Crucifers and related vegetables and supplements for neurologic disorders: what is the evidence?

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Purpose of review
Neurologic disorders have varied pathophysiology, yet many of them appear to have core molecular pathways that are aberrant. We review the evidence that a dietary component may have utility in ameliorating or preventing at least some of them.

Recent findings
The weight of evidence supporting prescriptive dietary recommendations to promote or enhance healthspan has been building for decades. Cruciferous vegetables are a key part of the arsenal of nutrition-based approaches for reducing the burden of chronic disease. Much new evidence suggests that neurological disorders are among the potential targets for this approach. This evidence includes at least nine clinical studies of neurodevelopmental conditions like autism spectrum disorder and schizophrenia, and there are a great many studies in animal model systems, of neurodegenerative disorders like Alzheimer's and Parkinson's diseases. This review highlights the most bioactive and most well-studied compounds from crucifers – the isothiocyanates, in particular sulforaphane.

Summary
There is great promise for the regular use of cruciferous vegetables or supplements containing standardized levels of bioactives in the treatment and prevention of neurologic disorders. Many clinical and animal studies are underway, and the evidence is building to support this strategy.

Keywords
autism, glucoraphanin, isothiocyanate, moringa, sulforaphane

INTRODUCTION

Isothiocyanates (ITC) are dietary phytochemicals found in commonly consumed cruciferous vegetables like broccoli, cauliflower, Brussels sprouts, and cabbage (otherwise known as 'cole crops' or 'crucifers'). ITCs are known in particular for their antibacterial, antifungal, antioxidant, and cytoprotective properties. They are formed by the conversion of the vacuole-entrained precursor glucosinolates to ITC mediated by myrosinase, an enzyme that is compartmentalized and sequestered in the cell, until released upon cell lysis. These glucosinolates are also converted to ITC by the microbiota in the gastrointestinal tract [1]. Apart from the crucifers, there are 15 other known plant families which produce over 120 different glucosinolates [2]. This includes glucomoringin from the *Moringa oleifera* plant, a widespread and widely cultivated tropical tree species [3]. Sulforaphane from broccoli [4] is derived from its precursor, glucoraphanin, and is the most widely studied ITC. It is a highly promising agent currently under preclinical and clinical evaluation for disease prevention. Depending on their use, ITC like sulforaphane and moringin from glucomoringin can be considered foods, dietary supplements or natural product-based drugs [1].

Chronic oxidative stress and inflammation are central to the pathogenesis of many chronic diseases, including neurologic disorders. The evidence supporting a protective effect of ITC in neurodevelopmental, neurodegenerative, and other neurologic disorders is rapidly accumulating both from preclinical and clinical studies. For example, several *in vitro* and clinical studies provide evidence that sulforaphane neutralizes a host of molecular

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KEY POINTS

- Cruciferous vegetables (also known as 'crucifers' or 'cole crops') are a key part of the arsenal of nutrition-based approaches for reducing the burden of chronic disease and increasing healthspan.
- Neurodevelopmental conditions such as autism and schizophrenia, neurodegenerative conditions such as Alzheimer's and Parkinson's diseases, as well as some other neurologic disorders, all seem to be potential targets for diet-based therapy and prevention, based upon higher crucifer consumption.
- Cruciferous vegetables or supplements containing standardized levels of sulforaphane or other ITC or their precursors are now being shown to have important and measurable pharmacodynamic activities, in the clinic and in preclinical studies.
- Several key cytoprotective pathways are common to different neurologic conditions and they are implicated in both the cure and prevention of these diseases; all these pathways are regulated by ITC from crucifers and from the tropical vegetable *Moringa oleifera*.

abnormalities associated with autism spectrum disorders (ASD), including lower antioxidant capacity and oxidative stress, defects in glutathione synthesis, mitochondrial dysfunction, increased lipid peroxidation, and neuroinflammation. Furthermore, because it readily crosses the blood–brain barrier, sulforaphane is able to exert its pharmacodynamic effects in the central nervous system [1].

