An Investigation into the Effects of Chemical, Pharmaceutical, and Herbal Compounds on Neuroglobin: A Literature Review

Sahar Golpour- Hamedani [1], Makan Pourmasoumi [2], Gholamreza Askari [3,4*], Mohammad Bagherniya [3,4], Thozhukat Sathyapalan [5], Amirhossein Sahebkar [6,7,8*]

[1] Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of medical science

[2] Gastrointestinal & Liver Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran

[3] Nutrition and Food Security Research Center and Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

[4] Anesthesia and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

[5] Department of Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, Hull, UK

[6]Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

[7] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

[8] School of Medicine, The University of Western Australia, Perth, Australia

Corresponding authors: amir_Saheb2000@yahoo.com; askarig@yandex.com

Abstract

Neuroglobin (Ngb) is an oxygen-binding globin protein that is mainly expressed in the neurons of the central and peripheral nervous system. However, moderate levels of Ngb have also been detected in non-neural tissues. Therefore, Ngb and Ngb modulating factors have been increasingly studied over the past decade due to their neuroprotective role in neurological disorders and hypoxia. Studies have shown that a number of chemicals, pharmaceuticals, and herbal compounds can modulate the expression of Ngb at different levels and with different doses, indicating a protective role against neurodegenerative diseases. Among these compounds are iron chelators, hormones, antidiabetic drugs, anticoagulants, plant derivatives and short-chain fatty acids. This review will discuss the possible effects and mechanisms of chemical, pharmaceutical, and herbal compounds on Ngbs.

Keywords: Pharmaceutical, herbal, chemical compounds; Nutrition; Neuroglobin (Ngb)

Introduction

Globins are present in all living organisms and, in fact, proteins that bind oxygen (O_2) and play a key role in the respiration and oxidative energy production in bacteria, plants, fungi, and animals. For many years, hemoglobin (Hb) and myoglobin (Mb) were the only two globins identified in vertebrates. Hb is found in red blood cells. It carries oxygen molecules from the lungs to all tissues and helps control the pH of body fluids. Mb is found in the cardiac and skeletal muscle tissue. It plays a role in storing and increasing the transfer of O_2 to mitochondria. Moreover, Mbs are also involved in nitric oxide and reactive oxygen species (ROS) detoxification [1]. Ngb is an O_2-binding globin protein whose presence in the nerve tissues was first identified and confirmed by Burmester et al. (2000) [2]. As a monomeric 151 amino-acid protein, Ngb is a member of the nerve globin family, which is widely present in vertebrates and expressed to a large extent in neurons of the central and peripheral nervous system and endocrine tissue [3]. Ngb is distributed widely in the human body, including the hippocampus, thalamus, hypothalamus, cerebral cortex, cerebellum, organs with endocrine function and retinal cells. As far as it is concerned with protein distribution in the central nervous system (CNS), the available data reveal a considerable presence in a relatively limited number of regions of a rat [4] and human CNS [5]. It seems that the presence of Ngbs corresponds to metabolically active, oxygen-consuming cell populations [3]. Several studies have shown the key neuroprotective role of Ngb [6]. According to previous studies, Ngb is also up-regulated in cerebral hypoxia and ischemic injury, indicating the neuroprotective role of this globin in cerebral disorders [7]. The Ngb concentration varies in different human brain areas [8]. Overexpression of Ngb has been reported to be associated with cytoprotective effects on neurons, anti-apoptotic properties in nerve tissue, and protection against oxidative stress [6, 8]. Although several studies have been performed in this regard, it is difficult to define the exact functions of Ngb.

As a globin, the main physiological functions of Ngb include O_2 binding and transport and inhibition and detoxification of reactive species (namely nitric oxygen, carbon monoxide, or hydrogen sulfide) [3, 6]. The neuroprotective role of Ngb is probably due to a synergistic mechanism, including the improvement of mitochondrial function, a reduction in the secretion of reactive oxygen species and nitric oxide, and the inhibition of the innate cell death pathway [9, 10]. Cell death is the final consequence of several pathological conditions of the central nervous system. The available evidence indicates that both acute injuries and neurodegenerative diseases are often accompanied by mitochondrial dysfunction. Therefore,

the possibility of preventing mitochondrial events involved in cell death may be an effective tool to limit neuronal damage. Much attention has been paid in recent years to Ngb protein because the evidence shows that the high level of Ngb expression is associated with maintaining mitochondrial function and increasing the survival of nerve cells in vitro conditions in various experimental cell models [11]. Additionally, using natural and chemical molecules to induce the Ngb expression in different pathologies, such as ischemia, hypoxia, Alzheimer's disease and Huntington's disease, can be a new therapeutic approach against neurological diseases [12, 13].

