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Nitric Oxide and the Improvement of Cognitive Functions in the Elderly: Role of Dietary Supplementation

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Abstract: It is normal for our cognitive abilities to decline with age. Recent research, however, has shown that this cognitive impairment can be exacerbated by reduced blood flow to the brain. Despite accounting for only 2% of the human body's weight, the brain consumes approximately 20% of the oxygen supply. Boosting blood flow to the brain can help avoid cognitive decline associated with age. Increased blood flow to the brain improves the distribution of oxygen, glucose, and nutrients. This enhanced circulation may decrease the progression of age-related cognitive impairment. Nitric oxide (NO) is a vital element in improving blood flow to the brain. NO has an important role in the brain, particularly in learning and memory. It functions as a neurotransmitter, readily passing through cell membranes and diffusing from one neuron to another. Unlike typical neurotransmitters, NO is released immediately upon formation and acts directly on intracellular components. It also has neuroprotective effects against oxidative stress. Numerous vital physiological functions of nitric oxide have spurred extensive research on the health benefits of dietary nitrate consumption. NO can be produced from L-arginine or through an enterosalivary nitrate-nitrite-NO pathway since nitrate (NO_3^-) is transformed into nitrite (NO_2^-), which is subsequently further reduced to NO. The goal of this review is to discuss recent findings in the role of nitric oxide and dietary nitrate supplementation on cognitive function and brain health.

Keywords: aging; cognitive function; nitric oxide; arginine; nitrate.

1. Introduction

Cognitive impairment is a prominent cause of disability and reliance in older persons, and it places a significant cost burden on the public health system [1]. The pathological phases of cognitive impairment range from moderate cognitive dysfunction to dementia, with the predominant clinical symptom in patients being a loss of memory function. It is anticipated that there would be 83.2 million cases of cognitive impairment among senior people globally by 2030 [2]. Cognitive impairment and dementia are the two leading causes of disability among the elderly. Maintaining independence and a high standard of living necessitates optimizing mental, physical, and social health [3]. The prevalence of moderate cognitive decline and advanced forms of cognitive diseases, such as Alzheimer's disease (AD), has increased along with the worldwide life expectancy and the percentage of the aging population [4].

Nitric oxide is a key signaling molecule in various physiological processes, including vasodilation, muscle contraction, neurotransmission, and host defense against microorganisms. Nitric oxide promotes cerebral blood flow (CBF) by regulating a range of neurobiological functions in the brain and vascular system, including immune responses, synaptic plasticity, vascular tone, and neurotransmission [5]. There are two known methods of producing NO in humans. The L-arginine pathway produces NO through the NO synthase (NOS) enzymes. The second mechanism involves the nitrate-nitrite-NO route, where common oral bacteria convert nitrate to nitrite, which is then converted to NO in the circulation and tissues. NO's primary function in the brain is to bind to guanylyl cyclase, a pre- or post-synaptic messenger [6]. Dietary nitrate may enhance cognitive performance, according to early studies conducted in older adults. Both naturally occurring foods and industrial food additives and processed meat can contain nitrates and nitrites. However, nitrate intake from plants, rather than from processed meat or food additives, is associated with nitrate's positive effects [7]. Dietary nitrate is transformed into nitrite in the oral cavity; some of the nitrite is reduced in the stomach to NO [8]. This cascade from nitrite to NO can be accelerated by a nitrate-rich diet, which may have physiological consequences that enhance prefrontal-dominant cognitive tasks, including executive function tasks that are essential for all performance [9]. According to Presley *et al*. [10] and Regan *et al*. [11], older and adolescent individuals who consumed a lot of nitrate-rich foods showed higher regional cerebral perfusion in the prefrontal cortex, an area of the brain linked to working memory and executive function. Unfortunately, a number of factors can interfere with our bodies' ability to produce NO. These include a lack of physical activity, inflammatory diets deficient in nitrate-rich vegetables, decreased stomach acid, environmental factors like pollution and heavy metals, and certain medications. Furthermore, age itself and personal genetics cause a decrease in nitric oxide synthesis. However, nutritional practices may be linked to health issues in older persons. Nitric oxide production is often decreased in older adults, and this is linked to worse vascular (blood vessel) and cognitive (brain) health. Additionally, few adults get enough dietary nitrate. Therefore, dietary intervention with plants rich in nitrates may play an important role in improving cognitive functions and brain health in older people. From this standpoint, this article will discuss cognitive functions, the role of nitric oxide in improving cognitive functions, and how foods contribute to nitric oxide formation.

