Review Article

GRP78/BiP/HSPA5 as a Therapeutic Target in Models of Parkinson’s Disease: A Mini Review

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Parkinson’s disease (PD) is a common neurodegenerative disorder characterized by selective loss of dopamine neurons in the substantia nigra pars compacta (SNpc) of the midbrain. Reports from postmortem studies in the human PD brain, and experimental PD models reveal that endoplasmic reticulum (ER) stress is implicated in the pathogenesis of PD. In times of stress, the unfolded or misfolded proteins overload the folding capacity of the ER to induce a condition generally known as ER stress. During ER stress, cells activate the unfolded protein response (UPR) to handle increasing amounts of abnormal proteins, and recent evidence has demonstrated the activation of the ER chaperone GRP78/BiP (78kDa glucose-regulated protein/binding immunoglobulin protein), which is important for proper folding of newly synthesized and partly folded proteins [9]. Thus, when there is a disturbance in function, oxidative damage, or disruption of glucose or calcium homeostasis, the unfolded/misfolded proteins exceeds the folding capacity of the ER resulting to a condition commonly known as ER stress [10, 11]. The induction of ER stress and the consequent aggregation of misfolded or unfolded proteins have been implicated in PD pathogenesis [12, 13].

1. Introduction

Parkinson’s disease (PD) is a neurological disorder characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain, resulting in loss of dopamine in the striatum. In patients with PD, there are four primary motor symptoms which include tremor at rest, postural instability, rigidity, and bradykinesia [1]. PD was previously considered to be a condition that affects only the motor system, but with more research, it is now known to be a multifaceted disorder with diverse clinical features that include sleep, cognitive, and neuropsychiatric disorders [2, 3].

Although the etiology of the disease is not entirely understood, reports indicate that several factors such as oxidative and endoplasmic reticulum (ER) stress promote neuronal degeneration. The ER is regarded as the largest organelle in the cell with multiple functions such as protein, steroid, and phospholipid synthesis, storage of calcium, and metabolism of carbohydrates [4–8]. In the ER, chaperones such as 78kDa glucose-regulated protein (GRP78), also known as binding immunoglobulin protein (BiP) or heat shock 70kDa protein 5 (HSPA5) and other stress sensor proteins, are needed to maintain quality control of proteins [9]. Thus, when there is a disturbance in function, oxidative damage, or disruption of glucose or calcium homeostasis, the unfolded/misfolded proteins exceed the folding capacity of the ER resulting to a condition commonly known as ER stress [10, 11]. The induction of ER stress and the consequent aggregation of misfolded or unfolded proteins have been implicated in PD pathogenesis [12, 13].
Existing treatment options for PD are inadequate as drugs are focused mainly on relieving symptoms. For example, levodopa is exceptionally effective for regulating PD symptoms, especially those linked to bradykinesia [14], and its combination with carbidopa improves the beneficial effects of levodopa. In cases where PD patients are sensitive to minor side effects such as nausea and vomiting, lodosyn may be taken with the routine carbidopa/levodopa therapy [15]. Other treatment options include dopamine agonists such as pramipexole [16], ropinirole [17, 18], and apomorphine [19, 20] while nondopaminergic drugs treatments include anticholinergics and amantadine [15] as well as entacapone [21] and tolcapone [22] catechol-o-methyl-transferase inhibitors.

Since there is no treatment for PD, there is an ever-increasing need to identify neuroprotective strategies with the ability to slow down or halt the advancement of PD. This search for new drug treatment options has paved the way for the discovery of such natural products as medicinal herbs, plant extracts, and their bioactive compounds. Some of these compounds are under clinical investigations owing to their remarkable potential as neuroprotective treatment options in PD [23, 24]. In this regard, while drug researchers are currently focused on discovering new remedies, plant-derived bioactive compounds targeting ER stress and its pathways could help in the identification and validation of novel treatment options in PD. Hence, this review presents an outline of the scientific literature on the research of plant-derived bioactive compounds and other neuroprotective agents targeting GRP78/BiP in experimental models of PD.

2. Endoplasmic Reticulum Stress Pathway and Disease

The ER stress pathway or unfolded protein response (UPR) is known to handle growing quantities of aberrant proteins in the ER [25]. This response program is tasked with the reduction of misfolded/abnormal proteins through various mechanisms (Figure 1). Firstly, GRP78/BiP disassociates from the ER stress sensors, namely, protein kinase RNA-like endoplasmic reticulum kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme 1 (IRE1) to initiate the ER stress response. Following dissociation of GRP78/BiP, autophosphorylation and activation of PERK facilitate the phosphorylation of eukaryotic translation initiation factor 2a (eIF2a) to inhibit further protein synthesis and translation [26–28]. ATF6 is cleaved in the Golgi after translocation from the ER and then migrates into the nucleus to upregulate ER chaperones such as GRP78/BiP and 94 kDa glucose-regulated protein (GRP94) which enhances the folding capacity of the ER [29]. Also, IRE1 is involved in endoribonuclease activity and activates X-box binding protein 1 (XBP-1) to promote ER-associated degradation [30–32].

The extent and degree of ER stress and UPR activation may determine if the ER stress response is either anti- or prosurvival (Figure 2). Certain aspects of the ER stress response such as increased expression of chaperones would appear to be advantageous by lessening the burden of misfolded proteins [33, 34], while other ER stress responses may be advantageous for a limited amount of time, thus leading to degeneration if sustained. Sustained activation of the UPR under stress would lead to apoptosis via the activation of ER-specific caspases, c-Jun amino-terminal kinase (JNK) and apoptosis signal-regulating kinase 1 (ASK1), induction of CCAAT-enhancer-binding protein homologous protein (CHOP), and the activation of p53 upregulated modulator of apoptosis (PUMA), BAX, and NOXA [35].

