



Neuroprotection through flavonoid: Enhancement of the glyoxalase pathway



Joel R. Frandsen, Prabakaran Narayanasamy*

Department of Pathology and Microbiology, College of Medicine, University of Nebraska Medical Center, Omaha, NE 68198-5900, USA

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ABSTRACT

The glyoxalase pathway functions to detoxify reactive dicarbonyl compounds, most importantly methylglyoxal. The glyoxalase pathway is an antioxidant defense mechanism that is essential for neuroprotection. Excessive concentrations of methylglyoxal have deleterious effects on cells, leading to increased levels of inflammation and oxidative stress. Neurodegenerative diseases – including Alzheimer's, Parkinson's, Aging and Autism Spectrum Disorder – are often induced or exacerbated by accumulation of methylglyoxal. Antioxidant compounds possess several distinct mechanisms that enhance the glyoxalase pathway and function as neuroprotectants. Flavonoids are well-researched secondary plant metabolites that appear to be effective in reducing levels of oxidative stress and inflammation in neural cells. Novel flavonoids could be designed, synthesized and tested to protect against neurodegenerative diseases through regulating the glyoxalase pathway.

1. Introduction

The glyoxalase pathway is a well-conserved antioxidant defense system found in all cells of the body [1–4]. The glyoxalase pathway facilitates the neutralization of highly reactive and oxidizing dicarbonyl molecules, with methylglyoxal (MG) being the most critical target [5]. Carbonyl molecules target the brain due to its high rate of metabolism and low antioxidant defense capacity [6]. The brain also contains high concentrations of oxidizable substrates including polyunsaturated fats and metal ions [7]. Accumulation of MG damages and influences the cellular environment, leading to a state of chronic inflammation and oxidative stress [4,5,8–12]. The glyoxalase system is present in all cells in the body, but has especially important functions in the brain [3,13].

Oxidative stress (OS) results from an imbalance between electrophilic prooxidative molecules and the capacity of antioxidants to reduce and neutralize the free radicals [14]. It is a chronic state of inflammation that prevents the proper function of integral cellular processes, causing irreversible damage to cells [10,14,15]. Excessive oxidative stress in the brain leads to accelerated aging, and impacts the severity of neurodegenerative diseases [16,17]. High levels of oxidative stress influence the onset and progression of aging, Alzheimer's disease (AD), Parkinson's disease (PD), and autism spectrum disorder (ASD)

[18,19]. Efficient and active function of the glyoxalase pathway is critical to reducing oxidative stress mediated damage to brain cells [20–24]. Flavonoid antioxidant compounds possess the capacity to enhance the glyoxalase pathway through several distinct mechanisms, including modulation of critical signaling pathways involved in cell proliferation [25–27].

OS and inflammation gradually increase during aging [28,29]. However, high levels of OS and inflammation can accrue over time and are contributing factors to aging and neurodegenerative diseases including AD, PD, ASD, dementia, and psychiatric disorders [1,30]. Hallmarks of these diseases are also shared in glyoxalase pathway dysfunction: increased reactive oxygen species (ROS) production, apoptosis, and oxidation of molecules [2,9,31,32]. The onset and progression of neurodegenerative disease can be influenced by substituents of the glyoxalase pathway. For example, inhibition of glo 1 reduces neuronal viability and increases accumulation of advanced glycation endproducts (AGEs), while overexpression of glo 1 reduces formation of ROS [4,21,33,34]. Aging is correlated with a decrease in glo 1 concentration and activity [16,35]. Depletion of GSH by MG can prevent astrocytic detoxification of reactive molecules and lead to an increase in oxidized proteins, lipids, and amino acids [21,36]. Increasing the capacity and efficiency of the glyoxalase pathway appears to be an

Abbreviations: OS, oxidative stress; ROS, reactive oxygen species; MG, methylglyoxal; glo 1, glyoxalase-1; glo 2, glyoxalase-2; AGEs, advanced glycation end products; ASD, autism spectrum disorder; GSH, reduced glutathione; cas-3, caspase-3; NeuN, neuronal specific nuclear protein; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; AD, Alzheimer's disease; A β , amyloid beta; PD, Parkinson's disease; HO-1, Heme oxygenase-1; Nrf2, nuclear factor erythroid 2-related factor 2; ARE, antioxidant response element; GCS, gamma-glutamyl-cysteine synthetase; PNO2, Paraoxygenase-2; ETC, Electron transport chain; MPTP, 1-methyl-4-phenyl 1,2,3,6 tetrahydropyridine; 6-OHDA, 6-Hydroxydopamine; MPP+

* Corresponding author.

E-mail address: p.narayanasamy@unmc.edu (P. Narayanasamy).

