction of a resilient phenotype could extend across an organism's entire lifespan, while emerging evidence from Johnson et al. [88] indicates the possibility of transgenerational epigenetic inheritance of hormetic protection.

These findings expand the conceptual boundaries of hormesis, positioning it not only as a transient cellular adaptation but also as a potential mechanism for long-term health maintenance and disease resistance. Particularly within the realm of neurodegenerative disorders such as Alzheimer's, Parkinson's, and ALS, the modulation of hormetic signaling pathways including NRF2/ARE, HSF1, and vitagene networks has demonstrated neuroprotective properties [89]. These mechanisms support antioxidant defense, mitochondrial function, proteostasis, and the suppression of neuroinflammation, all of which are critical to preserving neuronal integrity and function in aging brains.

Neurohormesis thus emerges as a compelling therapeutic model, especially given the limitations of current pharmacological approaches that often fail to address the multifactorial nature of neurodegeneration or lack sufficient neuronal bioavailability [90]. The modest yet reproducible nature of hormetic responses (typically 30–60% above control) emphasizes the need for precision in both dosing and timing, while raising the question of whether and how the amplitude of these responses might be safely augmented in clinical contexts.

In this regard, the integration of neuronutrition represents a promising frontier. Nutritional interventions, particularly those involving neuroactive micronutrients and phytochemicals, can act as mild stressors capable of inducing hormetic responses [91]. Compounds such as sulforaphane, hydroxytyrosol, curcumin, resveratrol, and EGCG exert their effects via modulation of redox-sensitive transcription factors and enhancement of cellular stress resistance [92]. Beyond their direct antioxidant action, these compounds influence epigenetic regulation, mitochondrial biogenesis, and inflammatory cascades [93,94].

In sum, hormesis, neurohormesis, and neuronutrition collectively offer a systems biology-based strategy for promoting brain health and delaying neurodegenerative progression. These findings underscore the necessity of refining dosing protocols, identifying reliable biomarkers of hormetic activity, and elucidating interindividual variability in response to bioactive nutrients. Such insights will be instrumental in translating preclinical observations into effective, personalized interventions for neuroprotection and functional longevity.

Author Contributions

E.J.C., V.C. and A.D.: conceptualization; A.K., A.T., C.G. and A.S.: literature review; A.B., D.G., U.W., and L.R.: writing—original draft preparation. All authors have contributed to editing and have read and agreed to the published version of the manuscript.

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The authors declare no conflict of interest. Given the role as Editorial Board Member, Vittorio Calabrese had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

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