2. The Aging Brain

In terms of clinical and biochemical alterations in numerous tissues, there is a continuum between healthy aging and illness. At both qualitative and quantitative levels, attempts are still being made to distinguish between disease and normal brain aging. Nevertheless, it is widely accepted that aging in both humans and animals is linked to changes in neurotransmitters, microscopic morphology, brain volume, and other phenotypic indicators of behavior and cognition. Such alterations can impair performance and raise brain vulnerability to neurodegenerative diseases like Alzheimer's disease and Parkinson's disease, even if they might not be severe enough to significantly disrupt everyday living activities [12]. Humans, primates, and rats have all shown behavioral and cognitive changes that correlate with age-related molecular and cellular alterations in brain cells. Given the significant roles of the hippocampus and prefrontal cortex in spatial memory [13], it is not unexpected that aging is associated with declines in both spatial and associative memory [14]. The prefrontal cortex, along with the hippocampus, is essential for high-level cognitive and executive functions, as well as working memory. Age-related declines in cognitive function have been attributed in

large part to the degradation of these two structures [15]. At the cellular level, abnormal myelination, astrogliosis, or oligodendrogliosis, among other events, promote a state of chronic inflammation, which directly increases microglial activation and, in turn, reduces processes such as synaptic plasticity, neurogenesis, and neurotransmitter levels. Thus, alterations such as DNA damage, lysosomal dysfunction, loss of protein homeostasis, or immunological dysregulation take place that are linked to cognitive impairment and neurodegeneration. Aging is also influenced by oxidative stress mechanisms originating in the cells, and given that free radicals increase with age, they are thought to be a crucial aspect of the aging process. Antioxidants may therefore be helpful in delaying the aging process [16].

3. Cognitive Functioning

The ability to process ideas is referred to as cognitive functioning. It is described as "an individual's capacity to carry out the different mental tasks that are closely related to learning and problem-solving. Language, executive processes, perceptual-motor function, memory and learning, and attention are all examples of cognitive functions that enable humans to perceive their surroundings and make decisions [17]. The brain may normally create personal ideas and beliefs about the world, as well as learn new skills in the previously stated domains, usually in early childhood. Cognitive functioning can be affected by age and illness, leading to memory loss and difficulty finding the right words when writing or speaking [18]. Learning, memory, perception, and problem-solving are among the cognitive functions most affected by cognitive disorders (CDs), also known as neurocognitive disorders (NCDs). Delirium, moderate neurocognitive disorders, and serious neurodegenerative disorders (formerly known as dementia) are examples of neurocognitive disorders. They are characterized by acquired (as opposed to developmental) cognitive capacity deficiencies, which usually indicate decline and may be caused by underlying brain pathology [19]. Depending on how severe the symptoms are, neurocognitive disorders are classified as moderate or serious. Although mood disorders, anxiety disorders, and psychotic disorders can also affect memory and cognitive performance, they are not considered neurocognitive diseases because the primary symptom is not loss of cognitive function (Causal symptom [20]. Furthermore, unlike neurocognitive disorders, which are acquired, developmental disorders like autism usually have a genetic basis and manifest at birth or early in life [21].

4. Neurocognitive Changes in Aging

The scientific literature has extensively shown cognitive change as a typical aging process. Vocabulary is one of the cognitive skills that resists brain aging and may even get better with age. Over time, other skills, including conceptual reasoning, memory, and processing speed, progressively deteriorate. The pace of decline in certain abilities, such as processing speed and perceptual reasoning, varies significantly among older adults [22]. Certain cognitive domains can be used to categorize cognitive capacity. We'll talk about processing speed, memory, and attention.

4.1. Processing speed.

Both the speed of motor reactions and the pace at which cognitive tasks are completed are referred to as processing speed. Throughout life, this fluid capacity continues to deteriorate, starting in the third decade. In healthy older persons, reduced processing speed is the cause of

many of the cognitive abnormalities observed. This "slowing" can hinder performance on a variety of neuropsychological tests that assess other areas of cognition (e.g., verbal fluency). Therefore, a decrease in processing speed may affect a number of different cognitive domains [23].

4.2. Attention.

The ability to focus and pay attention to particular stimuli is referred to as attention. When a series of numbers is repeated, the simple auditory attention span (sometimes called instantaneous memory) only slightly decreases in late life. On more difficult attention tasks, such as split and selective attention, the age effect is more pronounced. The ability to ignore unimportant information while focusing on specific aspects of the environment is known as selective attention [24].