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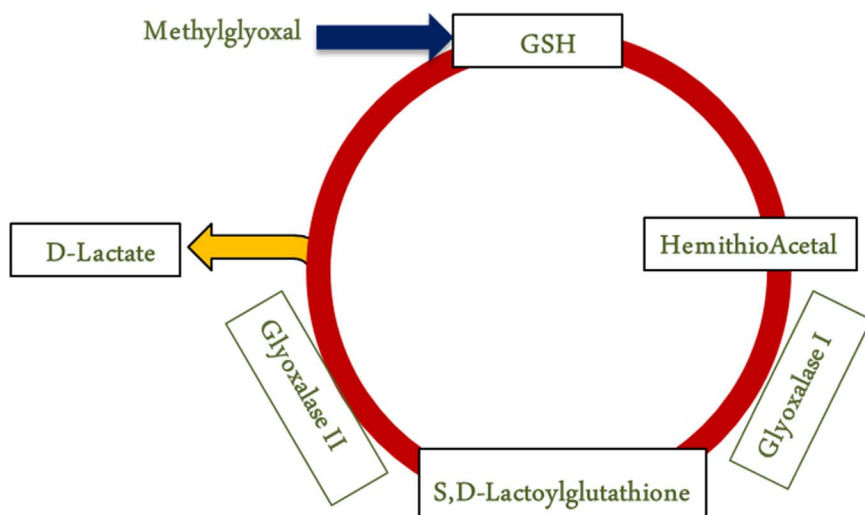


Fig. 1. The glyoxalase pathway functions to detoxify methylglyoxal. Methylglyoxal reacts with reduced glutathione (GSH) to form a hemithioacetal (HTA). Glo 1 uses the hemithioacetal as a substrate to form S,D-lactylglutathione. Glo-2 reacts with the resulting intermediate compound, and the pathway produces D-lactate. This step also reduces glutathione and recycles it into the pathway.

effective means of reducing the onset and severity of aging and neurodegenerative disease [37].

1.1. Glyoxalase pathway

The glyoxalase pathway consists of proteins glyoxalase 1 (glo 1) and glyoxalase 2 (glo 2), reduced glutathione (GSH), and a dicarbonyl substrate (Fig. 1) [4,16,21]. The pathway is a series of two reactions that neutralize MG to produce D-lactate. MG spontaneously reacts with GSH to form a hemithioacetal. It is catalyzed by glo 1 into an intermediate compound S,D-lactylglutathione. Glo 2 catalyzes the final reaction producing D-lactate and recycling GSH into the pathway [21]. The rate of glyoxalase activity varies based on the type, location, and environment of the cell [30,38,39]. The glyoxalase pathway is a dynamic system able to respond to the constantly changing cellular environment. The glyoxalase pathway is in every cell, and is implicated in cancer cell proliferation, maintenance of blood glucose, liver enzymes, and cardiovascular and renal function [40].

MG is a byproduct of glycolysis and the metabolism of proteins and lipids [5]. MG is an electrophile and highly reactive glycating agent, able to irreversibly modify proteins, lipids, and nucleic acids, forming advanced glycation end products (AGEs) [5,10]. Structural modifications to molecules can significantly reduce function, and may lead to degradation by immune cells [41]. MG is a stable molecule, and membrane permeable in certain forms. Excess MG is able to leak into surrounding cells and tissues [42]. In a functioning glyoxalase system, MG is degraded and prevented from accumulating [21]. Under a state of dysfunction - caused by damage to pathway constituents, high levels of metabolism, or high levels of carbonyl precursors present - MG will be produced at a higher level and disrupt macromolecular functions [58]. Accumulation of MG has many deleterious effects that lead to a cellular environment with high levels of inflammation and oxidative stress (OS) [4].

MG is directly able to cause impairment to the glyoxalase system [5]. ROS can be directly produced during its formation and degradation [43–45]. MG can also deplete the concentration of antioxidant enzymes [46]. MG is also able to modulate important signaling pathways, resulting in excessive ROS, inflammation, apoptosis, and ultimately chronic oxidative stress, leading to death of brain cells, tissues, and disease [5].

MG can neutralize enzymes that are able to catalyze reactions and scavenge substrates, including GSH [1,5,39,40,42]. MG can also increase NADPH oxidase activity, preventing the reduction of GSH and its recycling back into the glyoxalase pathway [1,6,39,40,42]. GSH protects against OS by directly scavenging ROS, and regulates redox

signaling [6,43]. It also plays a vital role in DNA and protein repair and synthesis, metal ion metabolism, and cellular survival [36,47]. It is one of the most important endogenous antioxidants, and proper levels are paramount to a cell's health and normal functioning.

2. Diseases of glyoxalase pathway

Impaired function of the glyoxalase pathway - especially in the brain - has very serious ramifications for cells and tissue. Aging, Alzheimer's, and Parkinson's, (Fig. 2) are neurodegenerative diseases that can be caused or influenced by elevated levels of oxidative stress [4,48,49]. These diseases are complex and multifactorial, and can be a cause and consequence of disrupted glyoxalase pathway function. Increased levels of oxidative stress can be a result of glyoxalase system impairment [19,50,51]. Psychiatric disorders like ASD, schizophrenia, anxiety, bipolar disorder, and depression can also be a cause/effect of impaired glyoxalase function [52–54]. The glyoxalase pathway exerts control over antioxidant defense mechanisms that are paramount for homeostasis of the redox environment of the cell [55,56]. Disrupted function of the glyoxalase pathway can lead to an inflammatory environment contributing to the pathogenesis of neurodegenerative disease [23,40]. MG can cause mutations of DNA and nucleic acids, culminating in telomere shortening, loss of heterochromatin, altered gene expression patterns, and mitochondrial dysfunction [23,57,58].

