Review

An overview on neuroprotective effects of isothiocyanates for the treatment of neurodegenerative diseases

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Abstract

The discovery of new natural compounds with pharmacological properties is a field of interest widely growing, especially for the management of neurodegenerative diseases. As no pharmacological treatment is available to prevent the development of these disorders, dietary intake of foods or plant-based extracts with antioxidant properties might have beneficial effects on human health and improve brain functions. Isothiocyanates (ITCs), derived from the hydrolysis of the corresponding glucosinolates (GLs), mainly found in Brassica vegetables (Brassicaceae) and, to a lesser extent, in Moringa plants, have demonstrated to exert neuroprotective properties. Specifically, strong evidences suggest that antioxidant effects may be ascribed mainly to their peculiar ability to activate the Nrf2/ARE pathway, but alternative mechanisms of action have also been suggested. This review summarizes the current knowledge about the neuroprotective effects of ITCs in counteracting oxidative stress as well as inflammatory and apoptotic mechanisms, using in vitro and in vivo models of acute and chronic neurodegenerative disease. Therefore, ITCs could be regarded as a promising source of alternative medicine for the prevention and/or treatment of neurodegenerative diseases.

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Abbreviations: ITCs, isothiocyanates; GLs, glucosinolates; R-SFN, R-sulforaphane; 4R-1-isothiocyanato-4-methylsulfonylbutane; GEA, glucosinolates; SFN, R-sulforaphane; GEA, glucosinolates; R-SFN; GMG-ITC, glucomoringin isothiocyanate; HO-1, heme oxygenase-1; NQO1, NADPH quinone oxidoreductase; 4-HNE, 4-hydroxynonenal; AQP4, aquaporin-4; COX-2, cyclooxygenase-2; 4-IPITC, 4-iodophenyl isothiocyanate; HO-1, heme oxygenase-1; NQO1, NADPH quinone oxidoreductase; 4-HNE, 4-hydroxynonenal; AQP4, aquaporin-4; COX-2, cyclooxygenase-2; 4-IPITC, 4-iodophenyl isothiocyanate; HO-1, heme oxygenase-1; NQO1, NADPH quinone oxidoreductase; 4-HNE, 4-hydroxynonenal; AQP4, aquaporin-4; COX-2, cyclooxygenase-2; MIF, macrophage inhibitory factor.

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1. Introduction

1.1. Glucosinolates and isothiocyanates

Several epidemiological and pharmacological studies have demonstrated that plant-derived chemical compounds potentially have health-promoting properties. A wide variety of phytochemicals, in particular dietary glucosinolates (GLs) and their breakdown products, isothiocyanates (ITCs), have been shown to prevent the risk of carcinogenesis and certain chronic diseases, such as neurodegenerative diseases [1–3]. Since the pioneering studies of Zhang et al. [4] on broccoli extract and sulforaphane, several hundred papers have focused on this ITC, which is one of the most potent naturally-occurring inducers of the Keap1/Nrf2/ARE pathway [3,5]. A number of mechanisms may contribute to the established bioactivity of the ITCs, the main one being a favorable modulation of the enzyme systems involved in the metabolism of chemical carcinogens. Contrary to what is reported in many articles, the ITCs are not produced as such by the plant, but rather released after cell damage by the enzymatic action of myrosinase (β-thioglucosideglucohydrolase; E.C. 3.2.1.147) on the glucosinolate (β-thioglucoside-N-hydroxysulfates; GLs) precursors. GLs are present in sixteen families of dicotyledonous angiosperms including a large number of edible species [6,7]. To date, about 130 different GLs have been identified in plants of the botanical order Brassicales, and their breakdown products have long been known for their fungicidal, bactericidal, nematocidal and allelopathic properties. In other respects, they have recently attracted intense research interest because of their protective effect against cancer and neurodegenerative disorders. R-sulfuraphane (4R-1-isothiocyanato-4-((methylsulfinyl)butane; R-SFN) is released by the enzymatic action of myrosinase on the GL precursor glucoraphanin (GRA; (R6)-4-methylsulfinylbutyl GL) [8], as reported in Fig. 1. The configuration of the sulfoxide stereogenic center in the GRA side chain was recently ascertained by NMR to be R6, a configuration retained in the hydrolysis product R-sulfuraphane [9]. Subsequently, quite a number of published studies using, either in vitro or in vivo, synthetic R,S-sulfuraphane (SFN), should be considered unreliable and confusing. As a matter of fact, marked differences in the modulation of cytochrome P450 and of the phase II enzymes by the two enantiomers of sulforaphane, have been recently reported [10]. In the course of the past two decades, several studies both in vitro and in vivo have been conducted on the health effect of synthetic SFN, which is by far the most extensively studied ITC. Reported health benefits of this compound and proposed underlying mechanisms have been recently disclosed [11]. The fact that most GLs, such as GRA which is the precursor of R-SFN, are not commercially available – at least not in the quantities required for pharmacological investigations – justified in part the use of synthetic compounds. The difficulty has recently been overcome by the development of a method for the gram-scale purification of GRA [8]. In the same laboratory, the procedure was further extended to the purification of another GL, glucoromoringin (GMG; 4-(α-L-rhamnosyloxy)-benzyl GL) found in the Moringaceae family. GMG, a member of an uncommon small group of glycosylated benzylic GLs, was best obtained from seeds of the most widely distributed Moringa oleifera Lam. [12]. Commonly known as drumstick tree, M. oleifera is a small sized tree belonging to the Moringaceae family, widely cultivated in Asia, Africa and other tropical parts of the world for food and valued for its medicinal properties as anti-inflammatory and antioxidant agent. The glycosylated isothiocyanate moringin [4-(α-L-rhamnosyloxy)-benzyl isothiocyanate; GMG-ITC], resulting from quantitative myrosinase-induced hydrolysis of GMG under neutral conditions [Fig. 1], has been shown to exert not only an effective antitumor-promoting activity [13] but also anti-inflammatory and antioxidant effects, protecting against neurodegenerative disorders [12].

2. Isothiocyanates (ITCs) in nervous system, neurodegeneration and neurodegenerative diseases

Nervous system (NS), both central (CNS) and peripheral (PNS), is composed of an extremely fine weave of nervous cells characterized by several and different functions aimed to regulate and coordinate body activities.