4.3. Memory.

Memory loss is one of the most prevalent cognitive concerns among older people. Indeed, on a range of learning and memory tests, older adults do not do as well as younger adults. Slow processing speed, diminished capacity to block out unnecessary information, and decreased use of learning and memory-enhancing techniques may all be associated with age-related memory loss [23].

5. Endogenous Nitric Oxide Formation

Numerous interrelated enzymatic and non-enzymatic processes work together to create NO [25]. Endogenous NO production occurs via the L-arginine-NO route (Figure 1). NO-synthases (NOSs) catalyze the conversion of L-arginine and molecular oxygen to NO. This NO is promptly reduced to nitrite and nitrate; however, these molecules can be recycled, resulting in the production of NO again. NOS is the only rate-limiting enzyme in NO production from L-arginine. NOS has three isoenzymes: neuronal NOS (nNOS or NOS1), inducible NOS (iNOS or NOS2), and endothelial NOS (eNOS or NOS3). Under normal physiological conditions, nNOS and eNOS are constitutively expressed; in pathological conditions, iNOS is more likely to be created [25].

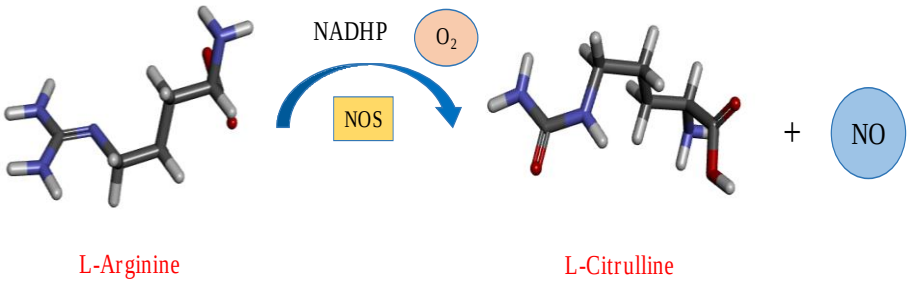

Figure 1. The metabolic pathway of nitric oxide formation from L-Arginine.

Nitrate, which is ingested through food and drinking water, is quickly absorbed by the stomach and small intestine before entering the bloodstream. After consumption, plasma nitrate levels remain elevated for 5-6 hours. The kidneys then eliminate a large portion of the circulating nitrate, while the salivary glands actively absorb, concentrate, and produce up to 25% of it. Commensal bacteria in the oral cavity use nitrate reductase enzymes to convert salivary nitrate into nitrite. These microorganisms live in the tongue's crypts and use nitrate as

an oxygen source when oxygen is unavailable. As a result, nitrite bioavailability is determined by the oral microbiota, and differences in its composition might affect nitrate reduction. Furthermore, the use of mouthwash and antibiotics may disturb the balance of oral bacteria, thereby increasing nitrite bioavailability [26].

Nitrite is consumed, absorbed in the upper gastrointestinal system, and then released into the bloodstream. The acidic environment in the stomach and other gastric organs can convert nitrite to nitric oxide, a key regulator of cell signaling. Furthermore, circulating nitrite can be converted into NO by different enzymes with nitrite reductase activity. These enzymes are present in various cell types and perform important functions in the body's physiological processes [26].

The considerable decrease in NO bioavailability can be due to a number of linked mechanisms, including lipid peroxidation, oxidative stress, inflammatory responses, and changes in angiogenesis within the cardiovascular system. Researchers and scholars increasingly recognize these issues as pivotal causes of endothelial injury, emphasizing the importance of maintaining NO levels [27].

6. Physiological Role of Nitric Oxide in Brain Function

The gaseous, extremely reactive molecule nitric oxide (NO) readily diffuses into the surrounding tissues. One neurotransmitter that controls several neurobiological functions, including synaptic plasticity, is NO [25]. Age-related declines in NO production are expected to contribute to degenerative processes in the central neurological and cardiovascular systems [28]. Cognitive, metabolic, and cardiovascular function gradually deteriorate with age. In middle-aged and older persons, vascular risk factors such as obesity and hypertension are independently linked to an increased risk of dementia and cognitive decline [29]. Numerous studies have shown a link between cognitive impairment and decreased cerebral blood flow (CBF), and dementia may develop as a result of this relationship [30]. Higher baseline CBF was linked to a decreased likelihood of cognitive decline and dementia diagnosis after a 6.5-year follow-up, according to data from 1730 older people (55 years of age or older) [31]. Furthermore, a recent observational study found that, among older white Europeans, higher CBF was associated with better executive, attentional, and memory function [32]. Nitric oxide promotes local vasodilation and increases CBF [33].