Oxidative stress results from the disequilibrium between levels of prooxidant molecules produced and the ability of a biological system to detoxify and neutralize the reactive molecules [14]. OS is a chronic, self-perpetuating state of damage to cells and increased inflammation resulting from the corresponding immune response [27,43]. Glyoxalase pathway dysfunction can result in the accumulation of MG in cells [3]. The build up of MG has a direct link to the propagation of OS and inflammation, and is an influencing factor in neurodegenerative disease [8,23,48].

The main source of damage from OS is ROS mediated inflammation [43]. ROS and free radicals have unpaired electrons, and act as nucleophiles to attack macromolecules. The donor molecule gives its electrons to ROS [14]. The molecules attacked by ROS have structural modifications, which causes the molecules to have limited or no function [5]. Under normal conditions, ROS are used in cell signaling and defense against pathogens by macrophages; their damaging effects are caused when they have accumulated past a normal amount [10]. Glyoxalase cycle dysfunction is one perpetrator to blame for the increased ROS production.

AGEs can be formed from modified proteins, lipids, or nucleic acids [59]. Structural changes can reduce biological activity of

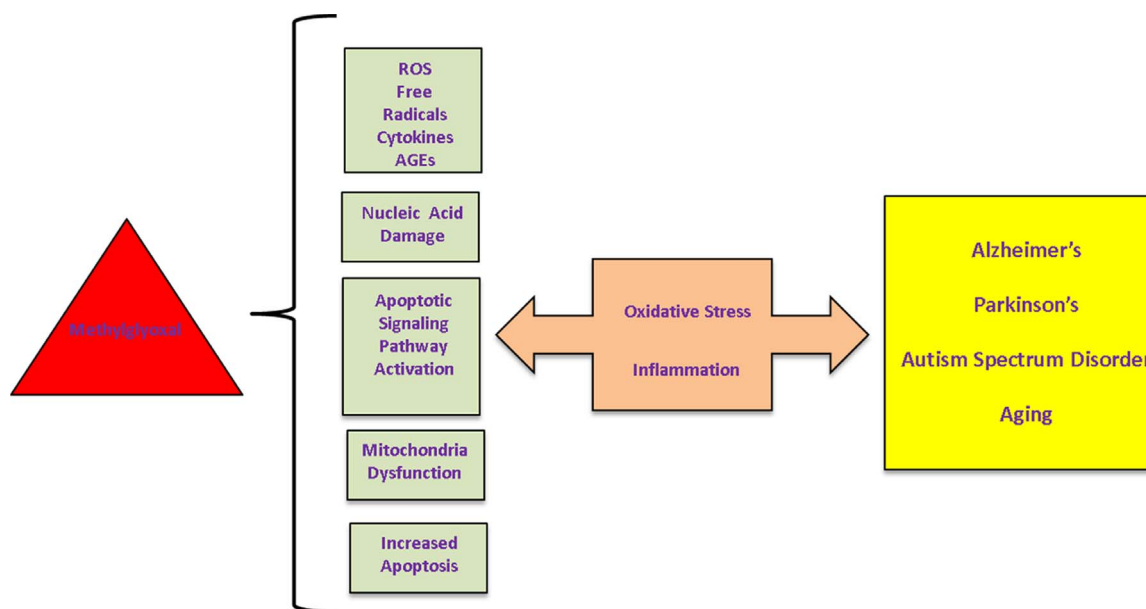


Fig. 2. Methylglyoxal is a highly reactive compound with many deleterious effects on neurons. MG mediates the increased production of ROS, free radicals, pro-inflammatory cytokines, and advanced glycation end products, has damaging effects on mitochondria function and nucleic acids, and increases apoptosis through multiple means, including signaling pathway activation. The resulting increase in oxidative stress and inflammation plays a major role in aging and development of neurodegenerative disease including Alzheimer's, Parkinson's, Autism Spectrum Disorder, and Huntington's.

macromolecules, and are often identified as misfolded or damaged and labeled for destruction [59,60]. Nucleic acid (and mtDNA) can undergo strand breaks, impaired repair mechanisms, and permanent mutations [61]. Lipids are easily oxidizable, and membranes, being rich in lipids, are prone to these modifications [43].

Research has shown a link between MG accumulation, glyoxalase system activity, and disease [21]. Glyoxalase activity is differentially expressed based on cell type and state. Glyoxalase activity has found to increase with age, but subjects over 50 years old exhibit a decline in glyoxalase I [62]. The low glo 1 activity in aging leads to a higher level of dicarbonyl compounds, and it was also discovered that decreasing glo 1 levels correlated with an accumulation of AGEs [35]. Elevated levels of MG leads to inflammation, OS, apoptosis, and DNA damage [40,63].

It has been shown the pathological hallmarks of AD and PD are colocalized to AGEs [41,63,64]. In a comparison of glyoxalase activity between healthy and AD brain tissue, the AD group had a significantly lowered glo 1 activity, at the mRNA and protein level [35].