Mitochondrial events in the CNS play a key role in controlling cell death, which has major implications for developing neuroprotective therapies. Agents that prevent mitochondrial membrane permeability or inhibit cell death may be efficient tools to limit neuronal damage. The probable stimulation of endogenous neuroprotective mechanisms has appeared as a promising strategy [14]. Therefore, over the last few years, much attention has been paid to Ngb as an endogenous neuroprotective molecule considering mitochondrial function and regulation [15]. The neuroprotective role of Ngb in a wide range of pathological conditions has been demonstrated by several experimental studies. In the cultured cortical neurons, antisense-mediated globin knockdown causes cells to be more vulnerable to hypoxia [16] and reduces viability in neuroblastoma cells under oxidative stress [17]. Ngb overexpression can reduce different diseases and injuries affecting the central nervous system [18]. As recombinant Ngb is an intracellular protein and does not cross cell membranes except in certain species of fish, its direct administration in therapy is unfortunately not appropriate [19]. However, it has been shown that using some small molecules (natural and synthetic) derived from pharmaceutical and food compounds that are capable of crossing the blood-brain barrier (BBB) can increase the Ngb upregulation resulting in the improved outcome of brain injuries and neurological disorders [20]. This foregrounds the overview of the chemical structure that can inspire future research to design new molecules capable of modulating the Ngb level. The endogenous neuroprotection caused by overexpression of Ngb can indicate a therapeutic strategy. Moreover, the pharmacological induction of Ngb by natural and synthetic molecules can be useful in the therapy of neurodegenerative diseases for which no effective treatments have been found so far. Several molecules have been identified in studies as Ngb modulators, either in chemical and pharmaceutical or food compounds. Considering the key role of Ngb in neuroprotection and given that few studies were found regarding the review and summarization of the effect of medicines and food on the function of Ngbs; therefore, the present study aimed

to review the literature on the effects of pharmaceuticals, chemicals, and herbal compounds on Ngbs function.

Methods

This narrative review was conducted by searching databases PubMed, Science Direct and Web of Science for studies published from 2010 to 2022 on humans and animals. The search terms were Neuroglobin, pharmaceutical, herbal, chemical compounds, food, nutrition, and pharmacological induction.

Results

Considering the results of the studies regarding the effects of different pharmacological and food compounds on Ngb modulation, the summary of the reviewed studies is discussed in the following sections separately: the effects of antidiabetic medications, non-steroidal anticoagulants, iron chelators and hormonal derivatives, plant-derived compounds and short chain fatty acids (Figure 1).

Antidiabetic medications

Metformin is an oral antidiabetic medication mainly used for treating type 2 diabetes [21]. Over recent years, metformin has been investigated for its potential role in neurodegenerative diseases [22]. In a study conducted on adult rats, neurotoxicity was induced in alcohol-treated animals. The study showed that after taking metformin orally for several days, metformin increases Ngb expression in the frontal lobe in response to alcohol-induced brain damage. Moreover, increased Ngb expression was also observed in rats treated with metformin alone, confirming the biological antioxidant and protective functions of metformin [23].

Non-steroidal anticoagulants

Ngb is a neuroprotective protein that plays a role in treating Alzheimer's disease and protects the brain from damage induced by Alzheimer's disease progression [24]. In a recent study, an ibuprofen-α-lipoic acid (IBU-LA) conjugate was investigated as a potential inductor of Ngb expression in the rat brain model of Alzheimer's disease [25]. IBU and LA have protective effects against Alzheimer's disease [26]. IBU-LA conjugate is very resistant to enzymatic degradation. It passes through the BBB and transmits IBU and LA directly to neurons. According to the obtained results, subcutaneous administration of IBU-LA guarantees a high level of Ngb in the brain of a rat model of Alzheimer's disease. The results also showed that IBU-LA administration is highly capable of maintaining the high level of Ngb and allows Ngb

to play an anti-apoptotic neuroprotective role, indicating that it is a valid tool in the therapeutic strategy of Alzheimer's disease progression [25].

Iron chelators

Deferoxamine (DFX) was the first molecule identified as an Ngb inductor. It is a natural BBB cross-chelating molecule synthesized by streptomyces pilosus in iron-limiting conditions [16]. DFX is used for the treatment or prevention of thalassemia-related iron overload. It has a chelating agent that can complex iron and remove it [27]. In addition, DFX has been shown to increase the expression of hypoxia-inducible factor 1 (HIF-1), one of the major hypoxia-signalling transcription factors involved in Ngb expression [16].