The endothelial isoform of the enzyme secretes NO in endothelial cells. It is tonically secreted to regulate systemic NO synthase. Vascular tone, including venous capacitance, cardiac output, and arterial tone, as well as platelet aggregation [34]. A physical and functional link between circulating blood corpuscles, blood fluid components (such as nutrients), and tissue metabolic activities is provided by the vascular endothelium [35]. One of the main pathogenic factors in the development of atherosclerosis and CVD is thought to be endothelial damage [36]. Animal studies have thoroughly examined the brain's production of NO and its function in regulating neuronal activity. Nonetheless, there is some evidence that NO plays a part in human brain activity. NO has been implicated in learning and memory processes in a limited number of studies. For instance, it has been shown that L-arginine and NO donors (molsidomine, S-nitroso-N-acetylpenicillamine, and sodium nitroprussiate) increase the amount of NO available in the brain, which improves learning and memory [37]. Several studies have looked into the role of NO in memory processes, and the findings have been positive. One study discovered that NO has long been required for long-term potentiation LTP, which is the process by which memories are formed and stored in the brain. LTP is a type of

synaptic plasticity that involves the strengthening of neural connections, and it has been shown to be essential for learning and memory [38]. Qi *et al*. [39] discovered that endogenous nitric oxide contributes to the positive benefits of running on cognition and hippocampus capillaries. Running exercise for 4 weeks dramatically improved spatial memory and increased the total number of capillaries in the cornu ammonis 1 region and the dentate gyrus of Sprague-Dawley rats. Running exercise also dramatically raised nitric oxide synthase activity and nitric oxide levels in the rat brain. Running exercise had no protective impact on spatial memory after blocking endogenous nitric oxide synthesis with an infusion of the nonspecific nitric oxide synthase inhibitor NG-nitro-L-arginine methyl ester into the lateral ventricle. Running exercise had no protective impact on angiogenesis in rats' cornu ammonis 1 sector and dentate gyrus following nitric oxide synthase inhibition. The function of NO in fear memory, the capacity to recall and react to threatening stimuli, was examined in a study. According to the study, mice's fear memory was impaired when a NOS inhibitor was administered, suggesting that NO is also required for fear memory [40]. According to this research, NO plays a critical role in the development and maintenance of various types of memory. However, memory function may also be negatively impacted by excessive NO generation. Neurodegenerative illnesses, including Alzheimer's and Parkinson's, which are characterized by memory loss and cognitive decline, have been linked to elevated NO levels [41]. Therefore, to ensure optimal memory function, it is crucial to maintain a balance in the brain's NO levels. Exercise has been shown to stimulate NO production and enhance cognitive performance, making it one of the many natural ways to support healthy NO levels in the brain and enhance cognitive function.

Additionally, it has been proposed that diminished NO and endothelial dysfunction may be linked to cognitive decline and the onset of Alzheimer's disease, maybe as a result of reduced oxygen delivery to the brain and dysfunctional cerebral blood flow. Thus, disruption of neurovascular function may be a significant risk factor for cerebral vascular dysregulation, which in turn may be affected by impaired neurovascular function. In contrast, beta-amyloid deposition was shown to be prevented by the treatment with NO donors [37]. Manukhina *et al*. [42] found that a reduction in NO production in rats following the treatment of the NO synthase inhibitor NG-nitro-L-arginine methyl ester (L.NAME) exacerbated the deleterious effect of beta amyloid and was associated with memory impairments resembling those observed in Alzheimer's disease. Since beta-amyloid is the primary component of extracellular plaques and is elevated in neurodegenerative illnesses, investigating the interaction between NO and beta-amyloid may help us better understand how vascular function is linked to neuronal damage.