3. ER Stress Response in Parkinson’s Disease

GRP78/BiP is a key chaperone essential for proper functioning of the ER and in various cellular processes [36–38]. Most notable is its dual role of regulating protein folding and the initiation of UPR signaling in the ER [39]. In PD, there are inconsistent reports on the expression of GRP78/BiP in various experimental models. For instance, treatment of MN9D cells with a neurotoxin 1-methyl-4-phenylpyridinium (MPP⁺; Figure 3) resulted in a reduction of GRP78/BiP expression, while treatment of SH-SYSY cells with a different neurotoxin 6-hydroxydopamine (6-OHDA; Figure 3) increased its expression [40, 41]. In a PD model using MPP⁺-treated rabbits, Ghribi and colleagues revealed the translocation of GRP78/BiP to the nucleus and cytosol from the ER as well as a significant decrease in TH-positive cells in the SNpc [42]. In a different study, Shimoke and coworkers demonstrated an increase in the expression of GRP78/BiP after exposure to tunicamycin; however, they observed no increase in the expression of GRP78/BiP in PC12 cells after treatment with a neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; Figure 3), for 24 hours [43]. Duan and Mattson utilized the MPTP-treated mouse model of PD to demonstrate that the upregulation of GRP78/BiP by 2-deoxy-D-glucose significantly prevented loss of dopamine neurons [44].

In PD patients, GRP78/BiP was reported to be more expressed in the cingulate gyrus and parietal cortex when compared to healthy controls [45]. The upregulation of GRP78/BiP in the cingulate gyrus was linked to an increase in α-synuclein expression, thus providing an association between GRP78/BiP and α-synuclein toxicity. This observation is confirmed by a report demonstrating that the knockdown of GRP78/BiP aggravates the toxicity of α-synuclein in rats [46] and in another study showing that miRNA-induced reduction of GRP78/BiP enhanced cell death induced by a neurotoxin-rotenone [47]. In contrast to studies mentioned above, reports demonstrate that the upregulation of GRP78/BiP suppresses α-synuclein aggregation and toxicity in PD models [48, 49]. For example, Gorbatyuk and colleagues in a rat model of PD induced by an elevated level of human α-synuclein demonstrated that although the accumulation of α-synuclein induced the expression of apoptosis-regulating ATF4, the upregulation of GRP78/BiP inhibited α-synuclein toxicity by regulating ER stress signaling pathways [49].

Leucine-rich repeat kinase 2 (LRRK2) is the most significant gene mutated in PD [50]. LRRK2 pathogenesis has...
been associated with ER stress as it partly localizes in the ER in dopaminergic neurons of individuals with PD [51]. Reports show that the neuroprotective activity of \textit{LRRK2} against \textit{6-OHDA} or \textit{α-synuclein} induced neurodegeneration in the nematode; \textit{C. elegans} is attributed to the activity of GRP78/BiP via signaling through the p38 mitogen-activated protein kinase (MAPK) pathway [26, 52]. In confirmation of these reports, Samann and colleagues reported that \textit{LRRK2} mutant \textit{C. elegans} were highly vulnerable to ER stress and developed spontaneous neurodegeneration [53, 54].

\textbf{Figure 1:} Simplified diagram highlighting the regulation of ER stress signaling pathways.

\textbf{Figure 2:} Important events during cellular response to ER stress.

\textbf{Figure 3:} Diagram showing the chemical structure of PD toxins: (a) MPTP; (b) MPP\textsuperscript{+}; (c) 6-OHDA.
Furthermore, ageing is the greatest risk factor for PD [55, 56], and various age-related changes in cellular structure and function are observed in PD patients. To corroborate these observations, studies reveal that ageing results in a significant reduction in the activity and expression of GRP78/BiP in the brain of old versus young rodents [57–59]. From the aforementioned, GRP78/BiP is undoubtedly an essential component of the UPR, and proper regulation of GRP78/BiP could prove valuable in identifying new treatment options in PD.

4. Regulation of GRP78/BiP by Therapeutic Agents in PD Models

Over the years, the use of neurotoxin-based experimental models of PD has contributed extensively to the understanding of PD and human health. For instance, such neurotoxins as MPTP, MPP+, 6-OHDA, paraquat, and rotenone have been utilized in the search, identification, and development of novel therapeutic agents in PD [60]. Also, the MPTP mouse and 6-OHDA rat models of PD have contributed immensely to the translation of animal experimentation into clinical practice and are still very much important for investigating different mechanisms of neuronal degeneration in PD. Considerable evidence shows that some experimental therapeutic agents have substantial antioxidant and anti-inflammatory activities, thus demonstrating an inhibitory effect in the oxidative and inflammatory mechanisms linked to neuronal loss in PD [61, 62].

The plant-derived bioactive compounds and other therapeutic agents highlighted in this review demonstrate significant neuroprotective effects and also regulate the activity of GRP78/BiP in experimental models of PD. One such compound is luteolin (3′, 4′, 5′, 7′-tetrahydroxyflavone), a naturally occurring flavonoid present in several herbs, fruits, and vegetables [63, 64]. It is a very potent antioxidant and is usually the most effective when compared to other flavonoids [65]. Plants containing luteolin have been utilized for the inhibition and treatment of such diseases as cancer and hypertension [66, 67]. Also, reports show that luteolin crosses the blood-brain barrier and has multiple biological, pharmacological, anticancer, anti-inflammatory, antibacterial, antiinflammatory, and neuroprotective activities [68–71].