Despite the presence of defense mechanisms, NS can result vulnerable to various dangers and damages, represented by more than 600 identified disorders.

Neurodegenerative disorders are a heterogeneous group of diseases of the NS, which have different etiologies [14]. Many are hereditary, some are secondary to toxic or metabolic processes, and others result from infections and trauma. Neuropathologically, these are chronic and progressive disorders characterized by the gradual loss of neurons in defined areas of the CNS. Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), traumatic brain injury (TBI), spinal cord injury (SCI) and cerebral ischemia/reperfusion (CIR) are considered the disorders with the highest incidence in the population worldwide. The cause of this neurodegeneration is still unknown; although it has been suggested that mainly oxidative stress plays a key role in its development [15]. Briefly, oxidative stress is the result of an imbalance in pro-oxidant/antioxidant homeostasis that leads to the generation of free radicals [16]. There are evidences which suggest that an increase in energy metabolism by aerobic pathways enhances the intracellular concentration of reactive oxygen species (ROS), which in turn increases the rate of the autocatalytic process of lipid peroxidation, inducing damage to brain structures. When oxidative stress occurs, cells function to counteract the resulting oxidant effect and to restore the redox balance.

![Fig. 1. Formation of R-sulfuraphane (R-SFN) from glucoraphanin (GRA) and of moringin (GMG-ITC) from glucoromoringin (GMG).](image-url)
To date, there is no cure for this kind of diseases. Existing therapies have aimed at treating the symptoms and trying to delay their progression. For this reason, a current trend in the field of pharmacology leads to look at natural compounds as a source of powerful and effective antioxidant agents in the treatment of these devastating pathologies. In this scenario, growing interest has been focused on the neuroprotective properties of natural compounds and in particular glucosinolates (GLs), a group of secondary metabolites found mainly in Brassica vegetables (Brassicaceae) and, to a lesser extent, in Moringaceae plants, to help in maintaining human health [17]. Increased consumption of these natural phytochemicals has been associated with a decreased risk of several neurodegenerative disease developments. Specifically, the hydrolysis of GLs by the plant enzyme myrosinase results in the formation of the corresponding biologically active ITCs [18].

Among ITCs, R-sulforaphane, derived from the hydrolysis of the glucosinolate GRA as well as morin (4-(α-L-rhamnosyloxy)-benzyl ITC, GMG-ITC) derived from the hydrolysis of the glucosinolate GMG isolated from M. oleifera plant, have been proven to have neuroprotective activity in either in vitro or in vivo models of neurodegeneration due to their ability not only to address many targets, but also to modulate different pathways in neuronal cells [11,17,19,20]. Espeically, evidences suggest that beneficial effects of ITCs could be mainly ascribed to their peculiarity to activate the nuclear factor erythroid-derived 2-related factor 2 (Nrf2)/ARE pathway, exerting consequently antioxidant functions [21].

ITCs can interact directly with sulfhydryl residues on the Kelch-like-ECH-associated protein 1 (Keap1), the repressor of Nrf2 which is normally present in cytoplasm, leading to its release into the nucleus (Fig. 2). Alternatively, SFN can activate the MAPK pathway, causing phosphorylation of Keap1 and release of Nrf2 [22]. Once translocated into the nucleus, Nrf2 activates ARE-responsive genes and induces the phase 2 response [23].

Furthermore, it is clear that ITCs are active on CNS and PNS, through mechanisms that involve the modulation of the inflammatory pathways as well as the reduction in the activation of cell death by apoptosis. Specifically, it was demonstrated in various experimental models of neurodegeneration that these phytochemicals are able to significantly decrease nuclear factor (NF)–κB translocation and consequent pro-inflammatory cytokine production (IL-1β, TNF-α), as well as the triggering of oxidative species generation (i-NOS, nitrotyrosine and PARP) and neuronal apoptotic death pathway (caspase 3 and Bax/Bcl-2 unbalance) (Fig. 2).

As R-SFN is a component of the usual human diet, it is most probably safe for administration and may be orally administered as a food supplement (Prostaphane® by Nutrinov). Therefore, ITCs could be promising compounds with neuroprotective effects in preventing and/or treating disorders related to nervous system at least in association with current conventional therapies.

In this review we report the most significant data regarding the current status of therapeutic effects of ITCs in counteracting oxidative stress as well as inflammatory and apoptotic mechanisms on acute and chronic neurodegenerative disease.

2.1. ITCs in Alzheimer’s disease

Alzheimer’s disease (AD) is the most common type of dementia with a prevalence of approximately 10% in humans over 80 years old. It seems that a small proportion of AD cases may have a genetic basis (early-onset), but the majority are sporadic (late-onset). Although AD has been widely investigated, its pathogenesis remains to be fully clarified.

A key event in AD pathogenesis certainly is the conversion of amyloid beta 1–40 peptide (Aβ) from its soluble form into aggregates in the brain [24,25]. Another pathological hallmark is the formation of intracellular neurofibrillary tangles caused by the hyperphosphorylation of microtubule-associated protein tau by altering interneuronal communication [26]. These features result in a progressive decline in memory and impairment of cognitive functions, including difficulties with thinking, problem-solving or language [27].

Evidences suggest that oxidative stress and abnormal deposition of Aβ increase the intracellular oxidative damage and contribute to an inflammatory response [28,29]. In addition to direct damage from oxidative stress, indirect damage due to by-products of lipid peroxidation is also likely. Therefore, it is possible that administration of antioxidants blocking or suppressing these detrimental processes of Aβ could protect or prevent AD development. These compounds could also be bound to ubiquitin–proteasome, a non-lysosomal protein degradation mechanism that controls protein turnover and removes abnormal proteins [30].

Several studies performed on neuronal cell lines have shown that neuroprotective effects of SFN against oxidative stress and Aβ-mediated cytotoxicity could be due in part to up-regulation of the proteasome system [31–33]. It has also been observed that the expression of multiple subunits of the proteasome was up-regulated by SFN through the Nrf2 pathway activation [31]. These findings suggest that the induction of proteasome by SFN may facilitate the clearance of the Aβ aggregates and lead to the improvement of protein misfolding in AD.