A key mechanism of action of sulforaphane is the activation of the transcription factor nuclear factor-erythroid 2-related factor 2 (Nrf2), which regulates the expression of at least 2% of the coding human genome, inducing an extensive array of cytoprotective responses [1]. These long-lasting enzymatic changes protect against oxidative and electrophilic stress and chronic inflammation. Upon its interaction with specific cysteine residue sensors on the cytoplasmic tether peptide Kelch-like ECH-associated protein 1 (Keap1), sulforaphane frees Nrf2 to translocate to the nucleus and activate transcription of a coordinate set of genes coding for phase 2 detoxification enzymes. Separately, sulforaphane also has potent anti-inflammatory, heat shock-response (HSR)-inducing, and histone deacetylase (HDAC) inhibiting properties within the cell. In this review, we explore recent reports on exploiting these critical cytoprotective responses to understand how a food-sourced phytonutrient may act on neurologic conditions associated with common physiological abnormalities, including oxidative stress and inflammation. These effects have been probed clinically using sulforaphane in various disease systems, as reviewed recently [5▪,6,7]. Within each category presented herein, we summarize clinical evidence if available, or else we present significant animal or cell-based work with near-term translational potential.

NEURODEVELOPMENTAL CONDITIONS

A number of small clinical studies have recently targeted neurodevelopmental conditions with ITC intervention. We believe these represent the first such attempts to intervene in these disorders of clearly disparate cause and pathophysiology, by targeting a small number of potentially common pathways with phytochemicals.

Autism spectrum disorders

ASD are a group of life-long neurodevelopmental disorders including deficits in social communication and interaction, and restricted and repetitive behavior, and affect an estimated one out of 59 children aged 8 years in the United States. There is no U.S.A. Food and Drug Administration (FDA)-approved medical therapy that addresses either its core symptoms or the pathophysiological processes associated with the disorder [1]. The first clinical trial in which an ITC was administered to individuals with ASD was conducted at the Massachusetts General Hospital with a hypothesis formed around targeting the HSR pathway and its connection to the 'fever response', which affects a sizable proportion of those on the autism spectrum [8]. Sulforaphane extracted from 3-day-old broccoli sprouts was delivered daily for 18 weeks to 44 male adolescents and young adults with ASD in a double-blind, randomized trial (NCT01474993). Significant improvements in behavioral symptoms were reported, including social interaction, aberrant behavior, and verbal communication. Symptoms returned to pretreatment levels at the end of a 4-week washout period. Responders in this trial have been followed for a further 3 years or more of self-administered broccoli-based supplements, and many continue to report positive results [9▪]. At this point, there are five studies underway or recently concluded that are attempting to replicate these findings (NCT02561481, NCT02879110, NCT02677051, NCT02909959, NCT02654743). The first of these studies reported that 77 urinary metabolites, including seven different sphingomyelins, correlated with symptom improvement following daily consumption of a broccoli sprout supplement producing sulforaphane for 12 weeks [10▪▪]. The second (led by A. Zimmerman who directed the original published trial [8]) has just concluded its intervention and

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behavioral assessment phase, and the correlated biomarker analyses are underway.

Schizophrenia

Schizophrenia interferes with a person's capacity for clear thinking, emotion management, decision-making, and management of relationships. It, like ASD, is complex, variable, and with a clear genetic component. Unlike ASD, it is generally managed with strong doses of antipsychotic drugs. Symptoms of schizophrenia can be detected prior to the onset of the disorder (prodromal) and thus there is an interest in early interventions, including dietary intake of potent indirect antioxidants like ITC. Biomarker-involved clinical trials are ongoing to evaluate the effects of sulforaphane on schizophrenia in China and the United States (NCT02880462, NCT02810964 and NCT01716858). Results of two other relevant human trials have also been reported. In a small open phase trial, improvement in the accuracy component of the One Card Learning Task was reported in patients with schizophrenia after treatment with sulforaphane for 8 weeks, though no other changes were detected [11]. When healthy human volunteers ingested sulforaphane, daily for 7 days, increases in glutathione (the body's most abundant antioxidant) in the blood correlated with glutathione increases at specific sites in the brain (using noninvasive 7-Tesla magnetic resonance spectroscopy imaging) [12▪]. Results from at least two mouse models have been reported. When pregnant dams were subjected to maternal immune activation, offspring of those fed with a glucoraphanin-rich diet were protected from cognitive defects and this effect was carried into adulthood [13]. Separately, attenuation of cognitive deficits in juvenile male mice after repeated administration of phencyclidine was reported when they were pretreated with either sulforaphane or glucoraphanin [14].

Cerebral palsy

The offspring of rat dams subject to chronic intrauterine ischemia and supplemented with broccoli sprouts were less likely to develop neurocognitive impairment than their nontreated counterparts. This ischemia-based impairment is thought to model cerebral palsy, a neurodevelopmental disorder associated with placental insufficiency and intrauterine growth restriction [15].