While luteolin is structurally composed of hydroxyl groups at carbons 5, 7, 3′, and 4′ positions (Figure 4), the presence of 2-3 double bonds are linked to its multiple biological activities [72]. In a study, Hu and colleagues investigated the neuroprotective activity of luteolin in PC12 cells treated with 6-OHDA using RT-Q-PCR and western blot techniques [73]. They reported that luteolin attenuated the 6-OHDA-induced upregulation of GRP78/BiP and downregulated UPR, leading to the reduction of phospho-eIF2α, ATF4, and CHOP [73]. Based on these findings, the authors attributed the neuroprotective activity of luteolin to the regulation of GRP78/BiP and other UPR related proteins.

Salidroside (6-OH-p-hydroxyphenethyl-β-D-glucoside; C_{14}H_{20}O_{7}; Figure 5), a phenol glycoside extracted as an active constituent from *Rhodiola rosea* L., is widely used in traditional folk medicine in Asia and Europe [74, 75]. In China, it is commonly used as an antifungal herb and as a supplement to improve kidney function, stimulate blood circulation, and clear chest congestion [76].

Salidroside exhibits a wide range of pharmacological activities including antioxidative, antiaging, anticancer, anti-inflammatory antitumour, antidepressive, antifatigue, adaptogenic, cardioprotective, and hepatoprotective effects [77–80]. In addition, reports show that salidroside is effective against cognitive decline during ageing and can protect neurons from apoptosis as well as mitochondrial dysfunction in experimental models of neurodegeneration [81–83]. To investigate salidroside’s ability to regulate GRP78/BiP in an experimental model of PD, Tao and coworkers treated SN4741 cells with 6-OHDA after pretreatment with salidroside. Findings revealed that salidroside reduced the expression levels of GRP78/BiP and other ER stress markers (p-PERK and p-IRE1) when compared with cells treated with 6-OHDA only [84]. From the study, they demonstrated that the protective effect of salidroside against the toxicity of 6-OHDA was partly due to the regulation of GRP78/BiP and other ER stress markers.

Lithospermic acid (C_{27}H_{22}O_{12}) is a key component of *Salvia miltiorrhiza*, a Chinese medicinal herb widely used to increase blood flow and treat diabetic as well as cardiovascular problems in humans [85]. Lithospermic acid shares a similar structure with salvianolic acid B (Figure 6) and is reported to have multiple pharmacological activities which include antihypertensive, antidiabetic, antiapoptotic, and antioxidant effects [86–88].
In a study by Lin and colleagues, MPP\textsuperscript{+}-treated CATH.a cells were utilized as a model of PD to investigate the role of lithospermic acid on ER stress [89]. Findings from western blots revealed that MPP\textsuperscript{+} triggered ER stress in CATH.a cells by increasing the expression of GRP78/BiP, while lithospermic acid treatment inhibited the upregulation of GRP78/BiP, thus acting as a neuroprotective agent [89].

Basic fibroblast growth factor (bFGF), a member of the FGF family, is an essential protein with multiple physiological roles in the peripheral and central nervous system (CNS) [90, 91]. It is involved in a series of neurotrophic activities contributing to CNS repair and cell survival [92]. Reports indicate that bFGF shares receptors and influences a range of biological activities such as inhibition of apoptosis, cellular proliferation, and morphogenesis [93–95]. Previous studies show that bFGF exhibits neuroprotective activities in PD models; for instance, bFGF protected against rotenone-triggered dopaminergic cell loss in SH-SY5Y cells and enhanced survival of dopaminergic cells in human fetal tissue strands transplanted into immunosuppressed rats injected with 6-OHDA [96, 97]. In a study by Cai and coworkers, bFGF was found to suppress 6-OHDA-triggered upregulation of ER stress response proteins in Sprague–Dawley rats. bFGF was found to suppress 6-OHDA-triggered upregulation with 6-OHDA [96, 97]. In a study by Cai and coworkers, MPP\textsuperscript{+}-treated CATH.a cells were utilized as a model of PD to investigate the role of lithospermic acid on ER stress [89]. Findings from western blots revealed that MPP\textsuperscript{+} triggered ER stress in CATH.a cells by increasing the expression of GRP78/BiP, while lithospermic acid treatment inhibited the upregulation of GRP78/BiP, thus acting as a neuroprotective agent [89].

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Sprague–Dawley rats injected with 6-OHDA, thus highlighting the neurotherapeutic potential of echinacoside in experimental models of PD [132]. Rifampicin is derived from rifamycins, a class of antibiotics obtained from Nocardia mediterranei through a process of fermentation [133]. It is commonly used against Mycobacterium tuberculosis and other mycobacterial infections [133, 134]. Its hydroxyl radical scavenging properties are ascribed to the naphthohydroquinone ring in its chemical structure (Figure 9), while its lipophilic ansa chain is believed to help in its transport into the brain parenchyma across the blood-brain barrier [135, 136]. Pharmacological reports show that rifampicin has immunosuppressive and antioxidant properties [137–139] and inhibits β-amyloid accumulation and neurotoxicity [140]. It also prevents lipopolysaccharide-triggered upregulation of proinflammatory mediators, decreases NF-κB and MAPK signaling [134, 141], attenuates apoptosis in focal ischemic stroke, and inhibits loss of dopaminergic neurons in PD models [133, 142, 143].

To investigate the primary mechanism by which rifampicin promotes neuronal survival, Jing and colleagues revealed a dose-dependent activation of GRP78/BiP in rifampicin-treated PC12 cells [144]. Upon silencing of the GRP78/BiP gene, they investigated if rifampicin-induced GRP78/BiP activation protected against toxicity in rotenone-treated PC12 cells. Western blots and morphological evaluation revealed that cells without the GRP78/BiP gene were more prone to rotenone-triggered damage when compared to cells with the GRP78/BiP gene irrespective of rifampicin treatment [144]. These findings show that silencing of the GRP78/BiP gene mitigated rifampicin-induced protection and thus confirmed that the regulation and activation of GRP78/BiP was responsible for the neuroprotective activity of rifampicin in the PD model.