MG is highly reactive and also cytotoxic. MG inhibits cell growth, and induces cell death at higher concentrations [65]. MG prevented proper hippocampal neurogenesis, adversely impacting neural differentiation, survival, and proliferation, it is believed due to reduced hippocampal BDNF levels [66]. MG concentration can act as a biomarker of severity of disease [23]. AD patients were found to have increased MG in CSF compared to healthy aged controls [64].

3. Aging

Aging is a progressive decline in physiological and metabolic functions of an organism [10]. The process is characterized by chronic, low level inflammation that progresses over time. The rate of aging can be accelerated and influenced by genetic and environmental factors. Age is also the biggest risk factor for Alzheimer's and Parkinson's [19]. Age is correlated with an increase in ROS formation, oxidized proteins and lipids, and apoptosis [14]. Also, during normal aging OS will increase while glutathione activity decreases. Decreasing glo 1 levels are strongly correlated with increasing levels of AGEs, and glo 1 levels drop in accordance to age [16].

The extent of damages can only be viewed posthumously, requiring

the determination of disease progression through biomarkers of oxidative stress and disease. Markers denoting oxidized substrates, nuclear abnormalities are directly related to the extent and progression of aging [15].

4. Alzheimer's disease

Alzheimer's disease is the most common neurodegenerative disorder, and the leading cause of dementia in the elderly [67]. It is a multifactorial disease characterized by progressive neural loss of the hippocampus and cortex, memory and learning impairment, and changes in behavior and personality [19,68]. It has pathogenic hallmarks of beta amyloid ($A\beta$) plaques and neurofibrillary tangles (NFT) [69]. Cognitive impairment reflects synapse loss in dentate gyrus of hippocampus, and neuron loss in frontal and parietal lobe of cortex [70–72].

The amyloid precursor protein (APP) is a membrane protein thought to be involved in plasticity, synapse formation and repair, and export of metal ions [68]. The APP present in the brain can be cleaved by three different secretases [73,74]. Cleavage of APP first by alpha secretase and then gamma-secretase results in a functional protein; while cleavage by beta-secretase results in $A\beta$. The product formed from this improper cleavage – beta amyloid - will aggregate into plaques, and disrupt function of normal cells [19,74]. These $A\beta$ plaques can be modified by MG and AGEs, forming crosslinks, affording them stability and defense against protease cleavage [75,76]. $A\beta$ plaques are very stable and have long lives - The progression of AD is preceded 15 years by appearance of $A\beta$ deposits [23,41]. $A\beta$ plaques will disrupt neuron function, and induce ROS production, ultimately leading to inflammation, damage to cell/tissue, and apoptosis [48,69,77,78].

$A\beta$ aggregates will clump around neurons and prevent their proper function [67]. The $A\beta$ plaques also attract and activate microglia, causing them to cluster and localize around the plaques [21,67]. These immune cells release signals inducing cellular toxicity [68]. The $A\beta$ plaques cause additional production of AGEs, which will reduce the activity of enzymes and proteins (especially in mitochondria) [41]. These AGEs will lead to increased ROS production, which increases the production of APP [23,68]. $A\beta$ plaques can also disrupt redox signaling by interacting with metal ions in active sites of macromolecule,

preventing proper function [48].

Impairment of the glyoxalase system can have a direct impact on the severity of AD [22,73]. Studies have shown glyoxalase I levels decrease with increased aging and severity of AD [14]. The imbalance of antioxidant affects causes a shift to a state of OS. Accumulation of MG and AGEs in the Alzheimer's disease brain is very deleterious [75]. Tissue from AD brain shows high amounts of AGEs and oxidized lipids and proteins, which is a marker of inflammation [41]. There is a correlation with the amount of MG/AGEs localized to specific brain regions and severity of AD [75].

NFT are filaments of bundled proteins formed from a disruption in the microtubule network of cells [67,74]. Microtubule associated protein tau is responsible for promoting and stabilizing microtubule formation in cells, however hyperphosphorylation of tau destabilizes and disrupts the proper assembly of microtubules [79,80]. Proteins aggregate and oligomerize forming toxic NFT, causing the death of neurons in the area [81].

Increased MG levels, apoptosis, and OS contribute to production of A β and hyperphosphorylation of tau [5]. MG can also disrupt cell signaling pathways that control kinases and phosphatases used to regulate phosphorylation of tau [1,59]. A β has an influential and contributing role in the production of NFT, and they are both stable molecules prone to glycation [76]. MG derived AGEs aggregate in NFT and beta amyloid plaques [19]. AGE crosslinking in A β affords it insolubility and protease resistance [75,76]. MG modified A β in plaques has a longer half-life, allowing it to accumulate more AGE modifications, which causes more A β to form [9,67].