Kim et al. [34] investigated neuroprotective effects of SFN in acute AD mouse model. In order to initiate learning and memory deficiency, mice subjected to a single intracerebroventricular (icv) injections of Aβ aggregates were then administered with SFN via intraperitoneal (ip) injection for 6 days. It was demonstrated that SFN improved spatial working memory and contextual memory of the disease model in mice subjected to Y-maze and passive avoidance behavior tests, although it did not directly interact with Aβ [34]. In this study, the exact mechanism of interaction of SFN in AD has not yet been ascertained. It shows only that SFN administration can aid in cognitive impairment and may protect the brain from amyloidogenic damages [34].

Moreover, using the same experimental mouse model of AD, the major constituents of Brussels sprouts (3’,4’,5,7-tetrahydroxyflavone (kaempferol), indole-3-carbinol, and phenethyl isothiocyanate) were tested [35]. Among these, kaempferol exhibited the most potent activity compared to the other compounds. It was found that dietary supplementation with kaempferol exerted a neuroprotective action against Aβ-induced neurotoxicity in mice due to its antioxidant activity, as shown by a decreased level of lipid peroxidation in brain tissues. Furthermore, Brussels sprout extract restored deficits in short-term memory. Additionally, in the same study, cell viability and intracellular stress were evaluated on PC12 cells. It was found that the beneficial effect of Brussels sprout extract treatment on cell viability was concentration-dependent. Specifically, there was a trend of increase in

![Fig. 2. Schematic summary of the main proposed mechanisms underlying neuroprotective effects provided by ITCs.](Image)
cell viability with the highest used concentration. On the contrary, intracellular oxidative stress levels were significantly decreased independently of the used concentration [35].

Recently it has been found that *M. oleifera* leaf extract, rich in ITCs, enhances memory via nootropic activity and provides substantial antioxidants into counteracting oxidative stress in rat model of AD induced by icv infusion of colchicine. Several lines of evidence also suggest that chronic oral treatment by an ethanolic extract of *M. oleifera* can alter electrical activity in brain and production of monoamines, including norepinephrine, dopamine and serotonin, involved in memory processing, thus ameliorating cognitive functions [36,37]. Moreover, it was found that this extract is able to increase the activity of superoxide dismutase (SOD) and catalase (CAT) enzymes as well as to decrease lipid peroxidase (LPO) activity in the cerebral cortex of AD rats by acting as free-radical scavenger [37].

Currently, there are no effective therapies available to prevent AD progression and neurodegeneration. Therefore, in light of the above findings, ITCs can be proposed for their antioxidant properties as a complementary and promising strategy to approach AD treatment.

Moreover, to date there are no significant data reported in the literature on the use of ITCs in the treatment of vascular dementia.

### 2.2. ITCs in Parkinson’s disease

Parkinson’s disease (PD) is the second most common neurodegenerative disorder, affecting about 6.3 million people worldwide. The age of onset is usually over 60, but about 1 in 10 people develop the disease below the age of 50. Patients affected by PD exhibit tremor, muscular rigidity, and postural instability as major symptoms. The disease is associated with progressive loss of pigmented dopaminergic neurons in the substantia nigra pars compacta with consequent reduction in dopamine (DA) content in striatum and the presence of Lewy bodies, consisting of alpha-synuclein aggregates [38]. The pathogenesis of PD is multifactorial with a complex combination of genetic and non-genetic components, whereas non-genetic or sporadic form represents the majority of these cases.

In order to better understand the etiopathogenesis of PD and find new therapeutic strategies, researchers use some experimental models. Among these, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) are the most used models that replicate typical hallmarks observed in human PD [39].

Recent studies have demonstrated that ITCs, isolated from cruciferous vegetables, may be used as potential candidates for the treatment and prevention of PD, due to their capacity to address several targets and modulate different pathways, involving inflammatory and oxidative events as well as cell death in neuronal cells [17,20].

In MPTP mouse model, intraperitoneal treatment with SFN counteracts the MPTP-induced loss of dopamine neurons from the substantia nigra pars compacta and preserves striatal dopamine levels [40]. It was demonstrated that SFN administration leads to an increase of Nrf2 protein levels in the basal ganglia and an upregulation of phase II antioxidant enzymes such as heme oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase (NQO1). SFN was also found to reduce astroglisis, microglia activation and the release of IL-6 and TNF-α proinflammatory cytokines [40].

Moreover, using 6-OHDA as a model of dopamine neuronal degeneration, Morrone et al. [41], demonstrated that SFN is able to slow down the progression of PD by counteracting oxidative stress and apoptotic pathways. In detail, PD was induced in mice with unilateral stereotaxic intrastriatal injection of 6-OHDA, and then mice were then treated with intraperitoneal SFN for 4 weeks. The authors found that SFN protected dopaminergic neurons from neurotoxic effect of 6-OHDA, probably due to its ability to increase glutathione levels and its related enzymes (glutathione-5-transferase and glutathione reductase) as well as to its ability to modulate ERK1/2 activation [41]. SFN has also been shown to protect against apoptosis via blocking DNA fragmentation and caspase-3 activation. In addition, SFN treatment significantly ameliorated behavioral impairments such as motor performance [41].

In 2012, Wellejus et al. [42] reported data obtained from different models of neurodegeneration, including MPTP mouse model, about effects of the synthetic 4-iodophenylisothiocyanate (4-IPITC). They demonstrated that 4-IPITC is able to bind to both monoamino oxides A and B (MAO-A and MAO-B) as well as to the dopamine transporter (DAT), resulting in this way as a promising agent for the treatment of PD [42].

A new formulation of glucoraphanin [GRA; (Rc)-4-methylsulfinylbutyl glucosinolate] extracted from Tuscan black kale seeds (*Brassica oleracea* L. var. *Acephala sabellica*) and bioactivated with myrosinase, providing a therapeutic natural agent to counteract the overall cascade of secondary events triggered by PD induction, was recently investigated [43]. In this study, a protective role of the bioactivated GRA against MPTP neurotoxicity in mice was demonstrated. Specifically, bioactivated GRA is able to reduce DAT degradation, tyrosine hydroxylase expression, as well as the triggering of neuronal apoptotic death pathway and the generation of free radicals by oxidative stress. In particular, the significant expression of Nrf2, found by immunohistochemical analysis of mice brain treated with bioactivated GRA, seems to play a protective action in MPTP-induced PD, decreasing GFAP expression through a mechanism related to the glutathione activity [43]. In addition, these effects have been correlated with the release of neurotrophic factors, such as GAP-43, NGF and BDNF, probably, playing a supporting role in the neuroprotective action of bioactivated GRA. Moreover, administration with bioactivated GRA ameliorated motor deficits such as movement coordination and tremors [43].