5. Conclusion

Protein misfolding and aggregation is implicated in the pathogenesis of PD, and the regulation of GRP78/BiP is critical for proper functioning of the UPR. As highlighted in this review, several studies have attempted to unravel the mechanism behind ER stress by targeting GRP78/BiP and the UPR as a way of halting dopaminergic neuronal loss in PD. Although it is established that GRP78/BiP is an essential chaperone in the UPR, studies discussed in this review indicate that the expression of GRP78/BiP is altered in various models of PD depending on the cell type and toxin used in inducing neuronal damage. Consequently, various neuroprotective agents induce the upregulation or downregulation of GRP78/BiP in response to the ER stress-inducing agent in these PD models to promote the survival of dopaminergic neurons. Also, evidence from this review indicate that a translational potential exists for the regulation of GRP78/BiP activity; however, further investigations are needed to properly understand the involvement of GRP78/BiP in the protection of neurons against degeneration in PD. This knowledge would be valuable in designing novel remedies targeted at combating PD and other neurodegenerative disorders linked to the aggregation of misfolded proteins.

Conflicts of Interest

The authors have no conflicts of interest to declare.

References

[1] J. Jankovic, "Parkinson’s disease: clinical features and diagnosis," Journal of Neurology, Neurosurgery & Psychiatry, vol. 79, no. 4, pp. 368–376, 2008.
[2] K. R. Chaudhuri and A. Sauerbier, "Unravelling the non-motor mysteries of Parkinson disease," Nature Reviews Neurology, vol. 12, no. 1, pp. 10-11, 2016.
[3] R. Krüger, J. Klucken, D. Weiss et al., "Classification of advanced stages of Parkinson’s disease: translation into stratified treatments," Journal of Neural Transmission, vol. 124, no. 8, pp. 1015–1027, 2017.
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[4] D. W. Reid and C. V. Nicchitta, "Diversity and selectivity in mRNA translation on the endoplasmic reticulum," *Nature Reviews Molecular Cell Biology*, vol. 16, no. 4, pp. 221–231, 2015.

[5] I. Braakman and D. N. Hebert, "Protein folding in the endoplasmic reticulum," *Cold Spring Harbor Perspectives in Biology*, vol. 5, no. 5, article a013201, 2013.

[6] P. Fagone and S. Jackowski, "Membrane phospholipid synthesis and endoplasmic reticulum function," *Journal of Lipid Research*, vol. 50, pp. 311–316, 2009.

[7] D. N. Hebert, S. C. Garman, and Y. Nomura, "Endoplasmic reticulum stress and Parkinson's disease: the role of HRD1 in averting apoptosis in neurodegenerative disease," *Oxidative Medicine and Cellular Longevity*, vol. 2013, Article ID 239854, 7 pages, 2013.

[8] S. Tsujii, M. Ishisaka, and H. Hara, "Modulation of endoplasmic reticulum stress and apoptosis regulator GRP78/BiP in development and human diseases," *FEBS Letters*, vol. 581, no. 3-4, pp. 3641–3651, 2007.

[9] D. R. Ron and P. Walter, "Signal integration in the endoplasmic reticulum," *Cold Spring Harbor Perspectives in Biology*, vol. 5, no. 5, pp. 488, 2006.

[10] D. Ron and P. Walter, "Signal integration in the endoplasmic reticulum unfolded protein response," *Nature Reviews Molecular Cell Biology*, vol. 8, no. 7, pp. 519–529, 2007.

[11] O. J. Freeman and G. R. Mallucci, "The UPR and synaptic dysfunction in neurodegeneration," *Brain Research*, vol. 1648, pp. 530–537, 2016.

[12] T. Omura, M. Kaneko, Y. Okuma, K. Matsubara, and Y. Nomura, "Endoplasmic reticulum stress and Parkinson's disease: the role of HRD1 in averting apoptosis in neurodegenerative disease," *Oxidative Medicine and Cellular Longevity*, vol. 2013, Article ID 239854, 7 pages, 2013.

[13] S. Tsujii, M. Ishisaka, and H. Hara, "Modulation of endoplasmic reticulum stress in Parkinson's disease," *European Journal of Pharmacology*, vol. 765, pp. 154–156, 2015.

[14] J. Jankovic, "Leverodopa strengths and weaknesses," *Neurology*, vol. 58, no. 1, pp. 19–32, 2002.

[15] J. Jankovic and L. G. Aguilar, "Current approaches to the treatment of Parkinson's disease," *Neuropsychiatric Disease and Treatment*, vol. 4, no. 4, p. 743, 2008.

[16] W. J. Weiner, S. A. Factor, J. Jankovic et al., "The long-term safety and efficacy of pramipexole in advanced Parkinson's disease," *Parkinsonism & Related Disorders*, vol. 7, no. 2, pp. 115–120, 2001.

[17] A. D. Korczyn, E. R. Brunt, J. P. Larsen, Z. Nagy, W. H. Poewe, and S. Ruggieri, "A 3-year randomized trial of ropinirole or levodopa," *Neurology*, vol. 35, no. 4, pp. 373–381, 2005.

[18] O. Rascol, D. J. Brooks, A. D. Korczyn, P. P. De Deyn, W. J. Weiner, S. A. Factor, J. Jankovic et al., "(The long-term safety and efficacy of pramipexole in advanced Parkinson's disease," *Parkinsonism & Related Disorders*, vol. 4, no. 4, pp. 743, 2008.

[19] A. M. Schrag, "Entacapone in the treatment of Parkinson's disease," *The Lancet Neurology*, vol. 4, no. 6, pp. 366–370, 2005.

[20] A. J. Lees, V. Ratziu, E. Tolosa, and W. H. Oertel, "Safety and tolerability of adjunctive tolcapone treatment in patients with early Parkinson's disease," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 78, no. 9, pp. 944–948, 2007.