5. Parkinson's disease (PD)

Parkinson's is the second common neurodegenerative disease. It is characterized by degeneration of dopamine producing neurons in the substantia nigra [19]. This leads to a decrease of dopamine levels in areas of the brain associated with movement, caused by deregulation in ganglion cell circuits [81–88]. The disease is characterized by motor deficiencies - including tremors, rigidity, and slowness of movement – and cognitive deficiencies [49]. Pathological markers of Parkinson's include the accumulation of alpha synuclein into Lewy bodies [57,84]. The degeneration of dopaminergic neurons and oxidation of dopamine causes altered mitochondrial respiration, inducing a state of oxidative stress in neural tissue [49,89].

Alpha synuclein (AS) is a protein located in presynaptic terminals of neurons that functions in recycling and storage of neurotransmitters [17]. Under conditions of inflammation and oxidative stress, AS proteins misfold and accumulate into aggregates [81,90]. The aggregates of misfolded AS oligomerize into Lewy bodies. These aggregates are cytotoxic, disrupt connections between neurons, and deplete levels of neurotransmitters [81]. AS also reacts with dopamine quinones leading to accumulation of toxic fibrils in the dopaminergic neurons [80,89,90]. Accumulation of AS and Lewy bodies have a detrimental impact on mitochondria activity, causing an elevation of ROS production and deficit in metabolic activity [57].

Neural dopamine can become oxidized if there are high levels of MG derived AGEs [49]. These dopamine quinones have impaired activity, and contribute to the degeneration of neurons [18,90]. MG accumulation can lead to production of ROS and depletion of NADPH, which is critical for reducing glutathione for use in the glyoxalase pathway [81,91,92]. The decline in synthesis of dopamine also causes disruption in vesicle transport, and makes the cell prone to damage and mtDNA mutations [84].

There is a correlation between progression of disease and biomarkers of oxidative stress [93,94]. Post mortem studies of PD brains show high levels of oxidized substrates, and colocalization of AGEs to Lewy bodies [89]. AD and PD have different clinical pathologies but share similar causes and symptoms and A β plaques can be commonly found in PD brains [19]. Patients with PD have been found to have

depleted levels of GSH, and disruption of GSH metabolism has been found to progress neurological disorders [36].

6. Autism spectrum disorder

Autism Spectrum Disorder is a multifactorial neurodevelopmental disorder categorized by impairment in communication, language, social behaviors and relationships [24]. The basis for ASD is still misunderstood, but there is evidence of cellular and metabolic dysfunction influenced by mitochondrial activity [95]. There are also physical abnormalities and alterations in ASD brains. Over 100 genes contribute to ASD, mutations in any of these can lead to ASD [20]. All genes participate in different brain functions controlled by the brain areas, which affect emotional formation, learning and memory, cognitive control, and social orientation [96].

Autistic brains also have a lowered level of viable GABA producing Purkinje neuron cells [97]. MG derived AGEs and ROS will modify the Purkinje neurons, leading to their ultimate death [98]. The OS exhibited in ASD can be a cause of loss of these integral neuron cells [53]. Combined with the high amounts of lipid peroxidation, the OS exhibited in ASD brains could be alleviated by glyoxalase dependent MG detoxification [99,100].

DNA and mtDNA mutations and abnormalities are common in ASD [97,101]. These can cause impaired electron transport chain (ETC) and mitochondria function (membrane potential/polarization, molecule transport, mito protein translocation, and apoptosis) [102,103]. ASD is also categorized by an abnormal immune response; this can have negative effects on brain growth factors, development, and neural transmitters [52,104]. Patients with autism demonstrated activated micro/astro glia and increased levels of proapoptotic cytokines [52]. Patients of ASD had significantly lower ratios of mitochondria proteins bcl-2/bak, which is an indicator of increased cell death and decreased function [24].

Abnormal neural brain maturation found in ASD is influenced by mitochondria dysfunction and MG mediated cellular signaling [97,101]. ASD can lead to chronic immune activation, causing OS in the ASD brain [101]. These can be caused by disequilibrium in MG and glyoxalase signaling [105]. Patients with autism have lower reduced glutathione levels, however it is not known if it is due to a deficit in synthesis or regeneration of glutathione [100].

7. Flavonoid function

Antioxidants are compounds - when present at a lower concentration compared oxidizable substrate - that delay or prevent oxidation of the substrate [14,106]. Antioxidants act as nucleophiles to reduce an oxidative molecule to prevent its interaction with another molecule [14,107]. Endogenous antioxidants produced by the body function in prevention and neutralization of ROS and free radicals, repair of damaged macromolecules, and redox signaling [14]. Exogenous antioxidants consumed through food and drink also play an important role in cellular defense and survival, and have shown to aid the body in combating oxidative stress and inflammation [108,109].

Flavonoids are secondary plant metabolites commonly found in fruits and vegetables [25]. Flavonoids are a family of polyphenol antioxidants that are effective in combating high levels of OS [10,14]. Flavonoids are distinguished by the presence of multiple phenol rings, C to C double bonds, and hydroxyl groups [26]. These structural characteristics confer the antioxidant function of flavonoids, and the number and location of hydroxyl groups influence the biological activity of the flavonoids [106,110]. The lipophilicity is also influenced by structure, which allows some flavonoids to favorably pass through the blood brain barrier [111–114]. The hydroxyl groups are critical for antioxidant activity, and scavenge free radicals and ROS by donation of a proton [114].