Furthermore, numerous studies have been performed in vitro in order to evaluate antioxidant properties of ITCs. According to Tarozzi et al. [44], treatment of the dopaminergic-like neuroblastoma SH-SY5Y cells with SFN prevented events of cell death induced by H2O2 or 6-OHDA, including mitochondrial depolarization, caspase-9 and -3 activations and DNA fragmentation, by increasing total GSH level and normalizing the intercellular redox status. Moreover, in Deng et al.’s studies, it was demonstrated that SFN is able to protect dopaminergic neurons against 6-OHDA-induced cytotoxicity in rat PC12 cells through the activation of Nrf2–ARE pathway [45], and to reduce caspase-3 activation and subsequent cell death [46].

It was also found that SFN can protect DAergic cells (CATHA and SK-N-BE(2)C) as well as mesencephalic DAergic neurons from the cytotoxicity of 6-OHDA and tetrahydrobipterin (BH4), compounds known to induce DA quinone production and oxidative stress, causing selective death of DAergic cells [47]. This beneficial effect seems to be due to its ability to remove intracellular quinone products, because NQO1 enzyme activity and mRNA level are increased and quinone-modified proteins are decreased following treatment with SFN [47]. SFN administration also prevents ROS production, DNA fragmentation and membrane breakdown [47].

Moreover, SFN is able to protect primary cortical neurons against the injury induced by the oxidized products of DA, that are able to form adducts with cellular thiolis [48,49]. In fact, 5-5-cysteinyl-dopamine (CysDA) adducts result elevated in the brains of patients affected by PD [50]. Neuroprotection exhibited by SFN was ascribed to a mechanism involving nuclear translocation of Nrf2 and a subsequent increase in the expression and activity of specific detoxifying phase I and II enzymes [51]. Furthermore, this seems to be correlated with the activation of the extracellular signal-regulated kinases 1 and 2 (ERK1/2) and Akt/protein kinase B (PKB) pathways [51].

Overall, these findings suggest that ITCs could prove to be an interesting approach in the treatment of PD.

### 2.3. ITCs in Huntington’s disease

Huntington’s disease is a progressive neurodegenerative disorder affecting 4–10 people in 100,000 [52]. It is caused by a mutant huntingtin (mHtt) gene consisting of a CAG triplet repeat expansion which leads to
a progressive motor and cognitive impairment due to the gradual loss of neurons within striatal and cortical brain regions [52]. As for other neurodegenerative diseases, compromised oxidative stress defense systems and insufficiency of protein degradation machinery have been implicated in HD pathogenesis.

ITCs may function as neuroprotective agents in HD due to their capability to reduce oxidative stress. ITCs might restore the balance between the excessive production of ROS and a relative deficiency in antioxidant properties by acting as ROS scavengers as well as improving antioxidant enzymes through the activation of signaling pathways triggered by Nrf2. Moreover, another mechanism for the neuroprotective effects of ITCs has been proposed and involves the proteasome.

Starting from recent data showing that SFN up-regulates expression of 26S proteasome subunit and increases proteasome activity in murine neuroblastoma Neuro2A cells [53], Liu et al. [54], tested SFN in in vitro cell cultures and in a transgenic mouse model of HD. Through in vivo experiments, authors demonstrated that SFN is able to enhance both proteasomal and autophagic activities in the brain and peripheral tissues, such as the liver, as well as to promote the turnover of ubiquitin proteasome system and ubiquitinated proteins, increasing cell survival. In addition, it was found that the treatment of cells expressing mHtt with SFN increased the degradation of mHtt and reduced its toxicity. These effects may be ascribed to multiple pathways activated by SFN and mainly through Nrf2/ARE transcription factor pathway [54].

These findings lead to believe that SFN and ITCs in general may be hopeful candidates in treating HD. However, studies about this disease are still limited.

2.4. ITCs in multiple sclerosis

Multiple sclerosis (MS) is a progressive inflammatory and demyelinating disease of the CNS caused by malfunction of the immune system. In northern industrialized countries, MS affects about 0.1% of the population and is the first cause of disability of non-traumatic origin in young adults [55].

To date, its etiology is still unknown. In order to better understand the etiopathogenesis of MS and to find new therapeutic approaches, experimental model of MS have been developed. The most common used model of MS is the experimental autoimmune encephalomyelitis (EAE) which mimics the main features of human MS, including paralysis, experimental model of MS have been developed. The most common used injection, induces a chronic demyelinating disease predominantly driven by peptide fragments 35

Bordetella pertussis (BBB) breakdown [56]. Moreover, immunization of mice with MOG peptide fragments 35–55 (MOG35–55) followed by Bordetella pertussis injection, induces a chronic demyelinating disease predominantly driven by CD4+ T cell-mediated immunity, especially Th1 and Th17 cells. These cells contribute to both the impairment of the BBB and their migration into the CNS, where they lead to further inflammation, demyelination, and axon damage [56].

According to a study performed using EAE mice, it was demonstrated that a treatment with SFN inhibited EAE development and severity in mice by its antioxidant activity and antagonizing autoimmune inflammation [57]. In detail, the protective effect of SFN was associated with significantly improved distribution of claudin-5 and occludin, and decreased levels of MMP-9 expression, preserving the BBB integrity. Furthermore, treatment with SFN inhibited oxidative stress by activating the Nrf2/ARE pathway and enhancing levels of antioxidant HO-1 and NQO1. Moreover, SFN inhibited antigen-specific Th17 responses, contributing to its therapeutic effect by inhibiting the development and severity of EAE in mice [57].

