Current Neuropharmacology, 2023, *21*, 353-379

REVIEW ARTICLE

Targeting Estrogen Signaling in the Radiation-induced Neurodegeneration: A Possible Role of Phytoestrogens

Sarmistha Mitra[1,#], Raju Dash[1,#], Md. Sohel[2], Apusi Chowdhury[3], Yeasmin Akter Munni[1], Md. Chayan Ali[4], Md. Abdul Hannan[5], Tofazzal Islam[6] and Il Soo Moon[1,*]

[1]*Department of Anatomy, Dongguk University College of Medicine, Gyeongju 38066, Republic of Korea;* [2]*Department of Biochemistry and Molecular Biology, Mawlana Bhashani Science and Technology University, Santosh, Tangail-1902, Bangladesh;* [3]*Department of Pharmaceutical Science, North-South University, Dhaka-12 29, Bangladesh;* [4]*Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, Uppsala SE-751 08, Sweden;* [5]*Department of Biochemistry and Molecular Biology, Bangladesh Agricultural University, Mymensingh-2202, Bangladesh;* [6]*Institute of Biotechnology and Genetic Engineering (IBGE), Bangabandhu Sheikh Mujibur Rahman Agricultural University (BSMRAU), Gazipur, Bangladesh*

Abstract: Radiation for medical use is a well-established therapeutic method with an excellent prognosis rate for various cancer treatments. Unfortunately, a high dose of radiation therapy comes with its own share of side effects, causing radiation-induced non-specific cellular toxicity; consequently, a large percentage of treated patients suffer from chronic effects during the treatment and even after the post-treatment. Accumulating data evidenced that radiation exposure to the brain can alter the diverse cognitive-related signaling and cause progressive neurodegeneration in patients because of elevated oxidative stress, neuroinflammation, and loss of neurogenesis. Epidemiological studies suggested the beneficial effect of hormonal therapy using estrogen in slowing down the progression of various neuropathologies. Despite its primary function as a sex hormone, estrogen is also renowned for its neuroprotective activity and could manage radiation-induced side effects as it regulates many hallmarks of neurodegenerations. Thus, treatment with estrogen and estrogen-like molecules or modulators, including phytoestrogens, might be a potential approach capable of neuroprotection in radiation-induced brain degeneration. This review summarized the molecular mechanisms of radiation effects and estrogen signaling in the manifestation of neurodegeneration and highlighted the current evidence on the phytoestrogen mediated protective effect against radiation-induced brain injury. This existing knowledge points towards a new area to expand to identify the possible alternative therapy that can be taken with radiation therapy as adjuvants to improve patients' quality of life with compromised cognitive function.

ARTICLE HISTORY

Received: December 30, 2021
Revised: February 01, 2022
Accepted: March 06, 2022

DOI:
10.2174/1570159X20666220310115004

Keywords: Radiation, brain, neurodegeneration, estrogen, phytoestrogen, radiation therapy.

1. INTRODUCTION

During aging, a progressive decline in brain function is associated with many neurodegenerative disorders (NDDs) where both genetic and environmental stressors, such as radiation, play an essential role [1-4]. Radiation has a great impact on human life [5-8]. Humans are confronted with radiation daily, albeit in low doses, from natural or artificial sources [9]. Radiation from natural sources may include cosmic, terrestrial, radioactive molecules, and exposure from inhalation or intake of radiation-contaminated materials. In comparison, medical imaging is one of the essential and rapidly rising artificial sources of radiation [10, 11], such as X-ray for imaging [12], computed tomography [13], radiation therapy (RT) for cancer treatment [14-16], nuclear medicine [17, 18] *etc* [19]. Accumulating evidence showed that diagnostic medical and contributed to 20% of the global yearly per capita actual radiation acquaintance from 1997 to 2007 [20]. RT prolongs the lifespan of many patients diagnosed with brain tumors with primary and metastatic stages; however, it leaves many survivors with long-term degeneration in the brain and cognitive impairments. Every year, more than 100,000 patients with primary and metastatic brain tumors encounter radiation-induced brain injury and survive for more than six months. Radiation at 2 to 45 Gy doses can inhibit neurogenesis in the brain in a dose-dependent manner [21], where a single dose higher than 30 Gy can induce acute central nervous system (CNS) syndrome, and fractionated doses greater than 60 Gy produce necrosis in white matter [22]. Growing evidence suggests that radiation induces multifactorial pathogenicity in the