This class of antioxidant molecules possesses several distinct

mechanisms of protection from oxidative stress. Flavonoids can directly scavenge and neutralize ROS and free radicals, increase intracellular GSH, prevent glutamate mediated Ca^{+2} influx, and modulation of signaling pathways involved in cellular survival [4,25,26]. Directly neutralizing ROS prevents the oxidation of proteins, amino acids, lipids, metal ions, and other macromolecules. Oxidative modification irreversibly changes structure and prevents normal function of macromolecules. The presences of flavonoids are able to protect these molecules from MG mediated modification into AGEs. Glutathione is a major constituent of the glyoxalase pathway, and one of the most important endogenous antioxidants for neutralization of dicarbonyl compounds and maintaining redox balance in cells [26]. Flavonoid treatment was found to increase GSH concentration, and increased mRNA transcript levels of both GSH constituent subunits [4,26]. GSH is also an essential substrate of astrocytic detoxification in the brain [47]. GSH is also critical for prevention of glutamate mediated apoptosis [115]. Elevated levels of glutamate are cytotoxic, and lead to apoptosis via influx of Ca^{+2} . Excess glutamate depletes GSH, leading to a decrease in activity of glo 1 [25]. Flavonoids have shown to reduce intracellular Ca^{+2} influx in the presence of toxic levels of glutamate [25].

Flavonoid molecules can regulate signaling pathways to modulate cellular, immune, and metabolic processes [4]. Flavonoids are able to modulate a variety of pathways including NF- κ B, MAPK, ERK, and Nrf2 [116,117]. Flavonoid molecules can modulate and reduce expression of proapoptotic and proinflammatory products of genes [118,119]. ROS are used as signaling molecules during immune responses, and the presence of antioxidants can prevent ROS mediated phosphorylation of molecules and pathway targets, preventing their activation and transcription [109]. Flavonoids can also inhibit activation of kinases and phosphatases that would contribute to apoptotic cell death [120,121,4]. After a flavonoid is oxidized by a free radical, the resulting quinones are involved in signaling pathways involved in cellular antioxidant and repair activities (Fig. 3).

Flavonoids can have a direct impact [122] and influence on the function of the glyoxalase pathway. Flavonoids can bind and scavenge free radicals, and also increase the intracellular levels of GSH, while flavonoids are able to scavenge free radicals, in physiological concentrations they are not effectively able to scavenge free radicals [25]. The most effective form of neuroprotection by flavonoids is preventing formation of free radicals by modulation of cell signaling pathways [109,123,124]. Flavonoid antioxidant treatment can lower the intracellular levels of free radicals and ROS, and also enhance the performance of the glyoxalase system by modulating signaling pathways involved in cellular proliferation and survival, glutathione synthesis and expression of antioxidative proteins [4,10,14,25,121].

Morin is a flavonoid that has shown to have effective anti-inflammatory and anti-tumor function [118]. Morin was able to block the activation of NF- κ B pathway by ROS and inflammatory cytokines, preventing a signaling cascade resulting in cell death [121]. Morin exerted its control over the signaling pathway by inhibiting TNF induced NF- κ B activation by inhibiting degradation of I κ B α , and morin was also able to inhibit TNF mediated p65 nuclear translocation [120,125]. Morin inhibited phosphorylation of Akt in a breast cancer cell line, preventing metastases and tumor proliferation [116]. Morin was shown to decrease survival of cancer cells, while increasing viability of normal endothelial cells [116]. These compounds are involved in the pAkt - NF- κ B signaling pathways in neuronal cells to enhance the glyoxalase expression [4].

Flavonoids have shown effectiveness in modulation of glyoxalase pathway and MG detoxification. Our previous research has shown treatment with catechin, morin, and quercetin was able to attenuate the effects of MG toxicity while retaining cellular function. The flavonoids increased glo 1 activity and GSH concentration, while reducing the concentration of MG [4,126].

While a lack of flavonoids does not cause any disease, Exogenous antioxidants can influence cellular health and offer protection against

inflammatory and degenerative diseases. A correlation exists between flavonoid consumption and low levels of dementia and neural pathology [127]. Intake of flavonoids can have a protective effect on neural cells in many diseased states [127,128]. Silymarin and naringin are flavonoids that have shown efficacy in protection against excitotoxicity in dopaminergic neurons. Silymarin protected mice against 1-methyl-4-phenylpyridinium (MPP⁺) induced toxicity by attenuating production of inflammatory cytokines, and prevented mitochondrial dysfunction [127]. Naringin protected neural cells from toxicity mediated by 6-Hydroxydopamine (6-OHDA), mediated by an increase in Nrf2 activation [127]. Morin has also shown to mitigate the damage caused by ischemia and stroke by downregulating expression and release of proinflammatory cytokines [118]. A grape powder extract was shown to reduce anxiety-like behavior, depression, and memory impairments caused by elevated OS [129].