Neuroprotective effects of ITCs are ascribed to their ability to pass the BBB and preventing its dysfunction [58]. Using the same model, the beneficial effects of R-SFN, an ITC obtained by exogenous bioactivation of GRA by myrosinase, were tested [59]. It was found that intraperitoneal treatment with bioactivated GRA preserves BBB integrity modulating tight junctions (Tj)-associated proteins, claudin-1, -3, -5 and HO-1, through a mechanism that involves a modulation of the inflammatory as well as apoptotic pathway. In addition, the same authors have demonstrated that treatment with bioactivated GRA significantly decreased c-Jun N-terminal protein kinase (JNK) and nuclear NF-κB expression as well as pro-inflammatory cytokine production such as IL-1β and apoptosis (Bax and caspase-3 expression) [60].

Interesting data about the neuroprotective effects of ITCs have recently been produced. Particularly, GMG, a typical glucosinolate present mainly in seeds of M. oleifera tree produces 4-α-(α-1-α-homoxylosyloxy) benzyl isothiocyanate (GMG-ITC) after myrosinase hydrolysis. A recent preclinical study published in 2014, performed on EAE mouse has clearly shown that the pharmacological treatment with GMG-ITC was able to counteract the inflammatory cascade that underlies the processes leading to severe MS [12]. In particular, GMG-ITC was effective against proinflammatory cytokine TNF-α and MAP kinase signal pathway. Oxidative species generation including the influence of iNOS, nitrotyrosine tissue expression and cell apoptotic death pathway was also evaluated resulting in a lower Bax/Bcl-2 unbalance. In addition, GMG-ITC exerts neuroprotective effects against MS, diminishing both clinical signs and histological score typical of the disease (lymphocytic infiltration and demyelination) [12].

Moreover, looking at other ITCs, it was found that synthetic 4-IPITC orally administered to EAE rats showed a delay of the disease onset and a decrease of clinical score [42]. This beneficial effect seems to be associated with the activation of Nrf2-induced genes and the inhibition of histone deacetylase (HDAC) [42]. HDAC is an anti-neoplastic agent that acts by enhancing acetylation of histones, and promotes unrolling of chromatin and activation of a large number of genes implicated in the regulation of cell survival like proliferation, differentiation and apoptosis. Neuroprotective effect of 4-IPITC was also confirmed in in vitro studies demonstrating that 4-IPITC is able to protect cortical neuronal cultures against a wide variety of different insults such as glutamate excitotoxicity, oxidative stress and oxygen-glucose deprivation [42].

2.5. ITCs in amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive muscular paralysis reflecting degeneration of motor neurones in the primary motor cortex, corticospinal tracts, brainstem and spinal cord. Most ALS cases are sporadic but 5–10% of cases are familial, and among these, 20% have a mutation of the SOD1 gene and about 2–5% have mutations of the TARDBP (TDP-43) gene [61].

According to a study performed using motor neuron-like cell line [62], it was demonstrated that mutant TDP-43 protein induced mitochondrial dysfunction, oxidative damage and nuclear accumulation of Nrf2. Treatment with SFN reduced the level of lactate dehydrogenase (LDH) and lipoperoxidation products in cells expressing TDP-43 mutant. SFN may also upregulate the expression of HO-1 and NAD(P)H/quinone oxidoreductase-1 (NQO-1) only in cells transfected with the empty vector and the wild-type TDP-43. On the contrary, mutant TDP-43 reduced HO-1 expression and prevented SFN from activating Nrf2 signaling [62].

As demonstrated by Malaguti et al.’s study [63], SFN acts as an indirect antioxidant in skeletal muscle of mice subjected to exhaustive exercise, playing a critical role in the modulation of the muscle redox environment. Specifically, systemic SFN treatment increased muscle NQO1, glutathione S-transferase, and glutathione reductase expression and activity. The observed SFN-induced regulation of phase II enzymes was accompanied by a significant increase in Nrf2 expression and correlated with a significant increase in total antioxidant capacity and a decrease in accumulation of glutamate and plasma LDH and creatine phosphokinase (CPK) activities, two well-known biomarkers of tissue damage [63].

As ALS is correlated also with progressive muscle loss, SFN could prove to be useful in the treatment of ALS.
In 2010, Chang et al. investigated whether SFN can act together with riluzole, the only medicine already approved in ALS treatment, in protecting motor neurons against glutamate induced excitotoxicity in organotypic spinal cord cultures [64]. In particular, the efficacies of the two treatments alone or in combination in inhibiting progression and severity of disease were tested. The results showed that the combination of SFN with riluzole is more effective than each drug used alone, as the combination not only stimulates the expression of Nrf2 pathway, but also reduces the extracellular accumulation of glutamate. Furthermore, the combination of the two treatments exerts significant and similar neuroprotection, as measured by the number of motor neuron, medium malondialdehyde (MDA) level and LDH level [64]. Therefore, SFN could be used in association with conventional therapy in ALS management.

In a recent study, the role of GMG-ITC in delaying the mechanisms that trigger the ALS development was investigated in an experimental genetic model of disease that physiologically develops in transgenic SOD1G93A (SOD1tg) rats at about 16 weeks of life [65]. In this study, it was demonstrated that systemic pre-treatment with GMG-ITC may shift forward the time of disease onset, characterized by hindlimb abnormal gait associated with degeneration of muscle integrity and function. About molecular mechanisms, it was found that GMG-ITC counteracts the overall cascade of events, such as oxidative injury by modulating iNOS, MMP-9, Nrf2 and PARP expression as well as neuronal cell death related to ALS (cleaved-caspase 3 and TUNEL assay) [65].

2.6. ITCs in ischemic brain injury

Ischemic stroke has been shown to be a substantial public health problem that leads to long-term disability in major industrialized countries [66]. However, treatments that effectively limit the tissue injury and brain dysfunction in these conditions remain restricted.

In adults, cerebral ischemic stroke often results from the occlusion of a cerebral artery caused by a thrombus or embolus that leads to an immediate loss of the normal intake of oxygen and glucose to cerebral tissues [67]. However, in infants, cerebral ischemia is mediated by complications during labor and delivery, leading to neonatal hypoxic–ischemic brain injury. In all cases, early initiation of reperfusion is the most effective treatment to reduce infarct area and behavioral deficits caused by ischemia. Paradoxically, reperfusion causes additional injury, called cerebral ischemia/reperfusion (CIR) injury.