[21] A. Sakani and S. K. Kutty, "Plant-derived compounds in clinical trials," *Drug Discovery Today*, vol. 13, no. 3–4, pp. 161–171, 2008.

[22] S. V. More, H. Kumar, S. M. Kang, S.-Y. Song, K. Lee, and D.-K. Choi, "Advances in neuroprotective ingredients of medicinal herbs by using cellular and animal models of Parkinson's disease," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 957875, 15 pages, 2013.

[23] O. A. Levy, C. Malagelada, and L. A. Greene, "Cell death pathways in Parkinson's disease: proximal triggers, distal effectors, and final steps," *Aptosis*, vol. 14, no. 4, pp. 478–500, 2009.

[24] H. P. Harding, Y. Zhang, and D. Ron, "Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase," *Nature*, vol. 397, no. 6716, pp. 271–274, 1999.

[25] D. T. Rutkowski and R. J. Kaufman, "A trip to the ER: coping with stress," *Trends in Cell Biology*, vol. 14, no. 1, pp. 20–28, 2004.

[26] Y. Shi, K. M. Vattem, R. Sood et al., "Identification and characterization of pancreatic eukaryotic initiation factor 2 α-subunit kinase, PEK, involved in translational control," *Molecular and Cellular Biology*, vol. 18, no. 12, pp. 7499–7509, 1998.

[27] M. Wang, S. Wey, Y. Zhang, R. Ye, and A. S. Lee, "Role of the unfolded protein response regulator GRP78/BiP in development, cancer, and neurological disorders," *Antioxidants & Redox Signaling*, vol. 11, no. 9, pp. 2307–2316, 2009.

[28] M. Caflon, H. Zeng, F. Urano et al., "Erratum: IRE1 couples endoplasmic reticulum load to secretory capacity by processing the XBP-1 mRNA," *Nature*, vol. 415, no. 6867, pp. 92–96, 2002.

[29] A.-H. Lee, N. N. Ikawaoshi, and L. H. Gimcher, "XBP-1 regulates a subset of endoplasmic reticulum resident chaperone genes in the unfolded protein response," *Molecular and Cellular Biology*, vol. 23, no. 21, pp. 7448–7459, 2003.

[30] H. Yoshida, T. Matsui, A. Yamamoto, T. Okada, and K. Mori, "XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor," *Cell*, vol. 107, no. 7, pp. 881–891, 2001.

[31] T.-B. Ahn and B. S. Jeon, "Protective role of heat shock and heat shock protein 70 in lactacystin-induced cell death both in the rat substantia nigra and PC12 cells," *Brain Research*, vol. 1087, no. 1, pp. 159–167, 2006.

[32] Z. Dong, D. P. Wolfer, H.-P. Lipp, and H. Büeler, "Hsp70 gene transfer by adeno-associated virus inhibits MPTP-induced nigrostriatal degeneration in the mouse model of Parkinson disease," *Molecular Therapy*, vol. 11, no. 1, pp. 80–88, 2005.

[33] J. Li, B. Lee, and A. S. Lee, "Endoplasmic reticulum stress-induced apoptosis," *Journal of Biological Chemistry*, vol. 281, no. 11, pp. 7260–7270, 2006.

[34] M. Ni and A. S. Lee, "ER chaperones in mammalian development and human diseases," *FEBS Letters*, vol. 581, no. 19, pp. 3641–3651, 2007.

[35] L. M. Hendershot, "The ER Function BiP is a master regulator of ER function," *The Mount Sinai Journal of Medicine*, vol. 71, no. 5, pp. 289–297, 2004.

[36] A. S. Lee, "The ER chaperone and signaling regulator GRP78/ BiP as a monitor of endoplasmic reticulum stress," *Methods*, vol. 35, no. 4, pp. 373–381, 2005.
Acknowledgments

References

[56] J. A. Driver, G. Logroscino, J. M. Gaziano, and T. Kurth, “Incidence and remaining lifetime risk of Parkinson disease in advanced age,” Neurology, vol. 72, no. 5, pp. 432–438, 2009.

[57] R. R. Erickson, L. M. Dunning, and J. L. Holtzman, “The effect of aging on the chaperone concentrations in the hepatic endoplasmic reticulum of male rats: the possible role of protein misfolding due to the loss of chaperones in the decline in physiological function seen with age,” The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, vol. 61, no. 5, pp. 435–443, 2006.

[58] M. P. Galvan, J. Vela, A. Castaño et al., “Cellular environment facilitates protein accumulation in aged rat hippocampus,” Neurobiology of Aging, vol. 27, no. 7, pp. 973–982, 2006.

[59] N. Naidoo, “The endoplasmic reticulum stress response and aging,” Reviews in the Neurosciences, vol. 20, no. 1, pp. 23–38, 2009.

[60] J. Bove and C. Perier, “Neurotoxin-based models of Parkinson’s disease,” Neuroscience, vol. 211, pp. 51–76, 2012.

[61] J. Joseph, G. Cole, E. Head, and D. Ingram, “Nutrition, brain aging, and neurodegeneration,” Journal of Neuroscience, vol. 29, no. 41, pp. 12795–12801, 2009.

[62] T. Hamazaki and M. Hashimoto, “Neuroprotective and ameliorative actions of polyunsaturated fatty acids against neuronal diseases—evidence from basic to clinical studies: preface,” Journal of Pharmacological Sciences, vol. 116, no. 2, p. 149, 2011.

[63] T. Sun, Z. Xu, C.-T. Wu, M. Janes, W. Prinyawiwatkul, and H. K. No, “Antioxidant activities of different colored sweet bell peppers (Capsicum annuum L.),” Journal of Food Science, vol. 72, no. 2, pp. 98–102, 2007.