8. Mechanistic interference

When under states of stress and cytotoxicity, cells initiate antioxidant defense mechanisms. Nuclear factor erythroid 2-related factor 2 (Nrf2) activation leads to the transcription of proteins involved in counteracting oxidative damage [56]. The Nrf2 pathway is activated during elevated OS. Unstimulated Nrf2 is bound to Keap1 in the cytoplasm, and subsequently ubiquitinated and degraded [130]. Under states of OS, ROS disrupt the association between Keap1 and Nrf2. Nrf2 is released from the complex, and translocates to the nucleus to bind the antioxidant response element (ARE), leading to the production of antioxidant molecules [55]. (Fig. 4) Gene products function in an antioxidant, anti-inflammatory, and neuroprotective fashion [119]. Among the products are glo 1, heme oxygenase-1 (HO-1), gamma-glutamyl-cysteine synthetase (GCS), and glutathione-S-transferase.

Keap 1 is a negative regulator of Nrf2. Keap 1 and Cullin-3 contain Nrf2 in the cytoplasm of cells. Cullin-3 ubiquitinates Nrf2 and it is transported to proteasome for degradation. High levels of OS and free radicals phosphorylate targets on Keap 1 and Cullin-3 and disrupt the Keap1-Cullin-3 degradation system. Nrf2 is not degraded, and builds up in the cytoplasm until it is translocated to the nucleus and binds to ARE [131]. Nrf2 is critical for mediating expression of protective genes in response to MG induced OS and toxicity, and Nrf2 expression has been showed to suppress accumulation of AGEs [56]. Neurons treated with a Nrf2 activator were protected from MG mediated damage [132]. The Nrf2 signaling pathway increased intracellular GSH levels, and increased the glyoxalase pathway's detoxification of MG protecting cells from OS mediated damage [133]. Neuron cells treated with N-acetyl serotonin showed enhanced nuclear translocation of Nrf2 from the cytoplasm [134]. Nrf2 activators have shown benefits in PD animal models, Nrf2 expression prevented 1-methyl-4-phenyl 1,2,3,6 tetrahydropyridine (MPTP) induced toxicity in cells [135]. Flavonoids are able to indirectly induce Nrf2 expression by activation of kinase pathways resulting in phosphorylation of Nrf2 and induction of dependent genes [56,136]. Nrf2 also provided a stress-responsive defense against AGEs and lead to transcriptional control of glyoxalase [56] and a temporal dynamic reciprocal regulation of Nrf2 and glo 1 was observed during disease development [137]. Mangiferin also upregulated glo 1 through activating Nrf2/ARE signaling pathway [138].

Flavonoids are able to modulate proinflammatory signaling pathways to prevent OS and apoptosis [139]. Paraoygenase-2 (PNO2) is an enzyme involved in neuroprotection by preventing OS mediated damage in mitochondria. Flavonoids can modulate the JNK/AP-1 pathway to increase expression of PNO2 [111]. Flavonoids are able to inhibit expression of TNF- α by modulating NF- κ B, inducing expression of antioxidant molecules like PNO2. PNO2 is primarily located in the mitochondria. PNO2 exerts its neuroprotection primarily through protecting against mitochondrial mediated oxidative stress [112].

Flavonoids can directly scavenge free radicals, but they have limited accessibility to the brain; antioxidant concentration in the brain is too