*Address correspondence to this author at the Department of Anatomy, Dongguk University College of Medicine, 123 Dongdae-ro, Gyeongju 38066, Republic of Korea; Tel: +82-54-770-2414;
Fax: +82-54-770-2447; E-mail: moonis@dongguk.ac.kr
[#]*These authors have contributed equally.*

1875-6190/23 $65.00+.00

brain, and one of these is neurodegeneration caused by long-term oxidative stress, rearrangement in cell-cell junctional complex, lipid bilayer oxidation, and alternation in microvascular permeability [23-25]. Furthermore, radiation either in low or high doses can alter the function of the protein clearance system, leading to senescence or apoptotic cell death and thus causing neurodegeneration [26]. Yet, the molecular events that changed during RT need further verification, as many studies have shown little success in clinical attempts to end the radiation-induced neurodegeneration [27, 28] to unveil a potential target for better therapy.

In line with the survivability rate in patients with brain tumors, several studies highlighted those female patients with gliomas have a high survival advantage over the females of reproductive age, where males confront glioma development more than females [29]. It is noteworthy to mention that many physiological and pathological states, such as brain development, neurodegeneration, and aging, are critically modulated by sex hormones, especially estrogen receptor (ER) signaling. Estrogen, also known as estradiol or 17β-estradiol (E2), confers a protective role in gliomas progression, reduces tumor progression, and increases chemotherapy response [30-34]. Moreover, E2 confers neuroprotective effects by increasing various growth factor expressions, reducing oxidative stress and inflammation, activating the protein clearance system, and promoting cell survival [35-38]. Furthermore, supplementation of ER agonists promotes neurogenesis, particularly axonal growth and dendritic spines, and improves cognitive and memory performance by increasing synaptic transmission and plasticity [39, 40].

In this context, the targeting of ERs can be an adjuvant in traditional RT to reduce radiation-induced brain injury. Therefore, in this appraisal, an effort was deployed to accumulate the current information regarding the therapeutic benefits of E2 or ER modulators on radiation-induced neurodegeneration and neuronal survival and propose an alternative strategy for better therapeutic outcomes in the management of radiation-induced cognitive impairment.

2. IMPACT OF RADIATION ON COGNITIVE FUNCTION AND AGING

The scenario of the brain's response to radiation has changed substantially over the last few decades as accumulating evidence from various clinical and preclinical studies showed that radiation causes deflected cognitive function and promotes aging, where onset is more than 6 months after irradiation with or without noticeable functional abnormalities [41, 42]. Two major regions of the brain are mainly affected by radiation, namely the subgranular zone (SGZ) and the subventricular zone (SVZ) of the dentate gyrus (DG) of the hippocampus, where radiation alters neurogenesis particularly. RT can cause cognitive dysfunction and memory impairment in younger and elderly patients [43]. Different clinical studies have shown that RT for cancer treatment, especially for brain tumors and cancer, can induce brain injury leading to cognitive and motor dysfunction. Investigating 81 patients with brain metastasis who received RT [44], a 2018 study observed a significant increase in cognitive impairment following RT. Patients with low-grade glioma have also suffered from cognitive dysfunction after RT. The study comparatively assessed a case of glioblastoma patients receiving RT from 1 to 22 years prior with hematological patients (low-grade) and healthy subjects and identified a connection between RT and poor cognitive function. Precisely, patients who received RT at doses of more than 2 Gy encountered cognitive impairment predominantly in the memory domain [45]. In a case study of brain tumor patients, who received postoperative RT, Asai *et al.* found that patients receiving whole-brain RT encountered a higher rate of radiation-induced dementia and brain atrophy than those who received focal RT [46]. A study conducted in 2001 investigated the effect of whole-brain irradiation on cognitive function [47], where 25 Gy/single dose of RT to the adult rat induced cognitive dysfunction and memory loss following whole-brain irradiation for a year, along with a higher body weight gain. In 2011, an *in vivo* study reported fractionated radiation of 20 and 40 Gy (5 Gy/day, five days/week) caused cognitive impairment four weeks post-irradiation in the rat [48]. The study also reported that radiation treatment significantly increased the water content of the brain, which was probably due to an increase in the permeability of the blood-brain barrier by irradiation. It also concluded that fractionated irradiation could cause early memory and learning deficits. The effect of radiation on neurodegeneration is not limited to brain cancer patients. Patients with other cancers who received RT also had neuronal dysfunction and memory deficit. A 2008 human study [49] that included therapeutic cranial irradiation (TCI) group comprised 11 lung cancer patients, three breast cancer patients, and two gastrointestinal cancer patients with a control group of 15 breast cancer patients reported that whole-brain irradiation caused cognitive dysfunction, including verbal memory impairments in patients. Another study conducted in 2011 revealed a substantial level of cognitive impairment and neuropsychiatric symptoms in patients with cerebral radionecrosis when RT was delivered for nasopharyngeal carcinoma in a fractionated manner [50]. From these pieces of evidence, it can be concluded that RT plays a significant role in developing neurodegenerative symptoms in patients in later phases of life.