[64] S. F. Nabavi, N. Braidy, O. Gortzi et al., “Luteolin as an anti-inflammatory and neuroprotective agent: a brief review,” Brain Research bulletin, vol. 119, pp. 1–11, 2015.

[65] G. Seelinger, I. Merfort, U. Wöllle, and C. Schempp, “Anti-carcinogenic effects of the flavonoid luteolin,” Molecules, vol. 13, no. 10, pp. 2628–2651, 2008.

[66] E. Middleton, C. Kandaswami, and T. C. Theoharides, “The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer,” Journal of Agricultural and Food Chemistry, vol. 56, no. 18, pp. 7653–7661, 2008.

[67] M. Lopez-Lazo, “Distribution and biological activities of the flavonoid luteolin,” Mini-Reviews in Medicinal Chemistry, vol. 9, no. 1, pp. 31–59, 2009.

[68] K. Dirscherl, M. Karlstetter, S. Ebert et al., “The flavonoid luteolin triggers global changes in the microglial transcriptome leading to a unique anti-inflammatory and neuroprotective phenotype,” Journal of Neuroinflammation, vol. 7, no. 1, p. 3, 2010.

[69] J. Lin, R. Shi, X. Wang, and H.-M. Shen, “Luteolin, a flavonoid with potential for cancer prevention and therapy,” Current Cancer Drug Targets, vol. 8, no. 7, pp. 634–646, 2008.
[70] R. Liu, M. Gao, G.-F. Qiang et al., “The anti-amnesic effects of luteolin against amyloid β25-35 peptide-induced toxicity in mice involve the protection of neurovascular unit,” *Neuroscience*, vol. 162, no. 4, pp. 1232–1243, 2009.

[71] D.-J. Guo, F. Li, P. H.-F. Yu, and S.-W. Chan, “Neuroprotective effects of luteolin against apoptosis induced by 6-hydroxydopamine on rat pheochromocytoma PC12 cells,” *Pharmaceutical Biology*, vol. 51, no. 2, pp. 190–196, 2013.

[72] A. K. Pandurangan and N. M. Esa, “Luteolin, a bioflavonoid inhibits colorectal cancer through modulation of multiple signaling pathways: a review,” *Asian Pacific Journal of Cancer Prevention*, vol. 15, no. 14, pp. 5501–5508, 2014.

[73] L.-W. Hu, J.-H. Yen, Y.-T. Shen, K.-Y. Wu, and M.-J. Wu, “Luteolin modulates 6-hydroxydopamine-induced transcriptional changes of stress response pathways in PC12 cells,” *PLoS One*, vol. 9, no. 5, Article ID e97880, 2014.

[74] M. Grech-Baran, K. Syklowska-Baranek, and A. Pietrosiuk, “Biotechnological approaches to enhance salidroside, rosin and its derivatives production in selected *Rhodiola* spp. in vitro cultures,” *Phytochemistry Reviews*, vol. 14, no. 4, pp. 657–674, 2015.

[75] B. Zhang, Q. Li, X. Chu, S. Sun, and S. Chen, “Salidroside reduces tau hyperphosphorylation via up-regulating GSK-3β phosphorylation in a tau transgenic drosophila model of Alzheimer’s disease,” *Translational Neurodegeneration*, vol. 5, no. 1, p. 21, 2016.

[76] X. Luo, N. Bao, L. Chen, and J. Sun, “Pharmacological activities and progress in structure modification of salidroside,” *Medicinal Chemistry*, vol. 7, no. 3, pp. 818–823, 2017.

[77] S. Guan, H. Feng, B. Song et al., “Salidroside attenuates LPS-induced pro-inflammatory cytokine responses and improves survival in murine endotoxemia,” *International Immunopharmacology*, vol. 11, no. 12, pp. 2194–2199, 2011.

[78] J. Wang, J.-Z. Li, A.-X. Lu, K.-F. Zhang, and B.-J. Li, “Anticancer effect of salidroside on A549 lung cancer cells through inhibition of oxidative stress and phospho-p38 expression,” *Oncology Letters*, vol. 7, no. 4, pp. 1159–1164, 2014.

[79] B. Zhang, Y. Wang, H. Li et al., “Neuroprotective effects of salidroside through PI3K/Akt pathway activation in Alzheimer’s disease models,” *Drug Design, Development and Therapy*, vol. 10, p. 1335, 2016.

[80] E. Skopinska-Rózewska, M. Malinowski, A. Wasużyński et al., “The influence of *rhodiola quadrifida* 50% hydro-alcoholic extract and salidroside on tumor-induced angiogenesis in mice,” *Polish Journal of Veterinary Sciences*, vol. 11, no. 2, pp. 97–104, 2008.

[81] H. Jin, L. Pei, X. Shu et al., “Therapeutic intervention of learning and memory decays by salidroside stimulation of neurogenesis in aging,” *Molecular Neurobiology*, vol. 53, no. 2, pp. 851–866, 2016.

[82] X. Li, X. Ye, L. Li et al., “Salidroside protects against MPP+-induced apoptosis in PC12 cells by inhibiting the NO pathway,” *Brain Research*, vol. 1382, pp. 9–18, 2011.

[83] S. Wang, H. He, L. Chen, W. Zhang, X. Zhang, and J. Chen, “Protective effects of salidroside in the MPTP/MPP+ induced model of Parkinson’s disease through ROS-NORelated mitochondrion pathway,” *Molecular Neurobiology*, vol. 51, no. 2, pp. 718–728, 2015.

[84] K. Tao, B. Wang, D. Feng et al., “Salidroside protects against 6-hydroxydopamine-induced cytotoxicity by attenuating ER stress,” *Neuroscience Bulletin*, vol. 32, no. 1, pp. 61–69, 2016.