The frequency of vascular dementia (VD), which is directly linked to cerebrovascular risk, is rising at an epidemic rate, and the number of persons suffering from cerebrovascular illnesses is rising along with the global aging population. However, there aren't many treatment alternatives that can significantly improve vascular dementia patients' cognitive impairment and prognosis. Similarly, synaptic disruption is identified as the primary cause of cognitive impairment in Alzheimer's disease and other neurological illnesses. The primary mechanism behind all pathological alterations in VD is the aberrant NOS/NO pathway. Age and vascular variables cause eNOS to become inactive in VD patients, which lowers NO production and bioavailability and can cause significant cognitive impairment. NO is a "double-edged sword": too much can cause cytotoxicity and mitochondrial damage, but too little can impair synaptic plasticity, promote neuron inflammation, and compromise the integrity of the blood-brain barrier. As a result, measuring the quantity of NO generated is crucial [43].

Nitric oxide plays crucial functions in intracellular signaling in neurons, regulating everything from dendritic spine growth to neuronal metabolic status. Furthermore, NO can modify proteins post-translationally through the thiol amino acid S's nitrosylation, a physiological mechanism that controls protein activity [25]. However, when NO combines with the superoxide anion to generate peroxynitrite, its behavior might become more complex with aging and pathogenic processes. This gaseous substance damages lipids, proteins, and nucleic acids by readily diffusing across neuronal membranes. Peroxy nitrite mostly combines with the phenolic ring of tyrosines in proteins to create nitro-tyrosines, which have a significant impact on the physiological functions of proteins. The irreversible process of nitrotyrosination also results in the buildup of altered proteins, which can cause neurological diseases like Parkinson's or Alzheimer's to develop and worsen [25].

7. Plant-based and Animal-based Nitrates and Nitrites

Supplementing with nitric oxide may increase the risk of adverse consequences in those with specific medical problems. These illnesses include low blood pressure, cirrhosis, and guanidinoacetate methyltransferase deficiency. Therefore, it is preferable to obtain nitric oxide from natural sources to prevent potential negative effects [44]. Nitrates and nitrites are naturally occurring chemicals found in plants, water, and processed meats. Dietary nitrate, which is mostly found in vegetables (Figure 2) such as beets, spinach, and other leafy greens, offers a promising non-pharmacological approach to increasing NO bioavailability. The lowest nitrate concentrations (less than 100 mg/Kg) were found in tomatoes, while the highest concentrations (greater than 1000 mg/kg) were found in potatoes, cabbage, spring greens, and lettuce [45]. The amount of dietary nitrates varies depending on a number of factors, including vegetable type, soil conditions, fertilizers, and cooking methods. For instance, spinach and arugula are considered high-nitrate vegetables, with concentrations ranging from 250 to 700 mg per kilogram; beets are also a rich source of nitrates, with concentrations ranging from 250 to 700 mg per kilogram; and cured meats are typically high in nitrite. The nitrate content of vegetables varies from 0.1 mg/100 g in peas and Brussels sprouts to 480 mg/100 g in rucola (rocket). Vegetable nitrate concentration varies depending on the processing. Boiling veggies can lower nitrates by up to 50%. Baking, freezing, and roasting help to maintain nitrate concentration [46].

Figure 2. Nitrate-rich plant sources.

Vegetables and drinking water are the primary sources of exogenous nitrate exposure, whereas processed meats and animal products are the main sources of nitrites. Vegetables, particularly green leafy vegetables like lettuce, spinach, and rocket, absorb between 80 and 95 percent of nitrates [45]. As a result, numerous nations have focused on the levels of nitrates and nitrites in various foods, particularly in vegetables and infant formula. According to Nezami and Fatemi [47], 3.65 mg kg^{-1} body weight is the acceptable daily intake (ADI) for nitrate. More than 80%-95% of nitrates can be taken up by vegetables, particularly green leafy vegetables, including lettuce, spinach, rocket, and beetroot [48]. Through an enterosalivary nitrate-nitrite-NO pathway, nitrate (NO_3^-) is transformed into nitrite (NO_2^-), which is subsequently further reduced to NO (Figure 3). While nitrate and nitrite may also play a role in the exogenous and endogenous production of carcinogenic N-nitroso compounds, the effects of dietary nitrate may vary depending on where it comes from: vegetables, processed meat, and water. While nitrates in processed meats should be avoided due to potential health risks, dietary nitrate intake from plants, particularly vegetables, appears to be beneficial for health. Carcinogenic N-nitroso compounds can be produced when processed meat nitrite is transformed into nitrosating species and reacts with secondary amines (Figure 2). It is thought that by affecting whether dietary nitrate causes the synthesis of NO or N-nitroso compounds, the food matrix and related molecules decide whether dietary nitrate poses a health danger or an advantage. The documented synergistic effects of vitamin C and Polyphenols with plant nitrate are excellent examples. These reducing chemicals can increase NO production and reduce the potential negative effects of nitrate by preventing the formation of N-nitrosamines [49].

