Indonesian Archives of Biomedical Research

SULFORAPHANE AS A POTENTIAL THERAPY FOR MULTIPLE SCLEROSIS: A REVIEW ARTICLE

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ABSTRACT

Multiple Sclerosis (MS) is a chronic immune-mediated Neuroinflammatory disease that attacks the Central Nervous System (CNS). It creates serious physical disabilities characterized by neuronal injury, demyelination, and axonal loss. Several mechanisms are responsible for the progression of MS, including the infiltration of T-cells from the peripheral to the CNS, the autoreactivity of B-cells that contribute to abnormal regulation of antibodies and antigen presentation, and the assault of Macrophage that lead to inflammation and neuron damage. Additionally, oxidative stress plays a more important role in chronic inflammation of MS. Sulforaphane (SFN) is an isothiocyanate derived from glucoraphanin (GRA) that is found mostly in broccoli. SFN can act as an anti-inflammatory and anti-oxidant agent by activating the Nuclear factor-erythroid 2-(NF-E2-) Related Factor 2 (Nrf2). Nrf2 is expressed in the central nervous system and upregulated in response to inflammation and cerebral insults. Nrf2 binds to the antioxidant response element (ARE) which is a DNA promoter region of genes codifying antioxidant enzymes, which in turn can reduce oxidative stress. Several in vitro and in vivo studies show that SFN can increase the anti-inflammatory and anti-oxidant genes. Thus, SFN is very promising as a potential therapy for MS.

Keywords: *Sulforaphane, Multiple Sclerosis, Nrf2, Oxidative Stress.*

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INTRODUCTION

Multiple sclerosis (MS) is a chronic neuroinflammatory disease of the central nervous system (CNS) that can cause serious physical disabilities such as disturbances of vision or speech, loss of balance, muscle weakness, extreme fatigue, and paralysis among adult with Approximately, 2.5 million individuals are affected worldwide.[1] MS prevalence rate per 100,000 populations was 12.48 in the Asian region, a woman usually affected with ratio female: male between 1.5:1, even 3.6:1 in the Asian population. Young individuals aged between 20- and 40-years are mainly affected.[2] This can create a serious socio-economic burden because it attacks a productive population with serious disability symptoms.

MS is characterized by inflammation, demyelination, gliosis and neuroaxonal degeneration that mainly induced by immune cell infiltration through the Blood-brain barrier (BBB). In almost 80% of cases, MS presents as a relapsing–remitting multiple sclerosis.[3] There is an initial episode of neurological dysfunction, then followed by clinical recovery and the relapse of the symptoms are the main characteristics of relapsing–remitting multiple sclerosis. One or two decades later the patient also had potential fall to a condition called secondary progressive disease, where the inflammatory lesions aren't longer become the main causes, its turn out to a progressive neurological decline which accompanied by CNS atrophy due to increased axonal loss and decreased brain volume.[3]

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Volume 1 Issue 2, July-December 2021

Several mechanisms play roles in contributing neuroaxonal degeneration in Multiple Sclerosis. Immunopathological evidence showed that not only T-cell mediated plays major roles, but it can also be summarized into different types based on pathological conditions. First type which triggered by autoreactive of T Cell in peripheral that migrating to CNS, Second type caused by complement-mediated multifocal damage via activated B-cells; Third Type, involving loss of myelin-associated glycoprotein and apoptosis of oligodendrocytes, resulting in diffuse low-grade inflammation; and Fourth type, characterized by non-inflammation-induced degeneration of oligodendroglia cells.[4] One of the most important keys of the neurodegenerative process is a consequence of Chronic inflammation as the result production of the reactive nitrogen species (RNS) and reactive oxygen species (ROS) which create "oxidate stress" that lead to promoting mitochondrial injury.[5]