Hormones and derivatives

Growth hormones and factors are capable of increasing Ngb expression in neuron-derived cells. For example, vascular endothelial growth factor (VEGF), which promotes angiogenesis, neurogenesis, and neuroprotection, provides a positive feedback pathway using Ngb. In fact, in the rat cerebral cortex neurons, VEGF stimulates Ngb expression through VEGF receptor tyrosine kinase (VEGFR2/Flk1), whereas Ngb overexpression suppresses VEGF expression [28]. Furthermore, neurological response to hypoxic/ischemic injury leads to the expression of neuroprotective proteins like VEGF. In the study conducted in neuron-enriched rat cerebrocortical cultures, a positive correlation was found between VEGF and Ngb. VEGF increased Ngb expression, and Ngb decreased VEGF expression [28].

Studies have shown the physiological role of estrogen hormones, especially estradiol (E2), in the brain, indicating that these hormones protect the brain from neurodegenerative disorders [29]. It was emphasized that women in menopausal periods are more likely to get Alzheimer's disease [30]. E2 reduces the toxicity of amyloid beta (Aβ) and glutamate. De Marinis et al. reported the first experimental evidence of the Ngb-E2 interaction (2010). They showed that E2 increases the Ngb level up to 300% in the SK-N-BE human neuroblastoma cell line and hippocampal neurons of the mouse. They also revealed that E2 could act as an endogenous modulator [31]. Moreover, the positive regulation of E2-induced Ngb expression in astrocytes may be associated with the mechanism, including estrogen receptor ERβ [32].

However, E2 can also bind to the ERα receptor subtype and induce a cancer survival effect and expression of Ngb. Experimental data reported the ERα/ERβ ratio in non-neuronal cancers (e.g., breast and liver) higher than normal tissue [33]. Further studies have shown that E2

increases the Ngb expression in hepatocytes and breast adenocarcinoma cells (MCF-7) that express the ERα receptor subtype [34].

In one study, testosterone alone did not increases the expression of Ngb in SK-N-BE cells (neuroblastoma cell line) and hippocampal neurons of a mouse [31]. However, another study found that when T98G cells (human astrocyte cell model) are deprived of glucose, testosterone leads to Ngb production. The recent result indicates that testosterone can regulate the neuroprotective protein levels in cellular damaging conditions [35].

Fucosterol (Fuc) is a phytosterol mainly found in brown seaweed with approved biological effects (e.g., anticancer, antidiabetic, antioxidant, antifungal, antihistamine, anticholinergic, antilipid, etc.) [36]. Fuc-treated Human neuroblastoma cell line (SH-SY5Y cells) revealed a significant increase in Ngb messenger RNA (mRNA) levels. Moreover, if the SH-SY5Y cells were pre-treated with Fuc before the therapy with toxicity induced by Aβ, the mRNA levels of Ngb would extremely increase, indicating the association of the Fuc neuroprotective effect with Ngb upregulation [37].

Thyroid hormones play a key role in brain development as they are essential for growth and differentiation. An in vivo study assessed the changes in the levels of two globins in the brain, i.e., Ngb and cytoglobin. The results showed that both proteins were overexpressed when rats were treated with triiodothyronine (T3) at high dosages. There is one hypothesis about Ngb that says T3 can upregulate the expression of Ngb indirectly on the hypoxia-inducible gene factor 1 [38]. The expression of Ngb in the cortex, hippocampus, and cerebellum of thyroidectomized animals increases 24 hours after thyroid hormone administration compared to the control group [38].

Besides the hormones mentioned above, erythropoietin also plays a neuroprotective role in inducing Ngb regulation [39]. Finally, it generally seems that Ngb should be considered a hormone-inducing protein required to be regulated for neuroprotective functions against harmful stimuli.

Plant-derived compounds

Plant-derived polyphenols are natural compounds containing phenolic groups. They form a broad research area in treating degenerative diseases, including neurodegeneration and cancer [40, 41]. Their biological effects have been attributed to their antioxidant capacity, their protective abilities in microcirculation, and their anti-inflammatory actions similar to estrogen

[42]. Naringenin (Nar) is a flavonoid investigated in several degenerative pathologies due to its neuroprotective potential [43, 44]. Nar was found to upregulate Ngb in SK-N-BE cells in the interaction with the ERβ subtype [31]. Interestingly, another study evaluated the effect of Nar on the MCF-7 cell line and found that it did not change the Ngb protein levels. Therefore, considering the contradictory results obtained, further research seems to be required in this regard [45].

Regarding other plant-derived compounds, it was found that daidzein (Dzn), genistein, polydatin, biocanin A, and especially formonontine increased the Ngb mRNA expression in primary mouse and human neurons [46]. Five natural inductors, including biochanin A, formonontine, genistein, polydatin and Dzn, are considered phytoestrogens [31]. In terms of structure and function, they are similar to estrogen hormones like E2, i.e., an endogen up-regulator of Ngb gene expression in neurons. Among the five new Ngb activators, formononetin shows the highest ability to induce Ngb overexpression. Formononetin can also induce Ngb up-regulation by activating cyclic adenosine monophosphate (cAMP) response element binding protein [46].