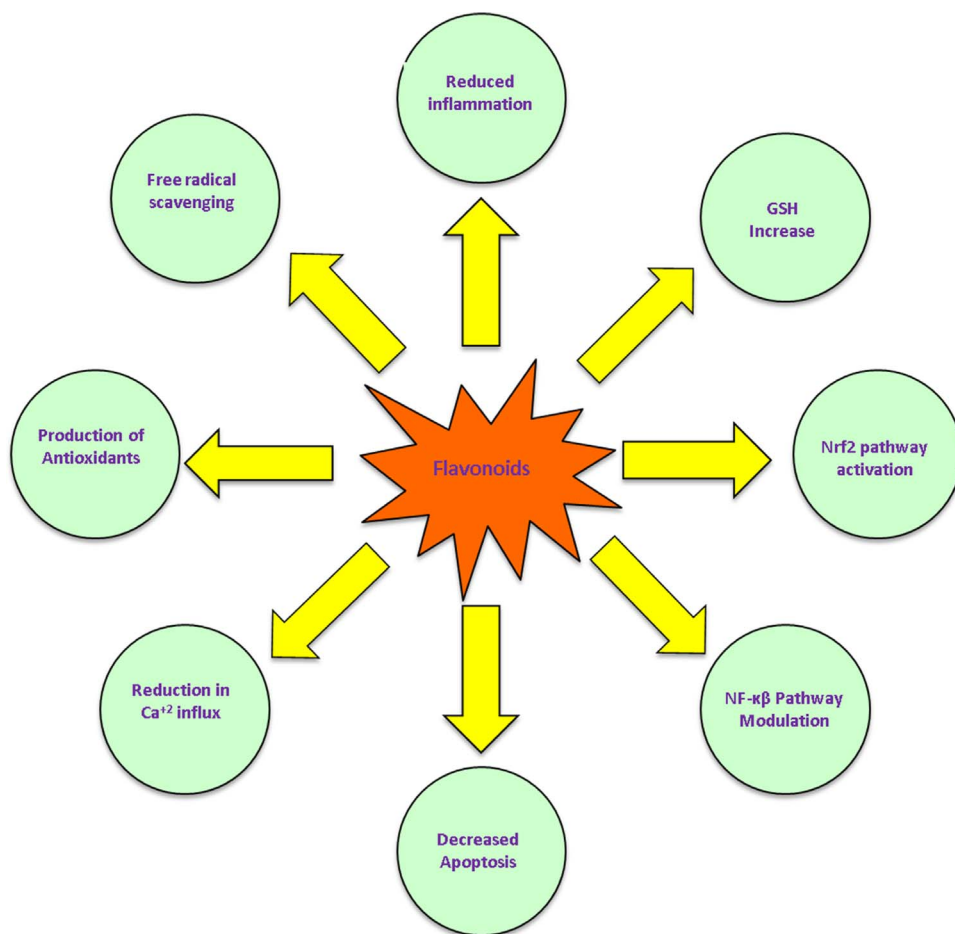


Fig. 3. Flavonoid antioxidants possess several distinct of cellular neuroprotection. Flavonoids reduced the amount of inflammation and oxidative stress in the cellular environment through multiple means. Flavonoid compounds directly scavenge free radicals and ROS, increase intracellular concentration of GSH and antioxidant molecules, modulate NF-κB signaling pathways to reduce apoptosis, and reduce glutamate mediated Ca²⁺ intracellular influx. These actions of flavonoids directly enhance the glyoxalase pathway.

low to have a significant impact on direct scavenging. Flavonoids exert their protective effects by modulation of cell signaling pathways and activation of cellular antioxidant defense mechanisms [112]. Flavonoids also inhibit AGE formation by preventing formation/presence of dicarbonyl compounds, and also attenuate damage [118]. Flavonoids were found to reduce MG mediated OS, and enhance the glyoxalase pathway activity [126].

9. Conclusion

The glyoxalase pathway is an integral part of the body's antioxidant system. Dysregulation can have deleterious and catastrophic events, leading to high levels of OS, and also neurodegenerative disease. This seemingly innocuous pathway found in all cells of our body can be responsible for production and formation of toxic intermediaries that alter a cell's normal function and leading to Alzheimer's disease, Parkinson's disease, ASD and Aging. Flavonoids were found to be

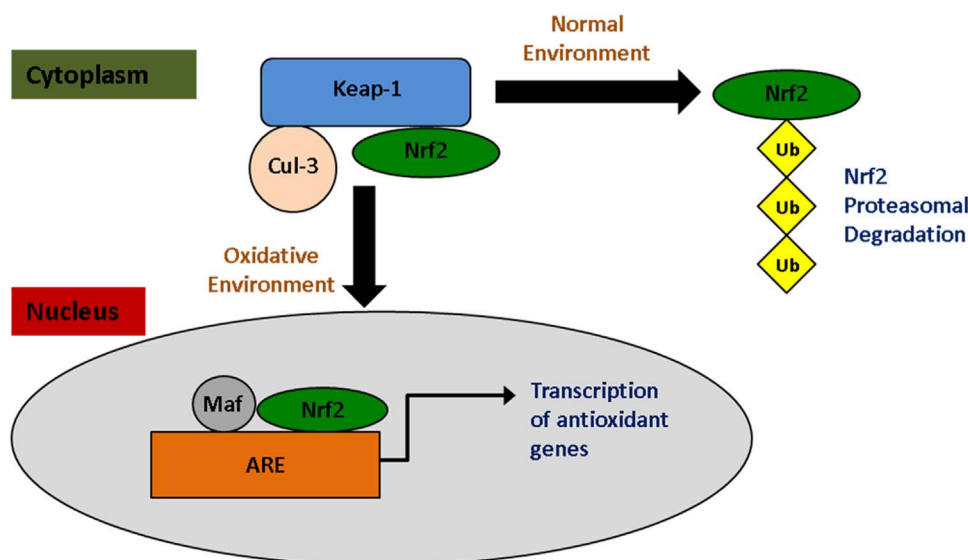


Fig. 4. Inactive Nrf2 is bound to Keap1 and Cullin-3 in the cytoplasm. Cullin-3 ubiquitinates Nrf2 and is targeted for proteasomal degradation. Elevated levels of electrophiles and ROS disrupt the ability of Cullin-3 to degrade Nrf2. Nrf2 builds up in the cytoplasm, and translocates to the nucleus. It forms a complex with Maf and binds to ARE, inducing the transcription of antioxidant defense molecules to protect the cell from cytotoxicity.

involved in the reduction of oxidative stress through mechanisms regulated by the glyoxalase pathway. Flavonoid compounds have shown the ability to scavenge ROS and regulate cell signaling pathways integral for antioxidant defense mechanisms and cellular survival. The glyoxalase pathway is a promising drug target for neurodegenerative diseases. Drug discovery [4,140–144] and delivery [145–147] processes could be explored in this target against neurodegenerative diseases. Novel flavonoids could be designed, synthesized, and tested to protect neurodegenerative diseases through glyoxalase pathway.

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