For the past times, the main target of currently available therapy for the MS is to reduce immune cell activity and its entry into CNS to reduce the frequency of relapse. It often associated with a side effect from flu-like syndrome into developed auto-immune disorder to malignancy, it indicates to find out an alternate therapeutic agent that can work out to be more specific to reduce neurodegenerative process but without inducing significant adverse reaction. Immunomodulatory therapies currently widely used as treatment of MS These therapies are marked by high cost and toxicity in neurological disorders. [6] Not many therapeutic agents that works in ROS pathway for the MS. In this review, we evaluate sulforaphane as potential therapy and supplement for MS, based on understanding in the involvement of Nuclear factor-erythroid 2-(NF-E2-) Related Factor 2 (Nrf2) activator in the ROS mechanism that works as neuroprotective agent and anti-inflammation.

PATHOGENESIS OF MULTIPLE SCLEROSIS

The exact causes of MS still elusive, but classically immune cell and mediators of inflammation known as the leading of demyelination, axonal damage, and neuronal/axonal loss. Commonly involvement of autoreactive T-Cell, B-cell, Macrophage attack is well observed in MS. At the early stages, immune cell infiltration from the periphery to CNS is the main mechanism. Evidence showed in experimental autoimmune encephalomyelitis (EAE) models, antigen-presenting cells (APCs) re-activated the infiltrating CD4+ T cells in the CNS, which include CD11c+ dendritic cells (DCs), with the resulting inflammatory response leading to monocyte recruitment into the CNS, and the activation of naive CD4+ T cell through epitope spreading that further aggravate the inflammation.[5, 7]

The numbers of infiltrating B cell in CNS are vary throughout the disease progression. Clonally expanded B cells can be found in the parenchyma, meninges, CSF, and intrathecal B cells produce antibodies which are detectable in the CSF and have a diagnostic value. The numbers of antibody-secreting plasma cells in patients with primary or secondary progressive MS are increased with age.[8]

Macrophages involvement can be seen as they infiltrate the CNS and accumulate in the lesion site. They are the predominant cell type in active and chronic MS plaques and continue to persist in late stage of MS when T cell density has subsided. Macrophages and the CNS phagocytizing residents, microglia, can drive toxicity to neurons and oligodendrocyte precursor cells (OPCs); release proteases, inflammatory cytokines, glutamate, and free radicals; and recruit/reactivate T cells in the CNS. Macrophages and microglia can also be known to be a source of matrix metalloproteinases (MMPs) that disrupt the integrity of the BBB, allowing other inflammatory mediators access to the CNS. [9]

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Later on, On the Chronic phase known as relapsing–remitting multiple sclerosis, the production of ROS and RNS play majors role in promote mitochondrial injury. Thus, as a result, it leads to the accumulation of detrimental mitochondrial DNA mutations. Both free radicals and energy imbalance leading to mitochondrial dysfunction are drivers of oxidative damage independent of inflammation.[5] Oxidative stress may contribute to MS progression via a number of pathways including damage to lipids, proteins, carbohydrates, and DNA directly from inflammatory products.

ROS IN MULTIPLE SCLEROSIS

In Multiple Sclerosis, Oxidative stress play an important role in Chronic Central Nervous System inflammation. ROS and RNS are the main mediators of it. ROS are routinely generated under physiological conditions and very important in different regulatory functions of the body. The Oxygen homeostasis is mediated by the Nuclear factor-erythroid 2-(NF-E2) Related Factor 2 (Nrf2) pathway that upregulates detoxifying enzymes and antioxidant proteins to mediate oxidative responses. Nrf2 is located in the cytosol and binds to kelch-like ECH-associated protein 1 (KEAP1) under physiological conditions. An E3 ubiquitin-ligase complex is formed through Cullin-3 binding to ring-box 1. The KEAP1/Nrf2 complex is prone to proteasomal degradation after ubiquitination. Nrf2 has a half life of 10–40 minutes during this condition. On the other hand, Nrf2 is released from Keap1 and translocates into the nucleus under the influence of oxidative stress caused by ROS. After dimerization with small Maf proteins, it will binds to antioxidant response element (ARE) and initiate the transcription of genes encoding for antioxidant proteins.[10] Nrf2 machinery includes glutathione synthase, thioredoxin, and detoxifying enzymes heme oxygenase and NAD(P)H quinone oxidoreductase; all are involved in scavenging oxidative species (including superoxides, hydroxyl radicals, nitrogens, and peroxynitrite) and converting them to harmless compounds. Therefore, Nrf2 activation can inhibit oxidative stress damage caused by ROS.