Phytochemicals are secondary plant metabolites that provide a broad area of research in treating degenerative diseases, including cancer and neurodegeneration. The effects of phytochemicals have been attributed to their antioxidant effects; however, they have also been reported for their phytochemical capability to bind to hormone receptors. Notably, flavonoid naringenin increases the level of Ngb in human neuroblastoma cells by binding to the ERβ subtype [31].

The new herbal formula, Ji-Sui-Kang (JSK) was accompanied by the theory of recovery in people with spinal cord injury (SCI). This herbal formula significantly increases Ngb expression and reduces the expression of caspase-3 and cyclooxygenase-2 [47]. Moreover, Yizhijiannao granule (a Chinese compound medicine) was found to be capable of enhancing cognitive performance in patients with Alzheimer's disease. Additionally, Ngb levels increased in Yizhijiannao granule-treated rats with learning and memory disorders for eight weeks [48]. However, further in vitro/in vivo clinical research is required to confirm the effectiveness and safety of these phytochemicals.

Short-chain fatty acids derivatives

Short-chain fatty acid derivatives induce fetal globin expression [49]. The cinnamic, valproic, butyric, levulinic and succinic acids were investigated in HN33 cells (hippocampal

neuroblastoma cells) [5]. Only cinnamic and valproic acids among the fatty acids showed induction related to Ngb. Valproic acid is a synthetic compound existing in the formulation of several anticonvulsants, while cinnamic acid is a natural compound extracted from cinnamic oil. The mechanism through these fatty acids, which can regulate the expression of Ngb, is not well understood. Studies show that the neuroprotective effects caused by valproic acid are attributed to the inhibition of histone deacetylase. However, it seems that this biological activity is not associated with the induction of Ngb expression. In addition, other anticonvulsant medicines were also examined owing to the anticonvulsant activity of valproic acid, but none exhibited Ngb induction [50].

Metalloids

The neurotoxic effects of sodium arsenite (NaAsO2) and other inorganic compounds on the exposed populations and experimental models have been shown. Cognitive disorders in children and adults chronically exposed to arsenite from drinking water have been described [51]. The transcriptional and expression levels of Ngb protein are significantly decreased in a dose-dependent manner in primary-cultured rat cerebellar granule neurons shortly after NaAsO2 exposure and become positively regulated after exposure for a long time. Higher expression of Ngb was found in rat cerebellum post NaAsO2 exposure for 16 weeks but not in other brain regions, such as the cerebrum, hippocampus, and midbrain [52]. Therefore, considering the results of the studies, metalloids seem to make changes to the expression of Ngbs in a dose-dependent manner, and more studies are warranted to determine the exact effect of metalloids in this regard.

Conclusion

This review identified a number of chemicals, pharmaceutical, and herbal compounds, including hormones such as thyroid hormones, estrogens, epithelial growth factor, iron chelators, some medicines like antidiabetic drugs, non-steroidal anticoagulants, and chemical and herbal compounds that modulate the expression of Ngb (**Table 1**). However, given the neuroprotective role of Ngb and the limited studies in this regard, further and more accurate research is required to be conducted on the effects of chemical, pharmaceutical, and herbal compounds on the Ngbs function.

Table 1. Characteristics and results of the studied articles.

Author/Year/ Reference	Study design	Research objective	Method	Results
Jin 2011[50]	In vitro	Identification of small molecules that are capable of inducing Ngb protein expression	-Examination: Examining the Ngb expression by Western blot in cultured mouse HN33 hippocampal neuron N18TG2 neuroblastoma cells	-Increasing the expression of Ngb by the short-chain fatty acids of cinnamic acid and valproic acid, but not by other short-chain fatty acids
Jin, Kunlin 2012 [28]	In vitro	Investigation of the probable interaction between the expression of vascular endothelial growth factor (VEGF) and Ngb in mouse cortical neurons	-Examination: The neuronal cells were grown in a neurobasal medium with B27 supplement, 2 mM glutamate, and 1% penicillin and streptomycin and half of the medium was replaced with a neurobasal medium after 4 days. The cultures were treated for 24 h with VEGF with or without the VEGF receptor tyrosine kinase inhibitors.	- Stimulation of Ngb expression by VEGF in a VEGFR2/Flk1 receptor-dependent manner -Suppression of VEGF expression by Ngb overexpression
De Marinis 2013 [53]	In vitro	Investigation E2 (estrogen) capability of modulating the intracellular expression of Ngb and Ngb interaction with mitochondrial cytochrome C following H2O2-human toxicity	-Examination: The pcDNA-flag-NGB (flag-NGB) was attained through NGB ORF subcloning from the NGBN1-pEGFP plasmid to the pcDNA-flag 3.1C The medium was changed six hours following transfection, and after 24h, the cells were processed for confocal microscopy analysis	-Strong increase of Ngb-cytochrome C relationship in mitochondria by E2 treatment -Reduction of cytochrome C level in the cytosol of SK-N-BE cells by E2 treatment - Dependence of estrogen receptor expression in nuclei, mitochondria and cytosol of SK-N-BE E2 cells, especially on mitochondrial ERβ activity