3. POSSIBLE ROLE OF RADIATION IN THE HALLMARKS OF NEURODEGENERATION

Multiple factors are associated with the etiology of different NDDs; nevertheless, one significant phenomenon that all NDDs share is the rise of brain oxidative stress [51]. Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) production and cellular antioxidant capacity, can be attained during aging [52, 53], dysfunctional mitochondria [54, 55], damage to mitochondrial DNA [56], or dysfunction of other ROS sources [3, 57]. Among other environmental factors, radiation, especially ionizing form, is also a principal source of ROS production [58], and this is accomplished by energy absorption. When radiation, such as infrared (IR) passes through water, water absorbs radiation energy, causing hydrolysis and resulting in a load of reactive species. Quantitatively, radiolysis of pure deaerated water is responsible for generating reactive species like e^-_{aq}, H•, H_2, •OH, and H_2O_2 [59]. Besides, IR stimulates the overproduction of intracellular inducible nitric oxide synthase (iNOS) [60] and accordingly produces nitric oxide (•NO) in a higher amount in

the cell. Excessive •NO produces peroxynitrite anion (ONOO−) following a direct reaction with O2•−, which is a higher rate constant than superoxide dismutase (SOD)-catalyzed dismutation of O2•− [61]. Therefore, under ambient oxygen, water radiolysis and early NOS activation act as significant ROS sources in irradiated cells. However, different types of radiation modulate ROS production, and the mode of cellular damage they cause also differs in terms of their concentration [62].

Numerous reports suggested that excessive oxidative stress can be induced either by environmental factors or other types of sources, leading to misfolded protein aggregation [63-65], which can also be a major pathogenic consequence of infrared irradiation [66]. IR decreases the protein stability by generating ROS, which ceases the protein's static function by upregulating the breakage of the polypeptide chain [67-70]. Furthermore, IR-induced ROS can initiate protein misfolding by targeting the thiol moieties of protein that are primarily oxidized by the ROS pathway, which is a primary target of radiation-induced protein oxidation. Upregulated ROS promotes glycoxidation or lipid peroxidation reactions, and the end products of these reactions and ROS also cause protein oxidation by direct interaction with native protein. Protein carbonylation, where aldehyde and ketone groups are added to the protein side chains, is the most shared protein modification. All residues are subtle to ROS-derived oxidation; yet, cysteine and methionine are significantly more sensitive to oxidation [71].

The cellular proteostasis network repairs or removes modified or misfolded protein; nevertheless, the proteins with methionine oxidation cannot be repaired but are subject to degrade selectively by clearance systems [57, 72]. The clearance systems in the proteostasis network, including the ubiquitin-proteasome system (UPS) and autophagy [73-76], play an essential role in suppressing non-functional and damaged protein aggregates, but the excess production of ROS markedly impairs function. The misfolded and aggregated proteins are recognized by a specific pathway when accumulated in mitochondria and endoplasmic reticulum (EnR), which recruits proteostasis functions, such as protein synthesis and degradation, known as unfolded protein response (UPR) [77, 78]. The UPR is activated by the influx of misfolded polypeptides and other factors, such as ROS, which are responsible for producing EnR stress when it rises at a higher level in EnR. The activation of UPR is perceived by three major singling pathways, including inositol-requiring enzyme-1(IRE1), PKR-like ER kinase (PERK), and activating transcription factor 6 (ATF6), which downstream regulates expressions of foldases, chaperones expression, and various autophagy-related genes [79]. During EnR stress, UPR promotes EnR-associated degradation (ERAD) and autophagy, regulates redox balance, and controls protein synthesis to restore protein homeostasis. However, prolonged UPR activation due to extended EnR stress leads to cell death by initiating degenerative cascades [80-82].