In CNS lesions of MS patients, ROS mainly produced by astrocytes, microglia, and macrophages.[11] The ROS can damage various parts of the CNS, such as axons, oligodendrocytes, myelin, and neurons. This may damage the mitochondria and aggravate the production and accumulation of ROS. The energy supply failure in mitochondria may play an essential role in the pathophysiology of MS because of the tissue alterations found in MS patients are similar to those found in white-matter stroke patients. Targeting this pathway to therapy for chronic neurodegeneration in MS could be beneficial to reduce the inflammation without suppressing the immune system.[10, 11]

SULFORAPHANE (SFN)

Sulforaphane (SFN) or *1-isothiocyanato-4-(methylsulfinyl)butane* is an isothiocyanate derived from glucoraphanin (GRA) that is found mostly in broccoli.[12-14] Broccoli is a cruciferous species that belong to the genus Brassica (families *Brassicaceae* and *Cruciferae*).[14] Broccoli sprouts is recognized as the best source of SFN and GRA compounds.[14] SFN is formed from GRA hydrolysis by myrosinase activity **(Figure 1)**.[13]

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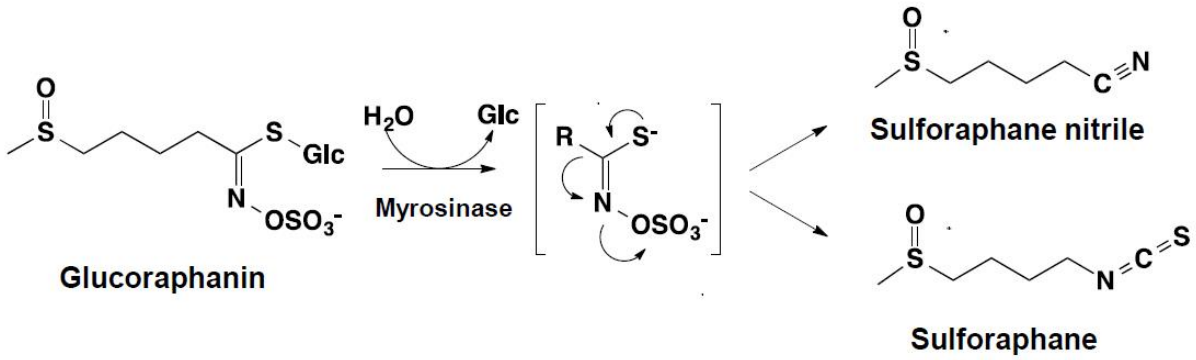

Figure 1. The formation of Sulforaphane.[13]

SFN is one of the Nuclear factor-erythroid 2-(NF-E2-) Related Factor 2 (Nrf2) activator.[12] Nrf2 is a transcription factor that essential to the regulation of cellular redox state.[14] Nrf2 is expressed in the central nervous system (CNS) and upregulated in response to cerebral insults and inflammation.[12,15] During normal physiological conditions, Nrf2 forming an inactive complex by bonding to kelch-like ECH-associated protein 1 (KEAP1) in the cytoplasm.[12,14,16] SFN can interact with KEAP1 when entering the cell, by oxidizing the KEAP1 critical cysteine and disrupt the Nrf2 and KEAP1 bond, which activates the Nrf2 and cause nuclear translocation of the Nrf2.[12,14,17] Nrf2 binds to the ARE in the nucleus. ARE is a DNA promoter region of genes codifying antioxidant enzymes, such as heme-oxygenase-1 (HO-1), gamma-glutamylcysteine synthetase, NADPH quinone oxidoreductase 1 (NQO1), peroxiredoxins, thioredoxin, catalase, superoxide dismutase, and glutathione reductase.[12,14,18,19] Increased transcription of Nrf2 target genes leads to increased cytoprotective response, including oxidative stress and carcinogenesis resistance.[14,16,20] SFN also increases the phase II enzymes activity which involved in the removal of xenobiotic compounds, such as quinone reductase and glutathione S-transferase (GST).[14,21]