Zara 2013 [25]	In vivo	Investigation of the conjugate neuroprotective role of ibuprofen and lipoic acid by Ngb/Akt intracellular signaling pathway in rat model with Alzheimer's disease	-Examination: Analyze the morphology of the brain using Biel-schowsky staining, Aβ(1–40) and Ngb expression by immunohistochemistry	-Reducing the level of Ngb in Aβ samples as compared with control and IBU-LA samples -Decreased the ratios of p-Akt/Akt and p-CREB/CREB in Aβ sample that goes back to the basal level in control and IBU-LA samples
Liu 2013 [52]	In vitro	Evaluation of the toxic effects of sodium arsenite (NaAsO2) on rat's cerebellar granule neurons (CGNs) using the primary culture of CGNs, Identification of Ngb expression in rats CGNs in the exposure of NaAsO2	-Examination: Evaluate The toxic effects of NaAsO2 on rat's CGNs in terms of Ngbs expression using the primary culture of CGNs	-Significant increasing intracellular reactive oxygen species production in cells exposed to NaAsO2. -Significant reduction in Ngb protein and mRNA expression in rat CGNs in a short time after NaAsO2 exposure and positively regulating after a longer time of exposure. -The toxic effect of NaAsO2 on Ngb expression depends on the dose
Su 2013 [47]	In vivo/ vitro	Evaluation of the effect of a novel herbal formulation (JSK-Ji-Sui-Kang) on rats with acute spinal cord injury	-Examination: Evaluate The JSK therapeutic effects via a standard behavioral assessment, histological, immunochemical and microarray analysis	-Observing a significant improvement in locomotor function - Attenuating tissue damage and more axons and myelin in animals treated with JSK than in control ones - Significantly increasing Ngb, vascular endothelial growth factor (VEGF) and growth-associated protein 43 expressions, and reducing in caspase 3, cyclooxygenase-2, RhoA, and fibrinogen expression with JSK

Oliveira 2015 [38]	In vivo	Evaluation of thyroid hormone (TH) effect on Ngb and Cygb metabolism in the brain and assessment of their response in the cerebellum, hippocampus and cortex after supraphysiological doses of TH	-Experiments groups: Control (C), thyroidectomy (Tx), and jugular intravenous (i.v) -Intervention: T3 (100 µl/100 g) injection - treated thyroidectomy, and the rats were studied after 30, 60, 120 min and 6, 12 and 24 h	-Increased expression of Ngb gene and protein in different time points as compared with the C group In the cerebral cortex -Increased expression of Ngb and Cygb in the hippocampus -The expression of Ngb and Cygb in the brain is affected by both overexpression and lack of expression of thyroid hormone
Liu 2016 [46]	In vitro/vivo	Screening of herbal neuroprotective compounds affecting Ngb expression systems	- Examination: Mouse and human stable Ngb reporter systems for screening a pool of natural herbal compounds were developed Neuroprotection effects in primary cultured neurons were tested using a neurotoxicity assay	-Identifying the polydatin, genistein, daidzein, biochanin A, and formononetin, which are capable of increasing Ngb promoter activity both in mouse and human -Significant increasing the expression of Ngb mRNA in primary neurons with polydatin, genistein and formononetin
Toro-Urrego 2016 [35]	In vitro/vivo	Assessing whether testosterone exerts protection in a human astrocyte cell model, the T98G cells	-Examination: Assessing whether testosterone exerts protection in a human astrocyte cell model, the T98G cells	-Positive regulation of neuroglobin with testosterone - Improved cell survival and mitochondrial membrane potential and reduced nuclear fragmentation and reactive oxygen species generation with testosterone.
Cipolletti 2019 [45]	In vitro	Evaluating the possibility that resveratrol (Res) in increasing the susceptibility of breast cancer cells to paclitaxel (Pacl) by affecting the E2/ERα/Ngb pathway	-Examination: Growing and evaluating human breast cancer cells as well as neuroblastoma cell and human embryo kidney cell in air containing 5% CO2 in either modified, phenol red-free, Dulbecco's Modified Eagle's Medium (DMEM) medium	-Decreasing Ngb levels interfering with E2/ERα-induced Ngb upregulation and with E2-induced ERα and protein kinase B phosphorylation in MCF-7 and T47D (ERα-positive) receptors -Increasing Ngb levels by Ngb