Additionally, it has been widely demonstrated that multiple biochemical mechanisms including excitotoxicity, formation of reactive oxygen and nitrogen species (ROS/RNS), ionic imbalance, inflammation and apoptosis contribute to the pathophysiology of stroke [68–70]. For this reason, antioxidants have been the focus of studies for the development of neuroprotective drugs to be used in cerebral ischemia treatment. To date there is no clinically effective therapy for stroke management except tissue-plasminogen activator (t-PA) [71].

It is well known that in experimental models of CIR as well as in vitro, activation of the Nrf2 system by administration of ITCs, leads to neuroprotection against brain damage. The neuroprotective effects of GRA purified from Tuscan black kale seeds and bioactivated with myrosinase were recently investigated in an acute experimental model of CIR [72]. CIR was induced in rats by the clamping of carotid artery for 1 h followed by 40 min of reperfusion. Then, bioactivated GRA was intraperitoneally administered after 15 min by CIR induction [72]. In this way, it was clearly demonstrated that the released ITC is active on central and peripheral nervous system, through mechanisms which involved both the modulation of the inflammatory pathways and the reduction in the activation of cell death by apoptosis. Specifically, it was proven that bioactivated GRA is able to significantly reduce NF-κB translocation and intercellular adhesion molecule 1 (ICAM-1), and to trigger the oxidative species generation (iNOS), and neuronal apoptotic death pathway [72]. The same authors tested the neuroprotective effects of Tuscan black kale sprout extract (TBK-SE) bioactivated with myrosinase in chronic experimental CIR model, demonstrating that this extract exerts pharmacological properties in protecting BBB integrity through a mechanism of action that involves a modulation of the inflammatory and oxidative pathway into the control of neuronal death by apoptosis (study in progress).

According to Noyan-Ashraf et al. [73], a diet rich in broccoli sprouts containing high amounts of GRA, precursor to phase 2 protein-inducing SFN, decreased the aging-related degenerative changes in the spontaneously hypertensive stroke-prone rats (SHRsp) CNS.

Moreover, in experimental rats suffering of focal ischemia, caused by a temporary left common carotid/middle cerebral artery (CCA/MCA) occlusion for 3 h followed by three days of reperfusion, Zhao et al. [74] found that systemic pretreatment with SFN reduces the infarct volume. Neuroprotective effects of SFN are probably due to its ability to induce the expression of Nrf2-responsive protective genes as proved also in several cell types including neurons, astrocytes, and endothelial cells [74].

In rats with intra-cerebral hemorrhage and treated with SFN, it was confirmed that the activation of Nrf2 is the primary mechanism that triggers the protective action of ITCs. The Nrf2-dependent genes were stimulated while markers of oxidative damage in the perihematoma area were reduced. On the contrary, Nrf2-knockout animals were not protected [75].

Likewise, SFN was proven to exert neuroprotective effects in neontal hypoxia–ischemia (HI) rat model [76]. SFN was systemically administered 30 min before HI induction in seven-day-old rat pups subjected to left common carotid artery ligation and hypoxia for 90 min [76]. It was found that SFN significantly increased Nrf2 and HO-1 expression which was accompanied by reduced infarct volume, and decreased oxidative stress indicators (8-hydroxy-2-deoxyguanosine (8-OHdG) and malondialdehyde (MDA) level) and the number of apoptotic cells [76]. Similar results were obtained using in vitro models of ischemia/reperfusion induced in primary mouse hippocampal neurons exposed to either oxygen and glucose deprivation or hemin [77]. Here, it was demonstrated that SFN treatment is able to activate antioxidant pathway mediated by Nrf2 and protect cells from cell death [77].

Activation of the Nrf2/ARE pathway and reduction of cell death was also confirmed in rat cortical astrocytes treated with SFN before or after transient exposure to oxygen and glucose deprivation [78].

Recently, there has been an increasing worldwide interest in identifying compounds from plant sources of M. oleifera, which are pharmacologically potent and have limited or no side effects for use in preventive medicine in human health and in the food industry. Pharmacological studies confirmed the therapeutic value of the drumstick tree. In particular, the isolation of 4-(α–1–rhamnopylosyloxy) benzyl glucosinolate (glucororingin; GMG) could lead to the development of a promising new pharmaceutical agent. In Galuppo et al. study [79], 4-(α–1–rhamnopylosyloxy) benzyl isothiocyanate, a bioactive phytochemical derived from GMG hydrolysis reaction, has demonstrated to exert neuroprotective properties into counteracting CIR and the related cascade of inflammatory and oxidative mediators that exacerbate the progression of this disease in rats subjected to carotid artery occlusion. It was shown that GMG-ITC is able to modulate iκBα/α–NF-κB pathway which in turn regulates the downstream-associated response showed by expression of indirect markers of inflammation, such as TNF-α, phospho-ERK p42/44 and p-selectin [79]. Moreover, GMG–ITC was proven to block the production of oxidative stress markers and related processes, decreasing MMP-9, as well as, iNOS over-expression, defending cerebral tissue and preventing severe damages caused by CIR [79].

According to another study where CIR was induced by occlusion of middle cerebral artery occlusion (MCAO) in rats [80], it was demonstrated that M. oleifera leaf extract, when orally administered, protected against brain damage, by decreasing infarction volume in both cortex and subcortex regions and against oxidative stress, by modulating MDA level, and the activities of SOD, CAT, and glutathione peroxidase (GPx) [80].
The natural text is as follows:

These observations indicate that ITCs may counteract CIR due to their ability to modify several pathways and intercellular redox signaling. Therefore, these natural phytochemicals may be potential candidates for the treatment of neonatal brain injury as well as cerebral stroke due to their antioxidative and anti-inflammatory properties.