The bioavailability of SFN has been studied *in vitro* and *in vivo*, including humans.[12] Due to its lipophilicity and molecular size, SFN can passively diffuse through enterocytes.[12] SFN is easily absorbed, bonded to glutathione, and metabolized thorugh the mercapturic acid pathway consecutively produce cysteinyl glycine (SFN-CG), cysteine (SFN-Cys), and N-acetylcysteine (SFN-NAC) conjugates which are excreted through the urine.[12] SFN bioavailability in humans is 74% and primarily absorbed in the jejunum.[12] As many as 70% of orally consumed SFN in humans and animal is eliminated through the mercapturic acid pathway within 12–24 hours.[22] A good CNS penetration is vital for SFN to produce its neuroprotective effect. One study with a mouse showed that SFN could cross the blood-brain barrier (BBB) and was detected in the cerebral tissue between 15-120 minutes after intraperitoneal injection.[23] Thus, SFN has the great potential as a new therapeutic modality for MS patients.

SULFORAPHANE (SFN) IN VITRO & IN VIVO STUDIES

The effect of SFN has been examined mostly in cancer and subarachnoid hemorrhage (SAH) cases. An in vitro study has been evaluated the effect of SFN in a rat SAH model, by exposing its aortic arch cells to OxyHb and SFN for 48-hours. This study found that the levels of Nrf2 and Nrf2-regulated genes (such as NQO1 and HO-1) were significantly increased and further upregulated after exposed to SFN. This study also found that the concentrations of inflammatory cytokines such as TNF-α, IL-6, and IL-1β were significantly reduced within the SFN group.[24]

Another study also has been evaluated the SFN effects in an *in vivo* SAH model.[25] SAH caused the upregulated of NQO1, GST-α1, and HO-1 expression in rat cortex. After the SFN administration, a further significant upregulation was found, which demonstrate that SFN can increase the Nrf2 activity. Apoptotic cell death, BBB permeability, and brain edema were all reduced after SFN treatment. SFN treatment was associated with a motor deficits reduction assessed at the 24-hours in rotarod test. Can be concluded from this study's results that SFN stimulates the Nrf2-ARE pathway after SAH and reduces early brain injury.[25]

An experimental study also has been evaluated the SFN effects on cerebral vasospasm in SAH model.[26] There was a significant difference in the cross-sectional areas of basilar arteries between the SFN and untreated SAH groups. SFN treatment increased the NQO1, HO-1, and Nrf2 mRNA expression levels, and also significantly upregulating the Nrf2 activity in smooth muscle and endothelial cells. The inflammatory cytokines (such as IL-6, TNF-α, and IL-1β) were significantly reduced after SFN administration. SFN was also found to improve the rats behavioral deficits after SAH which reflected by the activity scores and appetite improvement. This study's results proved that SFN early administration increases the Nrf2 pathway activity following SAH, reduces vasospasm, and improves outcome following SAH.[26]

SULFORAPHANE (SFN) IN MULTIPLE SCLEROSIS

Oxidative stress secondary to cell-mediated inflammation plays an important role in the pathology of multiple sclerosis (MS).[27, 28] Oxidized lipids and nucleic acids occur in many types of cells within MS plaques, including oligodendrocytes, astrocytes, and neurons, correlating with inflammation and loss of neuronal dendritic integrity.[29]