Fetal alcohol syndrome disorders

Neural crest cells (NCCs) are a particularly ethanol-sensitive population of cells in the embryo and are implicated in this syndrome. Treatment with sulforaphane significantly diminished apoptosis in mouse embryos exposed to ethanol *in vivo* [16]. In NCCs, sulforaphane prevented ethanol-induced apoptosis by inhibiting HDAC and increasing histone acetylation, which suggest that sulforaphane may prevent fetal alcohol syndrome disorder through epigenetic regulation of the expression of antiapoptotic genes [16].

Although we can find no evidence of relevant studies in which crucifers or their ITCs were tested against other neurodevelopmental disorders, such as intellectual development disorder (IDD), attention deficit hyperactive disorder (ADHD), Tourette syndrome, Down syndrome, or Minamata disease, they share some common physiological abnormalities targeted by ITC with ASD and schizophrenia that are definitely worth exploring.

NEURODEGENERATIVE CONDITIONS

Oxidative stress is involved in the pathophysiology of many neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, and multiple sclerosis [17]. As such, induction of Nrf2 by sulforaphane and moringin, along with other inducers of the transcription factor, has been receiving increasing attention for their potential to ameliorate the debilitating effects of these disorders. Several researchers have done such studies in preclinical models of these disorders as reviewed below.

Alzheimer's disease

Alzheimer's disease is the most common neurodegenerative disease with over 46 million cases of dementia across the globe [18]. Several animal studies have shown promising effects of ITC on prevention of the tau protein and amyloid-β plaques, two well-known markers of Alzheimer's disease, as well as other beneficial functions in reducing cognitive decline. Enhanced brain-derived neurotropic factor (BDNF) expression was reported in sulforaphane-treated mouse primary cortical neurons and a triple-transgenic Alzheimer's disease mouse model, and increased acetylation of certain histones and inhibition of HDAC prompted the hypothesis that sulforaphane has the potential to prevent Alzheimer's disease by epigenetically enhancing neuronal BDNF expression [19]. In the same mouse model, oral gavage of sulforaphane reduced protein levels of amyloid-β and tau by upregulating the heat shock protein HSP70 and cochaperone CHIP, and in so-doing ameliorated memory deficits as revealed by novel object/location recognition tests and

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contextual fear conditioning tests [20▪]. Four other rodent studies also showed protective effects of sulforaphane against Alzheimer's disease. In the first, sulforaphane administration ameliorated spatial cognitive impairment and locomotor activity decrease, and reduced the number of amyloid-β plaques in the hippocampus and cerebral cortex of Alzheimer's disease lesion mice [21]. These authors further found that sulforaphane regulated specific HDAC, resulting in a reduced burden of amyloid-β plaques in the Alzheimer's disease mouse model [22]. Others have reported a reduction of amyloid-β aggregates and a delayed cognitive decline when transgenic Alzheimer's disease mice were treated with sulforaphane [23]. Further, administration of sulforaphane in adult mice induced a variety of changes that are involved in memory consolidation and spatial learning [24]. And finally, rats supplemented with *Moringa peregrina*, presumably rich in the ITC moringin, displayed significant enhancement in their short-term and long-term memories, and had increased brain-derived neurotrophic factor (BDNF), glutathione and glutathione peroxidase (GPx) levels and decreased oxidized glutathione in the hippocampus [25]. An array of *in vitro* experiments complements these animal data [26].

Parkinson's disease

Parkinson's disease is a progressive neurodegenerative disorder characterized by loss of motor function due to the degeneration of dopaminergic neurons in the substantia nigra of the brain. The pathogenic process involves neuroinflammation, oxidative stress, mitochondrial dysfunction, and protein aggregation. We are aware of only one relevant clinical study (now underway), which is examining the effects of a moringa supplement (presumably rich in the ITC moringin) for its effect on X-linked Dystonia–Parkinsonism in the Philippines (NCT03019458). There have recently been a number of studies including the use of a knockout mouse model in which mitochondrial respiration is inhibited, ultimately leaving rodents vulnerable to dopamine-induced neurodegeneration. Sulforaphane treatment of cocultured midbrain neurons and astrocytes isolated from the knockout mice reduced dopamine-induced cell death and restored the mitochondrial membrane potential [27]. Separately, human neuroblast cells treated with sulforaphane had increased levels of glutathione and Nrf2, and were resistant to apoptosis induced by a selective neurotoxin, and the *in vitro* finding was confirmed in a Parkinson's disease mouse model [28]. In another Parkinson's disease mouse model, sulforaphane treatment inhibited rotenone-induced locomotor activity deficiency and dopaminergic neuronal loss by Nrf2-dependent reductions in oxidative stress, mTOR-dependent inhibition of neuronal apoptosis, and the restoration of normal autophagy [29]. Although not from cruciferous vegetables, two synthetic ITC protected dopaminergic neurons from degeneration and prevented motor deficits associated with Parkinson's disease in mice [30,31].