[85] G. M. She, C. Xu, B. Liu, and R. B. Shi, “Polyphenolic acids from mint (the aerial of *Mentha haplocalyx* Briq.) with DPPH radical scavenging activity,” *Journal of Food Science*, vol. 75, no. 4, pp. 359–362, 2010.

[86] K. Kamata, M. Noguchi, and M. Nagai, “Hypotensive effects of lithospermic acid B isolated from the extract of *Salvia miltiorrhiza* Radix in the rat,” *General Pharmacology: The Vascular System*, vol. 25, no. 1, pp. 69–73, 1994.

[87] D. Y. Soung, S. H. Bhee, J. S. Kim et al., “Peroxynitrite scavenging activity of *Salvia miltiorrhiza*,” *Journal of Pharmacy and Pharmacology*, vol. 55, no. 10, pp. 1427–1432, 2003.

[88] B.-W. Lee, S. W. Chun, S. H. Kim et al., “Lithospermic acid B protects beta-cells from cytokine-induced apoptosis by alleviating apoptotic pathways and activating anti-apoptotic pathways of Nrf2-HO-1 and Sirt1,” *Toxicology and Applied Pharmacology*, vol. 252, no. 1, pp. 47–54, 2011.

[89] Y.-L. Lin, H.-J. Tsay, T.-H. Lai, T.-T. Tzeng, and Y.-J. Shiao, “Lithospermic acid attenuates 1-methyl-4-phenylpyridine-induced neurotoxicity by blocking neuronal apoptotic and neuroinflammatory pathways,” *Journal of Biomedical Science*, vol. 22, no. 1, p. 37, 2015.

[90] A. Baird, “Fibroblast growth factors: activities and significance of non-neurotrophin neurotrophic growth factors,” *Current Opinion in Neurobiology*, vol. 4, no. 1, pp. 78–86, 1994.

[91] A. Bikfalvi, S. Klein, G. Pintucci, and D. B. Rifkin, “Biological roles of fibroblast growth factor-2,” *Endocrine Reviews*, vol. 18, no. 1, pp. 26–45, 1997.

[92] M. Roceri, R. Molteni, F. Fumagalli et al., “Stimulatory role of dopamine on fibroblast growth factor-2 expression in rat striatum,” *Journal of Neurochemistry*, vol. 76, no. 4, pp. 990–997, 2001.

[93] N. Itoh and D. M. Ornitz, “Fibroblast growth factors: from molecular evolution to roles in development, metabolism and disease,” *Journal of Biochemistry*, vol. 149, no. 2, pp. 121–130, 2011.

[94] A. Beenken and M. Mohammad, “The FGF family: biology, pathophysiology and therapy,” *Nature Reviews Drug Discovery*, vol. 8, no. 3, pp. 235–253, 2009.

[95] J. Xiao, Y. Lv, S. Lin et al., “Cardiac protection by basic fibroblast growth factor from ischemia/reperfusion-induced injury in diabetic rats,” *Biological & Pharmaceutical Bulletin*, vol. 33, no. 3, pp. 444–449, 2010.

[96] S.-L. Hsuan, H. M. Klintworth, and Z. Xia, “Basic fibroblast growth factor protects against rotenone-induced dopaminergic cell death through activation of extracellular signal-regulated kinases 1/2 and phosphatidylinositol-3 kinase pathways,” *Journal of Neuroscience*, vol. 26, no. 17, pp. 4481–4491, 2006.

[97] G. Chadi, C. Silva, J. R. Maximino, K. Fuxe, and G. O. da Silva, “Adrenalectomy counteracts the local modulation of astroglial fibroblast growth factor system without interfering with the pattern of 6-OHDA-induced dopamine degeneration in regions of the ventral midbrain,” *Brain Research*, vol. 1190, pp. 23–38, 2008.

[98] P. Cai, J. Ye, J. Zhu et al., “Inhibition of endoplasmic reticulum stress is involved in the neuroprotective effect of bFGF in the 6-OHDA-induced Parkinson’s disease model,” *Aging and Disease*, vol. 7, no. 4, p. 336, 2016.

[99] Y. Zhang, Z. Zeng, Y. Cao, X. Du, and Z. Wan, “Effect of rhodiola quadrifida 50% hydroalcoholic extract and salidroside on tumor-induced angiogenesis in the rat,” *Polish Journal of Veterinary Sciences*, vol. 11, no. 10, pp. 1427–1432, 2016.
immunosuppression and its molecular mechanism,” Experimental and Therapeutic Medicine, vol. 14, no. 4, pp. 3583–3588, 2017.

[101] H. Shigetomi, A. Onogi, H. Kajiwara et al., “Anti-inflammatory actions of serine protease inhibitors containing the Kunitz domain,” Inflammation Research, vol. 59, no. 9, pp. 679–687, 2010.

[102] Y. H. Wang, Z.-H. Xuan, S. Tian, and G.-H. Du, “Echinacoside protects against 6-hydroxydopamine-induced mitochondrial dysfunction and inflammatory responses in PC12 cells via reducing ROS production,” Evidence-Based Complementary and Alternative Medicine, vol. 2015, Article ID 189239, 9 pages, 2015.

[103] B. D. Sloley, L. J. Urichuk, C. Tywin, R. T. Coutts, P. K. T. Pang, and J. J. Shan, “Comparison of chemical components and antioxidant capacity of different Echinacea species,” Journal of Pharmacy and Pharmacology, vol. 53, no. 6, pp. 849–857, 2001.

[104] L. Dalby-Brown, H. Barsett, A.-K. R. Landbo, A. S. Meyer, and P. Mølgaard, “Synergistic antioxidative effects of alkaloids, caffeic acid derivatives, and polysaccharide fractions from Echinacea purpurea in vitro oxidation of human low-density lipoproteins,” Journal of Agricultural and Food Chemistry, vol. 53, no. 24, pp. 9413–9423, 2005.