### 2.7. ITCs in traumatic brain and spinal cord injury

Traumatic events may involve damages to the brain as well as to the spinal cord. Traumatic brain injury (TBI) usually occurs when an external mechanical force causes brain damage and dysfunction [81]. The

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### Table 1

Neuroprotective effects of ITCs in neurodegenerative disorder treatment.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Product/extract</th>
<th>Proposed mechanism of action</th>
<th>Neuroprotective effects</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>SFN</td>
<td>Up-regulates the proteasome system through the Nrf2 pathway activation, Decreases markers of oxidative stress and lipid peroxidation by acting as antioxidant.</td>
<td>Ameliorates cognitive and memory impairment</td>
<td>[31–34]</td>
</tr>
<tr>
<td></td>
<td><em>M. oleifera</em> extract</td>
<td>Increases Nrf2 and upregulates phase II antioxidant enzymes (HO-1, NAD(P)H and NQO1). Reduces astrogliosis, microglia activation and release of IL-6 and TNF-α. Increases glutathione enzyme levels and modulates ERK1/2 and Akt/PRB pathways. Inhibits mitochondrial depolarization, DNA fragmentation and caspase-9 and -3 activations.</td>
<td>Enhances memory and cognitive functions.</td>
<td>[36,37]</td>
</tr>
<tr>
<td>PD</td>
<td>SFN</td>
<td></td>
<td>Ameliorates behavioral impairments and motor performance.</td>
<td>[40,41,44–51]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>SFN</td>
<td></td>
<td>Improvement of cognitive functions.</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ameliorates motor deficits such as movement coordination and tremors.</td>
<td>[43]</td>
</tr>
<tr>
<td>MS</td>
<td>SFN</td>
<td></td>
<td>Inhibits progression and severity due to disease.</td>
<td>[57]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Delays disease development and decreases clinical signs.</td>
<td>[59,60]</td>
</tr>
<tr>
<td></td>
<td>Bioactivated GRA</td>
<td>Preserves BBB function modulating claudin-1, -3, -5 and HO-1 expression. Decreases JNK and NF-κB expression as well as pro-inflammatory cytokine production (IL-1β) and apoptosis (Bax and caspase-3).</td>
<td>Delays disease development and decreases clinical signs.</td>
<td></td>
</tr>
<tr>
<td>ALS</td>
<td>SFN</td>
<td>Up-regulates phase II antioxidant enzymes (HO-1, NAD(P)H and NQO1) and Nrf2 expression. Counteracts oxidative stress by modulating iNOS, MMP-9, Nrf2 and PARP expression, as well as apoptotic pathway (cleaved-caspase 3 and TUNEL assay).</td>
<td>Activates Nrf2-induced genes and inhibits HDAC.</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td>Bioactivated GRA</td>
<td>Reduces NF-κB translocation and ICAM-1 expression, as well as the triggering of oxidative species generation (iNOS), and neuronal apoptotic death pathway (caspase 3).</td>
<td>Promotes neurotrophic factor release (GAP-43, NGF and BDNF).</td>
<td>[54]</td>
</tr>
<tr>
<td></td>
<td>TBK-SE</td>
<td>Restores alterations of tight junction components (claudin-5). Reduces NF-κB translocation, p-selectin, GFAP, Iba-1 and ERK1/2 expression, as well as the triggering of neuronal apoptotic death pathway (Bax/Bcl-2 balance, p53 and cleaved-caspase 3).</td>
<td>Ameliorates motor deficits and delays disease development.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreases markers of oxidative stress (iNOS, nitrotyrosine and Nrf2).</td>
<td></td>
<td>[In progress]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreases markers of oxidative stress (B-OHdG and MDA levels) as well as number of apoptotic cells by activating Nrf2 pathway. Increases Nrf2 and HO-1 expression.</td>
<td>Reduces the infarct volume and ameliorating behavioral functions.</td>
<td>[74–78]</td>
</tr>
<tr>
<td></td>
<td>GMG-ITC</td>
<td>Modulates proinflammatory cytokine TNF-α and MAP kinase pathway as well as oxidative species generation (iNOS and nitrotyrosine) and apoptosis (Bax/Bcl2 unbalance).</td>
<td>Ameliorates motor deficits and delays disease development.</td>
<td>[12]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Modulates Nrf2-induced genes and inhibits HDAC.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-IPITC</td>
<td></td>
<td></td>
<td>[42]</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[62–64]</td>
</tr>
<tr>
<td>CIR</td>
<td>SFN</td>
<td></td>
<td>Inhibits progression and severity due to disease.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bioactivated GRA</td>
<td>Reduces NF-κB expression and consequent expression of indirect markers of inflammation (TNF-α, ERK1/2 and p-selectin) and decreases oxidative stress markers (MMP-9, iNOS).</td>
<td>Decrease markers of oxidative stress (iNOS, nitrotyrosine and Nrf2).</td>
<td>[79]</td>
</tr>
<tr>
<td></td>
<td>M. oleifera extract</td>
<td>Modulates MDA level, and the activities of SOD, CAT and GSH-Px.</td>
<td>Reduction of brain edema and improvement of cognitive functions.</td>
<td>[80]</td>
</tr>
<tr>
<td>TBI</td>
<td>SFN</td>
<td>Increases AQP4 channels levels. Preserves BBB function through the reduction of endothelial cell markers and tight junction protein loss by a mechanism dependent on Nrf2. Increases mRNA levels of Nrf2-driven genes such as GST-α3, GPx and HO-1.</td>
<td>Reduction of brain edema and improvement of cognitive functions.</td>
<td>[83–85]</td>
</tr>
<tr>
<td></td>
<td>Bioactivated GRA</td>
<td>Regulates IkB-α/NF-κB pathway and IL-1β production. Decreases oxidative stress markers (Nrf2 and GFAP), as well as apoptotic markers (Fast, Bax and caspase 3).</td>
<td>Reduction of brain edema and improvement of cognitive functions.</td>
<td>[36,37]</td>
</tr>
<tr>
<td></td>
<td>GMG-ITC</td>
<td>Modulates NF-κB translocation and IkB-α degradation, triggers neuronal apoptotic death pathway (Bax/Bcl-2 balance and caspase 3), and generates free radicals by oxidative stress, such as iNOS.</td>
<td>Ameliorates motor deficits due to damage and reduces inflammatory damage, as well as spinal cord edema.</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ameliorates severity of disease.</td>
<td>[92]</td>
</tr>
</tbody>
</table>

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damage can be focal — confined to one area of the brain or diffuse — involving more than one area of the brain. Survivors are left with long-term disabilities, and even a mild TBI can leave people with cognitive impairments, difficulty in concentrating, headache and fatigue. TBI can be defined as an early phase of mechanical damage of brain tissues and a secondary phase of cellular and molecular events that cause oxidative damage and brain cell death [82].