Multiple sclerosis

Multiple sclerosis is an inflammatory-mediated demyelinating disease of the human central nervous system with neurodegeneration as the major cause of irreversible neurological disability in multiple sclerosis patients. Two recent studies have reported on the protective effects of the ITC moringin on experimental autoimmune encephalomyelitis mice (the most widely used rodent model for multiple sclerosis). Mice pretreated with moringin daily for 1 week had increased expression of Nrf2, decreased cell apoptosis, and suppressed aberrant Wnt-β-catenin signaling [32]. Further, application of a 2% moringin cream as a topical treatment for multiple sclerosis in this model relieved neuropathic pain by attenuating the production of proinflammatory cytokines interleukin-17 and interferon-γ, while increasing the expression of interleukin-10 (IL-10), an anti-inflammatory cytokine [33].

Amyotrophic lateral sclerosis

ALS is a progressive neurodegenerative disease in which motor neurons degenerate and die, resulting in the inability to control muscle movement. The effects of moringin on a transgenic rat model for ALS were evaluated following daily treatment for 2 weeks prior to onset of disease. There were protective effects of the ITC, based on biomarkers, as well as inhibition of the motor neuron degradation that is central to ALS pathophysiology [34].

Huntington's disease

Huntington's disease is an inherited autosomal dominant neurodegenerative disorder characterized by adult-onset of motor dysfunctions, psychiatric disturbances, and intellectual decline. Mitochondrial dysfunction is a molecular feature implicated in several neurologic diseases, such as ASD and Huntington's disease. An experimental rodent model of Huntington's disease was used to demonstrate that

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sulforaphane exhibited neuroprotective effects against quinolinic acid-induced damage by reestablishment of the mitochondrial function [35].

Friedreich's ataxia

Friedreich's ataxia is an inherited, progressive neurodegenerative disease involving oxidative stress and mitochondrial dysfunction, with the expression of the mitochondrial protein frataxin (a protein involved in voluntary movement of muscles) consistently decreased in patients. Treatment of frataxin-silenced motor neurons with sulforaphane activated phase 2 cytoprotective response, restored glutathione balance, increased frataxin expression, and triggered axonal re-growth. Sulforaphane treatment also restored Nrf2 transcriptional activity in fibroblasts of patients with Friedreich's ataxia [36].

OTHER NEUROLOGIC DISORDERS

Both neurodevelopmental and neurodegenerative conditions have striking overlaps in their underlying pathological mechanisms. These mechanisms include neuronal cell death, activated microglia, neuroinflammation, disrupted redox homeostasis, mitochondrial dysfunction, and synaptic dysfunction, and all are involved in the pathophysiologies of ASD and schizophrenia, as well as that of Alzheimer's disease, Parkinson's disease, and Huntington's disease. Each of these mechanisms is affected by activation or inhibition of major regulatory pathways in the body, including Nrf2, NFκB, and HSR. These pathways are implicated in other neurologic disorders as well.

Spinal cord injury

This is a condition in which neurologic dysfunction and neuronal death is clearly a result of inflammatory and oxidative insult. In two separate mouse models, when inflammatory pain was induced in the spinal cord of mice using complete Freund's adjuvant, sulforaphane treatment increased the expression of Nrf2 and phase 2 cytoprotective enzymes, and inhibited inducible nitric oxide synthase 2 and other markers induced by inflammation [37]. Sulforaphane also enhanced the antinociceptive actions of morphine, making the alleviation of pain more effective than morphine alone [37]. When spinal cord injury was induced by the application of vascular clips, moringin administered postinjury protected against the secondary damage after spinal cord injury by reducing oxidative stress, inflammation, and apoptosis [38].