				expression vector transfection preventing Pacl or Res/Pacl effects
Gan 2019 [37]	In vitro	Assessing the ability of fucosterol, a phytosterol found in brown alga, to protect SH-SY5Y cells against Aβ-induced neurotoxicity	-Examination: -Exposed SH-SY5Y cells to fucosterol before Aβ treatment -Determined the effect of apoptosis using Annexin V FITC staining and studied RNA expression using RT-PCR	-Confirming the protective effects of fucosterol on SH-SY5Y cells against Aβ-induced apoptosis with flow cytometry -Increasing the Ngb mRNA levels with pretreatment with fucosterol
Bonea 2020 [23]	In vivo	Modulatory effect of metformin on ethanol-induced anxiety, redox imbalance and extracellular matrix levels in rat brain	-Experimental groups: Control, alcohol (ALC), ALC + MET, and MET -Intervention: Prescription ALC (2 g/kg body weight) and MET (200 mg/kg body weight) through the mouth for 21 days, once per day Conduct the open field test (OFT) and elevated plus maze (EPM) On the 22nd day	-Increasing the time that was spent in unprotected open arms with MET -Reducing oxidative stress in the frontal lobe and hippocampus with MET -Increasing expression of Ngb in the frontal cortex with MET
Montalesi 2020 [54]	In vitro	Evaluating the impact of daidzein (Dzn) and its metabolites on an estrogen-dependent anti-apoptotic pathway in breast cancer cells	-Examination: Treating and evaluating estrogen receptor α-positive breast cancer cells with Dzn and its metabolites, ERα activation and Neuroglobin levels	-Increasing the Ngb levels and rendering breast cancer cells more prone to the paclitaxel treatment by daidzein and its metabolites

Declaration

Funding and/or Conflicts of interests/Competing interests

None of the authors have any conflict of interest to declare with respect to this manuscript

No funding was obtained for this manuscript

References

1.1 Rassaf T, Totzeck M, Hendgen-Cotta UB, Shiva S, Heusch G, Kelm M. Circulating nitrite contributes to cardioprotection by remote ischemic preconditioning. Circulation research. 2014;114(10):1601-10.

.2 Burmester T, Weich B, Reinhardt S, Hankeln T. A vertebrate globin expressed in the brain. Nature. 2000;407(6803):520-3.

.3 Burmester T, Hankeln T. Function and evolution of vertebrate globins. Acta Physiologica. 2014;211(3):501-14.

.4 Fabrizius A, Andre D, Laufs T, Bicker A, Reuss S, Porto E, et al. Critical re-evaluation of neuroglobin expression reveals conserved patterns among mammals. Neuroscience. 2016;337:339-54.

.5 Jin K, Mao Y, Mao X, Xie L, Greenberg DA. Neuroglobin expression in ischemic stroke. Stroke. 2010;41(3):557-9.

.6 Ascenzi P, di Masi A, Leboffe L, Fiocchetti M, Nuzzo MT, Brunori M, et al. Neuroglobin: From structure to function in health and disease. Molecular aspects of medicine. 2016;52:1-48.

.7 Li RC, Guo SZ, Lee SK, Gozal D. Neuroglobin protects neurons against oxidative stress in global ischemia. Journal of Cerebral Blood Flow & Metabolism. 2010;30(11):1874-82.

.8 Luyckx E, Van Acker ZP, Ponsaerts P, Dewilde S. Neuroglobin expression models as a tool to study its function. Oxidative medicine and cellular longevity. 2019;2019.

.9 Khan AA, Mao XO, Banwait S, Jin K, Greenberg DA. Neuroglobin attenuates β-amyloid neurotoxicity in vitro and transgenic Alzheimer phenotype in vivo. Proceedings of the National Academy of Sciences. 2007;104(48):19114-9.

.10 Li RC, Pouranfar F, Lee SK, Morris MW, Wang Y, Gozal D. Neuroglobin protects PC12 cells against β-amyloid-induced cell injury. Neurobiology of aging. 2008;29(12):1815-22.

.11 Guidolin D, Tortorella C, Marcoli M, Maura G, Agnati LF. Neuroglobin, a factor playing for nerve cell survival. International Journal of Molecular Sciences. 2016;17(11):1817.

.12 Jin K, Mao XO, Xie L, Khan AA, Greenberg DA. Neuroglobin protects against nitric oxide toxicity. Neuroscience letters. 2008;430(2):135-7.

.13 Ciccone L, Nencetti S, Socci S, Orlandini E. Neuroglobin and neuroprotection: the role of natural and synthetic compounds in neuroglobin pharmacological induction. Neural Regen Res. 2021;16(12):2353-8.

.14 Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature. 2006;443(7113):787-95.

.15 Yu Z, Poppe JL, Wang X. Mitochondrial mechanisms of neuroglobin's neuroprotection. Oxidative medicine and cellular longevity. 2013;2013.