In the experimental autoimmune encephalomyelitis (EAE) model, preventive and therapeutic treatment with sulforaphane reduced the severity of EAE clinical symptoms, the demyelination, and the immune cell infiltration.[30, 31] Sulforaphane increased the upregulation of HO-1 and NQO1 in the treated mice.[31] In vitro studies with microglial cells confirmed the activation of Nrf2 and recently, this pathway was found to result in an upregulation of the efflux transporter P-glycoprotein at the BBB. Sulforaphane also suppressed IL23 and IL12 expression in an EAE model possibly mediated by inhibition of TLR4 signaling and NF-κB inhibition.[30]

SFX-01 which is a more stable, solid form, pharmaceutical product of sulforaphane also has been developed.[32] SFX-01 is a novel composition comprised of synthetic sulforaphane stabilized within the pocket of an α-cyclodextrin complex.[32] SFX-01 was well-tolerated for other indications in phase II clinical trials.[32] SFX-01 reduced residual disability in the therapeutic and prophylactic experiments of mice with relapsing EAE, a model of relapsing-remitting MS (RRMS). This effect was caused by a reduce in the relapses maximum severity and improved recovery during follow-up. The spinal cord histological examination was consistent with the clinical findings, including demyelination improvement and the reduced number of apoptotic cells, compared to the vehicle group. Thus, SFX-01 is effective in EAE.[32]

There is also a study that evaluated the SFN anti-inflammatory effect in an EAE mouse model.[33] The behavioral study in this study found that the SFN-treated EAE mice showed a higher clinical scores compared to the phosphate-buffered saline (PBS)-treated EAE mice at the 13th and 14th day. The biochemical studies also showed that SFN administration reduced the spinal cords demyelinating injury, inflammatory infiltration, and inducible nitric oxide synthase in the EAE mice.[33] The SFN administration exhibited anti-oxidative and anti-inflammatory effects in the EAE mice. In conclusion, this study proved that SFN has

neuroprotective effects through anti-inflammatory processing, so SFN had the potential to be the treatment modality for MS.[33]

CONCLUSION

Multiple Sclerosis still a burden as the disease create a serious disability and progressive damage to the neurological condition. Several comprehensive insight is needed to look up the MS Pathogenesis. Several key pathways that lead to demyelination, axonal damage, and neuronal/axonal loss needed further examination and research. Beside Immune-related process, other pathways such as oxidative damage need more insight to create an alternative approach as therapy for the progressivity of the MS. Sulforaphane (SFN) or *1-isothiocyanato-4-(methylsulfinyl)butane* is one of the agents that works in the ROS – Nrf2 pathway. Several shreds of evidence showed that SFN can be a potential therapeutic for the MS. But, they are still only examined the SFN in an in vivo and in vitro studies. A larger scale of human studies are required to support Sulforaphane as a recommendation for MS treatment.

LIST OF ABBREVIATION

APCs = antigen-presenting cells
ARE = antioxidant response element
BBB = Blood-brain barrier
CNS = Central nervous System
DCs = dendritic cells
EAE = experimental autoimmune encephalomyelitis
GRA = glucoraphanin
GST = glutathione S-transferase
HO-1 = heme-oxygenase-1
KEAP1 = kelch-like ECH-associated protein 1
MMPs = matrix metalloproteinases
MS = Multiple Sclerosis
NQO1 = NADPH quinone oxidoreductase 1
Nrf2 = Nuclear factor-erythroid 2-(NF-E2-) Related Factor 2
OPCs = oligodendrocyte precursor cells
RNS = reactive nitrogen species
ROS = reactive oxygen species
SAH = subarachnoid hemorrhage
SFN = Sulforaphane
SFN-CG = Sulforaphane cysteinylglycine
SFN-Cys = Sulforaphane cysteine
SFN-NAC = Sulforaphane N-acetylcysteine

DECLARATIONS

1. Ethics approval and consent to participate – Not applicable.
2. Consent for publication – Not applicable.
3. Availability of data and material – Not applicable.
4. Competing interests - The authors declare that they have no competing interests.
5. Funding - No specific grant was provided for this article.
6. Authors' contribution - All authors took part in design of study, literature review and writing the manuscript.

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