Traumatic brain injury

Traumatic brain injury is generally caused by blunt force and is similar in its pathophysiology to stroke-induced cerebral ischemia in that there is cellular damage due to excitotoxicity, oxidative stress, apoptosis, and inflammation. Moringin treatment of rats with cerebral ischemia/reperfusion (CIR) injury (to model traumatic brain injury) prevented CIR-induced damage and decreased the related cascade of inflammatory and oxidative mediators that exacerbate the progression of the disease [39]. Two other rat studies utilized a similar CIR model and found congruent protective effects of sulforaphane against CIR-induced damage and inflammation [40,41]. In parallel, use of a model in which vascular cognitive impairment was induced by ischemia led to similar findings of sulforaphane's protective effects [42]. Nrf2 upregulation and reduced inflammation were also reported as a result of sulforaphane treatment in rodent models of subarachnoid hemorrhage [43] and intracerebral hemorrhage [44].

Diabetes-related cognitive decline

There is strong evidence showing correlation and perhaps even a pathophysiologic link between type 2 diabetes and cognitive dysfunction/decline including increased risk of Alzheimer's disease [45▪]. Mechanisms appear to include defects in insulin signaling, neuroinflammation, and mitochondrial metabolism, at a minimum [45▪]. ITC effectors of Nrf2 have been studied for their ability to attenuate diabetic complications and related cognitive decline [46,47]. In a streptozotocin diabetic rat model, supplementation with sulforaphane prevented impairment in learning and memory; sulforaphane treated mice exhibited reduced decline in memory, apoptosis of their hippocampal neurons, and abnormal expression of critical signaling molecules (e.g., caspase-3 and induced myeloid leukemia cell differentiation protein (MCL-1)) [48]. Similarly, hyperglycemic rats supplemented with *M. oleifera* leaves or seeds (presumed to be rich in moringin) had higher levels of a number of antioxidant enzymes and glutathione compared to control rats without supplementation, and concomitant decreases in a number of biomarkers of hyperglycemia-associated cognitive decline [49].

Depression/anxiety

Mice subject to acute or chronic stress display depressive and anxiety-like behaviors, now shown to be linked with immune dysregulation. The response of acute and chronically stressed mouse models to treatment with sulforaphane has been

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evaluated [50]. Sulforaphane treatment significantly reversed anxiety-like behaviors of acutely and chronically stressed mice. Serum corticosterone, adrenocorticotropic hormone, interleukin-6, and tumor necrosis factor (TNF)-α were all reduced following sulforaphane treatment of chronically stressed mice, leading to speculation that the antidepressant-effects and anxiolytic effects of sulforaphane occur via inhibition of the hypothalamic–pituitary–adrenal axis and the inflammatory response [50]. A separate study treated chronically stressed mice with 0.1% dietary glucoraphanin during juvenile and adolescent stages, which prevented the depression-like phenotype evoked in adulthood [51]. Nrf2 knockout mice were more sensitive than wildtype mice to the effects of chronic stress suggesting that the Nrf2 cytoprotective response may play a key role in depression. And finally, sulforaphane was shown to be prophylactic for depression induced by lipopolysaccharide (LPS; inflammation) injection in mice [52]; treatment with sulforaphane suppressed the increase in TNF-α, increased microglial activity and IL-10, and ameliorated depressive behaviors among other effects compared to untreated mice.

N.B. Although not within the window of very recent publications covered herein, we would also like to point out a complimentary, well-done review that covers similar subject matter, focusing primarily on neurodegenerative conditions [53].

CONCLUSION

The consumption of cruciferous vegetables or supplements rich in phytochemicals present in the cruciferous vegetables as a dietary means of enhancing healthspan and reducing chronic diseases is associated with greatly diminished toxicologic potential compared to the administration of existing drugs. Although, of course, components of the glucosinolate/myrosinase/ITC system described herein are not the only phytochemicals in these vegetables, they are the potent, and very biologically available compounds that most make these vegetables unique in the plant world, and that have been most associated with their medicinal properties. Surely, there are also well-documented toxic effects associated with overconsumption of cruciferous vegetables (e.g., cabbages rich in indoles and thiocyanates), and there are many plant-derived frank toxins. However, many classes of plants including the crucifers have been safely consumed by wide swaths of the world's population for millennia. It was not the objective of this review to summarize the extensive epidemiologic evidence underpinning much of the basic and translational science that makes it to the clinic, but we would be remiss not to point out that hundreds of epidemiologic studies point to a chemoprotective effect of cruciferous vegetables. Our understanding of the mechanisms of protection now allows us to understand better why this protection appears to span a very large range of chronic conditions including those of both neurodevelopmental and neurodegenerative origin.

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Conflicts of interest

The authors confirm that this article has no conflicts of interest.

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