.16 Sun Y, Jin K, Mao XO, Zhu Y, Greenberg DA. Neuroglobin is up-regulated by and protects neurons from hypoxic-ischemic injury. Proceedings of the National Academy of Sciences. 2001;98(26):15306-11.

.17 Ye S-q, Zhou X-y, Lai X-j, Zheng L, Chen X-q. Silencing neuroglobin enhances neuronal vulnerability to oxidative injury by down-regulating 14-3-3γ. Acta Pharmacologica Sinica. 2009;30(7):913-8.

.18 Greenberg DA, Jin K, Khan AA. Neuroglobin: an endogenous neuroprotectant. Current opinion in pharmacology. 2008;8(1):20-4.

.19 Watanabe S, Wakasugi K. Zebrafish neuroglobin is a cell-membrane-penetrating globin. Biochemistry. 2008;47(19):5266-70.

.20 Yu Z, Liu N, Liu J, Yang K, Wang X. Neuroglobin, a novel target for endogenous neuroprotection against stroke and neurodegenerative disorders. International journal of molecular sciences. 2012;13(.6995-7014:(6

.21 Thomas I, Gregg B. Metformin; a review of its history and future: from lilac to longevity. Pediatric diabetes. 2017;18(1):10-6.

.22 Rotermund C, Machetanz G, Fitzgerald JC. The therapeutic potential of metformin in neurodegenerative diseases. Frontiers in endocrinology. 2018;9:400.
.23 Bonea M, Filip GA, Toma VA, Baldea I, Berghian AS, Decea N, et al. The modulatory effect of metformin on ethanol-induced anxiety, redox imbalance, and extracellular matrix levels in the brains of Wistar rats. Journal of Molecular Neuroscience. 2020;70(12):1943-61.
.24 Brittain T, Skommer J, Raychaudhuri S, Birch N. An antiapoptotic neuroprotective role for neuroglobin. International journal of molecular sciences. 2010;11(6):2306-21.
.25 Zara S, De Colli M, Rapino M, Pacella S, Nasuti C, Sozio P, et al. Ibuprofen and lipoic acid conjugate neuroprotective activity is mediated by Ngb/Akt intracellular signaling pathway in Alzheimer's disease rat model. Gerontology. 2013;59(3):250-60.
.26 Weggen S, Eriksen JL, Das P, Sagi SA, Wang R, Pietrzik CU, et al. A subset of NSAIDs lower amyloidogenic Aβ42 independently of cyclooxygenase activity. Nature. 2001;414(6860):212-6.
.27 Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. Blood . .739-61:(3)89;1997
.28 Jin K, Mao X, Xie L, Greenberg DA. Interactions between vascular endothelial growth factor and neuroglobin. Neuroscience letters. 2012;519(1):47-50.
.29 Vasudevan N, Pfaff DW. Non-genomic actions of estrogens and their interaction with genomic actions in the brain. Frontiers in neuroendocrinology. 2008;29(2):238-57.
.30 Uddin M, Rahman M, Jakaria M, Hossain M, Islam A, Ahmed M, et al. Estrogen signaling in Alzheimer's disease: molecular insights and therapeutic targets for Alzheimer's dementia. Molecular Neurobiology. 2020;57(6):2654-70.
.31 De Marinis E, Ascenzi P, Pellegrini M, Galluzzo P, Bulzomi P, Arevalo MA, et al. 17β-estradiol–a new modulator of neuroglobin levels in neurons: role in neuroprotection against H2O2-induced toxicity. Neurosignals. 2010;18(4):223-35.
.32 De Marinis E, Acaz-Fonseca E, Arevalo M, Ascenzi P, Fiocchetti M, Marino M, et al. 17β-Oestradiol anti-inflammatory effects in primary astrocytes require oestrogen receptor β-mediated neuroglobin up-regulation. Journal of neuroendocrinology. 2013;25(3):260-70.
.33 Acconcia F, Totta P, Ogawa S, Cardillo I, Inoue S, Leone S, et al. Survival versus apoptotic 17beta-estradiol effect: role of ER alpha and ER beta activated non-genomic signaling. Journal of cellular physiology. 2005;203(1):193-201.
.34 Fiocchetti M, Nuzzo M, Totta P, Acconcia F, Ascenzi P, Marino M. Neuroglobin, a pro-survival player in estrogen receptor α-positive cancer cells. Cell death & disease. 2014;5(10):e1449-e.
.35 Toro-Urrego N, Garcia-Segura LM, Echeverria V, Barreto GE. Testosterone protects mitochondrial function and regulates neuroglobin expression in astrocytic cells exposed to glucose deprivation. Frontiers in aging neuroscience. 2016;8:152.
.36 Abdul QA, Choi RJ, Jung HA, Choi JS. Health benefit of fucosterol from marine algae: a review. Journal of the Science of Food and Agriculture. 2016;96(6):1856-66.
.37 Gan SY, Wong LZ, Wong JW, Tan EL. Fucosterol exerts protection against amyloid β-induced neurotoxicity, reduces intracellular levels of amyloid β and enhances the mRNA expression of neuroglobin in amyloid β-induced SH-SY5Y cells. International journal of biological macromolecules. 2019;121:207-13.
.38 Oliveira KC, Da Conceição RR, Piedade GC, de Souza JS, Sato MA, de Barros Maciel RM, et al. Thyroid hormone modulates neuroglobin and cytoglobin in rat brain. Metabolic Brain Disease. 2015;30(6):1401-8.
.39 Milano M, Collomp R. Erythropoietin and neuroprotection: a therapeutic perspective. Journal of Oncology Pharmacy Practice. 2005.145-9:(4)11;
.40 Renaud J, Martinoli M-G. Considerations for the use of polyphenols as therapies in neurodegenerative diseases. International Journal of Molecular Sciences. 2019;20(8):1883.
.41 Di Meo F, Valentino A, Petillo O, Peluso G, Filosa S, Crispi S. Bioactive polyphenols and neuromodulation: Molecular mechanisms in neurodegeneration. International journal of molecular sciences. 2020;21(7):2564.