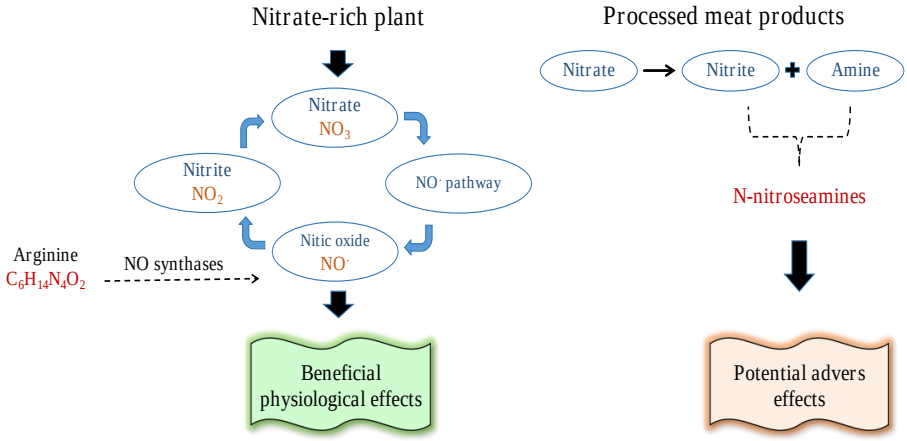

Figure 3. Nitrate and nitrite pathway according to their source.

8. Dietary Interventions for Improving Cognitive Function: Beyond Nitric Oxide

In 16 older persons (mean age 74 years), arginine supplementation has been demonstrated to improve cerebral blood flow and cognitive function [37]. To validate these early findings, however, larger and more reliable clinical trials are required. Supplementing with dietary nitrate has also been linked to notable improvements in endothelial function and blood pressure [50]. The impact of dietary nitrate on cerebral blood flow has been examined in a few studies. Overall, dietary nitrate has been linked to better cognitive functions and has been shown to increase cerebral blood flow in people of all ages; however, the longer-term nitrate supplementation effects on cognitive function in older adults (≥60 years) with cognitive impairment are yet unknown [45]. Nitrate supplementation may enhance cognitive performance by improving neurovascular coupling [51]. NO is essential for brain and

cardiovascular function. Additionally, there is a substantial correlation between brain health and vascular risk factors. Therefore, dietary nitrate intake may be linked to improved cognitive function and a lower risk of cognitive decline. Over a period of 126 months, higher dietary nitrate intake has been linked to improved language ability in non-APOE ε4 carriers and better episodic recall and recognition memory in APOE ε4 allele carriers [7]. A study discovered that consuming raw beetroot for eight weeks enhanced components of cognitive performance, including sustained attention, processing speed, and fatigue resistance, in older adults with diabetes [52].

9. Conclusions and Perspectives

Older persons have reduced nitric oxide production, which is linked to poorer cardiovascular and cognitive health. NO plays a crucial role in memory function. In the brain, NO plays an important role in neurovascular coupling, a delicate mechanism that dynamically regulates cerebrovascular blood flow to meet the metabolic needs of neurons and is critical for maintaining brain function. Despite abundant data demonstrating nitric oxide's neuroprotective effects, its use in humans is highly constrained, largely due to its side effects and pharmacokinetics. A diet rich in vegetables and leafy greens contains dietary nitrate, which plays a critical role in the exogenous production of NO, which in turn may improve cognitive functions. Most notably, there is little evidence from large prospective studies on the relationship between dietary nitrate intake and cognitive impairment. Large-scale, long-term randomized trials involving participants with or at risk of cognitive impairment are rare. These investigations are urgently needed. Future research should examine factors that influence dietary nitrate bioavailability, including age, gender, the oral microbiome's ability to reduce nitrate, comorbid diseases, and dietary and pharmaceutical medications that affect NO bioavailability. These assessments will be therapeutically useful in evaluating which people are most likely to benefit from eating more nitrate-rich plant foods.

Author Contributions

Conceptualization, M.M.H. and S.E.; software, R.S.M. and K.F.; investigation, M.M.H and R.S.M.; writing—original draft preparation, M.M.H and R.S.M.; writing—review and editing, S.E. and K.F.; visualization, R.S.M. and K.F. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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