[105] H.-f. Li, S.-x. Zhao, B.-p. Xing, and M.-l. Sun, “Ulinastatin, a urinary trypsin inhibitor, for the initial treatment of patients with Kawasaki disease: a retrospective study,” Circulation, Circulation, vol. 111, article 028423, 2011.

[106] J. Y. Lagoo, M. C. D’Souza, A. Kartha, and A. M. Kutappa, “Chinese herbs and herbal extracts for neuroprotection of Parkinson’s disease,” China Journal of Chinese Materia Medica, vol. 34, no. 4-5, pp. 365–383, 2007.

[107] M. Boyce, K. F. Bryant, C. Jousse et al., “A selective inhibitor of eIF2 dephosphorylation protects cells from ER stress,” Science, vol. 307, no. 5711, pp. 935–939, 2005.

[108] M. Paschen, "Endoplasmic reticulum: a primary target in various acute disorders and degenerative diseases of the brain," Cell Calcium, vol. 34, no. 4-5, pp. 355–363, 2003.

[109] M. Gasparetto, T. Gentry, S. Sebti et al., “Identification of compounds that enhance the anti-lymphoma activity of rituximab using flow cytometric high-content screening,” Journal of Immunological Methods, vol. 292, no. 1-2, pp. 59–71, 2004.

[110] Y. H. Chou, P. L. Chao, M. J. Tsai et al., “Arsenic-induced cytotoxicity in dorsal root ganglion explants,” Free Radical Biology and Medicine, vol. 44, no. 8, pp. 1553–1561, 2008.

[111] H. Guo, C. Jiang, and X. Sun, “Therapeutic effects and mechanism of salubrinal combined with ulinastatin on treating paraquat poisoning,” Cell Biochemistry and Biophysics, vol. 70, no. 3, pp. 1559–1563, 2014.

[112] Y. Huang, J. Xu, M. Liang et al., “RESP18 is involved in the cytotoxicity of dopaminergic neurotoxins in MN9D cells,” Neurotoxicology Research, vol. 24, no. 2, pp. 164–175, 2013.
[131] X. Geng, X. Tian, P. Tu, and X. Pu, "Neuroprotective effects of echinacoside in the mouse MPTP model of Parkinson’s disease," European Journal of Pharmacology, vol. 564, no. 1-3, pp. 66–74, 2007.

[132] Y. Zhang, H. Long, F. Zhou et al., "Echinacoside’s nigrostriatal dopaminergic protection against 6-OHDA-induced endoplasmic reticulum stress through reducing the accumulation of seipin," Journal of Cellular and Molecular Medicine, vol. 21, no. 12, pp. 3761–3775, 2017.

[133] B. Yulug, Ü. Kilic, E. Kilic, and M. Bähr, "Rifampicin attenuates brain damage in focal ischemia," Brain Research, vol. 996, no. 1, pp. 76–80, 2004.

[134] W. Bi, L. Zhu, X. Jing et al., "Rifampicin improves neuronal apoptosis in LPS-stimulated co-cultured BV2 cells through inhibition of the TLR-4 pathway," Molecular Medicine Reports, vol. 10, no. 4, pp. 1793–1799, 2014.

[135] T. Mindermann, H. Landolt, W. Zimmerli, Z. Rajacic, and O. Gratl, "Penetration of rifampicin into the brain tissue and cerebral extracellular space of rats," Journal of Antimicrobial Chemotherapy, vol. 31, no. 5, pp. 731–737, 1993.

[136] L. Kilic, E. Kilic, P. Lingor, B. Yulug, and M. Bähr, "Rifampicin inhibits neurodegeneration in the optic nerve transection model in vivo and after 1-methyl-4-phenylpyridinium intoxication in vitro," Acta Neuropathologica, vol. 108, no. 1, pp. 65–68, 2004.

[137] B. S. Nilsson, "Rifampicin: an immunosuppressant?", The Lancet, vol. 298, no. 7720, p. 374, 1971.

[138] B. M. Dajani, M. S. Canady, J. S. Thompson, and J. E. Kasik, "Rifampicin: an immunosuppressant?", The Lancet, vol. 300, no. 7786, p. 1094, 1972.

[139] B. Yulug, L. Hanoglu, E. Kilic, and W. R. Schabitz, "Rifampicin: an antibiotic with brain protective function," Brain Research Bulletin, vol. 107, pp. 37–42, 2014.

[140] Y. Namba, K. Kawatsu, S. Izumi, A. Ueki, and K. Ikeda, "Neurofibrillary tangles and senile plaques in brain of elderly leprosy patients," The Lancet, vol. 340, no. 8825, p. 978, 1992.

[141] W. Bi, L. Zhu, C. Wang et al., "Rifampicin inhibits microglial inflammation and improves neuron survival against inflammation," Brain Research, vol. 1395, pp. 12–20, 2011.

[142] Y. Oida, K. Kitaichi, H. Nakayama et al., "Rifampicin attenuates the MPTP-induced neurotoxicity in mouse brain," Brain Research, vol. 1082, no. 1, pp. 196–204, 2006.

[143] S. Chen, Y. Sun, Z. Zeng, and E. Tao, "Rifampicin inhibits apoptosis in rotenone-induced differentiated PC12 cells by ameliorating mitochondrial oxidative stress,” Neural Regeneration Research, vol. 5, no. 4, pp. 251–256, 2010.

[144] X. Jing, Q. Shi, W. Bi et al., "Rifampicin protects PC12 cells from rotenone-induced cytotoxicity by activating GRP78 via PERK-eIF2α-ATF4 pathway," PloS One, vol. 9, no. 3, Article ID e92110, 2014.