.42 Poschner S, Maier-Salamon A, Thalhammer T, Jäger W. Resveratrol and other dietary polyphenols are inhibitors of estrogen metabolism in human breast cancer cells. The Journal of Steroid Biochemistry and Molecular Biology. 2019;190:11-8.
.43 Chen C, Wei Y-Z, He X-M, Li D-D, Wang G-Q, Li J-J, et al. Naringenin produces neuroprotection against LPS-induced dopamine neurotoxicity via the inhibition of microglial NLRP3 inflammasome activation. Frontiers in Immunology. 2019;10:936.
.44 Ciccone L, Tonali N, Nencetti S, Orlandini E. Natural compounds as inhibitors of transthyretin amyloidosis and neuroprotective agents: Analysis of structural data for future drug design. Journal of Enzyme Inhibition and Medicinal Chemistry. 2020;35(1):1145-62.
.45 Cipolletti M, Montalesi E, Nuzzo MT, Fiocchetti M, Ascenzi P, Marino M. Potentiation of paclitaxel effect by resveratrol in human breast cancer cells by counteracting the 17β-estradiol/estrogen receptor α/neuroglobin pathway. Journal of cellular physiology. 2019;234(4):3147-57.
.46 Liu N, Yu Z, Gao X, S Song Y, Yuan J, Xun Y, et al. Establishment of cell-based neuroglobin promoter reporter assay for neuroprotective compounds screening. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2016;15(5):629-39.
.47 Su C, Zhang D, Truong J, Jiang C, Lee S, Jarouche M, et al. Effects of a novel herbal formulation JSK on acute spinal cord injury in rats. Restorative neurology and neuroscience. 2013;31(5):597-617.
.48 Zhu H, Luo L, Hu S, Dong K, Li G, Zhang T. Treating Alzheimer's disease with Yizhijiannao granules by regulating expression of multiple proteins in temporal lobe. Neural Regeneration Research. 2014;9(13):1283.
.49 Pace BS, White GL, Dover GJ, Boosalis MS, Faller DV, Perrine SP. Short-chain fatty acid derivatives induce fetal globin expression and erythropoiesis in vivo. Blood, The Journal of the American Society of Hematology. 2002;100(13):4640-8.
.50 Jin K, Mao XO, Xie L, John V, Greenberg DA. Pharmacological induction of neuroglobin expression. Pharmacology. 2011;87(1-2):81-4.
.51 Escudero-Lourdes C. Toxicity mechanisms of arsenic that are shared with neurodegenerative diseases and cognitive impairment: Role of oxidative stress and inflammatory responses. Neurotoxicology. 2016;53:223-35.
.52 Liu X, Gao Y, Yao H, Zhou L, Sun D, Wang J. Neuroglobin involvement in the course of arsenic toxicity in rat cerebellar granule neurons. Biological trace element research. 2013;155(3):439-46.
.53 De Marinis E, Fiocchetti M, Acconcia F, Ascenzi P, Marino M. Neuroglobin upregulation induced by 17β-estradiol sequesters cytocrome c in the mitochondria preventing H2O2-induced apoptosis of neuroblastoma cells. Cell death & disease. 2013;4(2):e508-e.
.54 Montalesi E, Cipolletti M, Cracco P, Fiocchetti M, Marino M. Divergent effects of daidzein and its metabolites on estrogen-induced survival of breast cancer cells. Cancers. 2020;12(1):167.