Recent studies have shown that ITCs and especially SFN, offer cellular protection in several models of TBI. In Dash et al.’s study, TBI was induced by bilateral cranietomies following a single impact on the right parietal lobe in rats. It was found afterwards that administration of SFN attenuates BBB permeability and reduces brain edema due to injury [83]. Furthermore, SFN improves hippocampal and prefrontal cortex-dependent cognitive functions, enhancing spatial learning and memory, and reducing working memory dysfunction. This was associated with reduced oxidative damage in the brains of TBI animals, as shown by the decrease of 4-hydroxynonenal (4-HNE), a marker of lipid peroxidation [83].

Moreover, it was demonstrated in a rodent TBI model that SFN decreased water channel aquaporin-4 (AQP4) loss in the injury core while moderately increasing it in the penumbra region surrounding the core and reduced brain edema [84]. These findings confirm the important role of AQP4 to clear water in excess and to maintain the brain water homeostasis. In addition, according to the authors, it is likely that SF exerts neuroprotective effects by a combination of mechanisms including decreased BBB permeability, enhanced cell survival and/or increased AQP4 channel level [84]. In this case, the role of Nrf2 in SF-mediated AQP4 gene expression remains to be addressed. However, we cannot rule out the possibility that might act via a yet undiscovered pathway to influence Nrf2 and protect neurovascular function.

Using the same model, Zhao et al. [85] showed that treating TBI animals with SFN preserved BBB function through the reduction of endothelial cell markers and tight junction protein loss. Here, these protective effects were dependent on the activity of Nrf2. SFN increased the mRNA levels of Nrf2-driven genes such as GSTα3, GPx, and HO-1 in the parietal cortex and brain microvessels [85]. As a result, the functions of the neurovascular unit after injury are ameliorated. These findings suggest that ITCs may protect against several pathophysiological consequences of TBI and other neurological traumatic injuries. Particularly, it was demonstrated that ITCs provide neuroprotective effects in the spinal cord after contusive damage.

Spinal cord injury (SCI) is a devastating pathology that leads to permanent disability. The functional decline, following SCI, is a consequence of both direct mechanical injury, which causes the death of a number of neurons that cannot be recovered and regenerated, and secondary pathophysiological mechanisms, called “secondary damage”, supported by a large number of cellular, molecular and biochemical cascades [86].

As widely demonstrated in several studies, neuroprotective effects of SFN are mediated by the activity of Nrf2. In Nrf2-deficient (Nrf2(−/−)) and wild-type (Nrf2(+/+)) mice, spinal cord compression injury was induced by the application of vascular clips. It was observed that SFN activated the Nrf2 pathway, reduced inflammatory damage, histologic injury, dying neurons count and spinal cord edema caused by SCI in Nrf2(+/+ ) mice, leading finally to an improvement of hindlimb locomotor function. On the contrary, Nrf2 knockout animals were not protected by SFN [87].

An improvement in functional and anatomical recovery as well as an increased number of serotonergic axons caudal to the lesion site was also found in rats subjected to contusion SCI and systemically administered with SF [88]. Regarding the anti-inflammatory effects of SFN, a hypothesis was elaborated for a mechanism that involves inhibition of the NF-κB pathway, resulting in a decreased expression of many proinflammatory factors, such as iNOS, cyclooxygenase-2 (COX-2), TNF-α, interleukins (IL-1β and IL-6) and proinflammatory cytokine macrophage inhibitory factor (MIF) [88].

Anti-inflammatory properties of SFN were investigated in mice subjected to SCI by the application of vascular clips (force of 10 g) to the dura after a three-level T8–T10 laminectomy. It was found that, following SCI, SFN decreases MMP-9 and TNF-α expression and changes vascular permeability [89]. In addition, more recent papers confirmed these results both in rat and mouse models of SCI, suggesting that SFN is an indispensable compound for neurotherapeutic intervention in blocking secondary mechanisms following SCI [90].

Neuroprotective effects of GRA purified from Tuscan black kale seeds, and bioactivated with myrosinase were also investigated in an experimental mouse model of SCI [91]. Here, the injury was induced by the application of an aneurysm clip (force of 24 g) for 1 min via four-level T5–T8 after laminectomy. Achieved results clearly demonstrated that the pharmacological treatment significantly decreased histological damage resulted by proinflammatory events as well as by apoptosis cascade [91]. Likewise, authors tested neuroprotective activity of GMG-ITC purified from seeds of M. oleifera and bioactivated with myrosinase in the same experimental model of SCI [92]. They found that GMG-ITC modulates NF-κB translocation and iκB-α degradation, triggers neuronal apoptotic death pathway (Bax/Bcl-2 balance and caspase 3), and generates free radicals by oxidative stress, such as iNOS [92]. According to these results, it is clear that ITCs exert a protective effect on the secondary damage, following SCI through an antioxidant mechanism of neuroprotection.

The reported beneficial effects of ITCs together with proposed underlying mechanisms of action are summarized in Table 1.

3. Conclusion

This review evaluates the current research trends on the properties of ITCs together with the potential for their application in management of neurodegenerative disorders. To date there is no cure for this kind of diseases. Existing therapies have aimed only at treating the symptoms and trying to delay their progression. For this reason, in recent years, usage of natural medicine as a source of powerful and effective antioxidant agents in the treatment of neurodegenerative diseases has attracted considerable attention. In this regard, the literature shows that ITCs, generated by myrosinase from the corresponding GLs, are phytochemicals which are active on the central and the peripheral nervous system. ITCs have been proven to exert neuroprotective effects in vitro and in vivo models of neurodegeneration, especially for their peculiar ability to activate the Nrf2/ARE pathway, acting consequently as antioxidants. In addition, ITCs are able to modulate other pathways, such as inflammation and apoptosis involved in neurodegenerative disease development.

Therefore, in view of all data reported, we suggest that ITCs, derived from the hydrolysis of corresponding GLs, could be promising compounds with neuroprotective effects in preventing and/or treating disorders related to nervous system at least in association with current conventional therapies.

Further research, mainly in human clinical trials, is still needed to evaluate the therapeutic efficacy of the already known as well as the novel ITCs in the treatment of neurodegenerative diseases. Finally, we believe that, being natural phytochemicals, they could be introduced as a dietary supplement without side effects.

Conflict of interest

None declared.

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