Compelling evidence suggested that IR exposure enhances cellular stress response and causes defects in DNA repair, impacting cell cycle progression and survival [83-85]. IR can disrupt mitochondrial DNA (mtDNA) by directly acting on it or indirectly via the generation of ROS like reactive hydroxyl radicals, leading to mitochondrial dysfunction [86]. IR also reduced total mitochondrial synthesis by inducing damage to mtDNA [87]. Furthermore, IR exposure enhances the accumulation of Drp1 in mitochondria and accelerates mitochondrial fission to manage overproduced mitochondrial ROS [88]. In addition to cellular respiration, mitochondria plays an essential role in the regulation of calcium homeostasis [89]. The imbalance of calcium homeostasis has been reported to enhance protein aggregation, autophagy deficits, and apoptosis, leading to a drastic alteration in proteostasis networks [90-93].

Intracellular Ca^{2+} maintains a reciprocal relationship with ROS, where ROS generation is induced by Ca^{2+} signaling and vice-versa [94]. Increased intracellular Ca^{2+} exerts excitotoxic neuronal death, as reported in many NDDs [95], and demonstrated by overproduction and a delayed mitochondrial depolarization along with mitochondrial cytochrome c release [96]. The superoxide anion (O_2-) is constantly being generated by the mitochondria. It has been shown that increased Ca^{2+} uptake by the mitochondria increases the production of reactive oxygen [97]. EnR stress is also a fundamental phenomenon related to the ROS production and Ca^{2+} excitotoxicity cycle [98].

Furthermore, soluble protein aggregates, following diffusion, colocalize and interact with the various membrane proteins and receptors, including Ca^{2+} regulating channels and receptors at the excitatory synapse, for example, like NMDARs [99] and mGluR5 [100]. These misfolded proteins assemblies with membrane receptors around the excitatory synapses initiate artificially activated signaling platforms that promote Ca^{2+} elevation and enhance ROS and other deleterious effects by causing excitotoxicity [101, 102]. Excessive excitotoxicity further impedes the proteostasis network and increases the total protein aggregates by establishing a "vicious cycle" [103, 104]. Oxidative stress derived from radiation and subsequent protein misfolding and protein aggregation, excitotoxicity, EnR stress together trigger neuroinflammation. Mounting evidence suggests that IR exposure induced a rapid rise in Ca^{2+} level, which persisted over time due to the higher increase of inositol triphosphate level [105-107]. Leach *et al.* proposed that IR causes mitochondrial depolarization by increasing Ca^{2+} permeability, where Ca^{2+} is involved in a chain reaction of ROS signaling propagation and amplification [108]. In immature dorsal root ganglion neurons, infrared irradiation with 24 Gy induced a high elevation of Ca^{2+} and promoted cell death in a dose-dependent manner [109]. Interestingly, nimodipine, a calcium antagonist, protected hippocampal neurons from the radiation-induced cognitive deficit and apoptosis in the rat model [110]. Thus, radiation-induced oxidative stress is closely related to the initiation of neurodegeneration, leading to NDDs.

4. ESTROGEN SIGNALING REGULATES THE HALLMARKS OF NEURODEGENERATION

E2 is one of the primary sex hormones and has a key role in maintaining diverse signaling systems, leading to neuroprotection [111]. Although ovaries are the primary source of E2, this hormone is also available in adipose tissue and adrenal glands [112]. The typical functions of ER signaling are regulated by binding E2 as a ligand of mainly two classical nuclear receptors, estrogen receptor-alpha (ERα) and estro-

gen receptor-beta (ERβ). Besides, ER signaling is also modulated by GPR30, an additional category of membrane G protein-coupled receptor, called GPER [113]. However, both receptors, ERα and ERβ, primarily initiate cellular signaling mediated by E2, and both of these receptors show variations in the cellular distribution and regulations [114-116].

Structurally, both the ERs, ERα and ERβ, shared high homology and are composed of different functional and structural domains, including the N-terminal domain (NTD) bearing the first activation function domain (AF1), ligand-binding domain (LBD), including the second activation function domain (AF2), DNA binding domain (DBD) and hinge region. A study based on the sequence homology represented that the LBD of both isomers has a sequence identity of around ~55%, DBD shows more than 95% of sequence identity, while NTD bears a low sequence identity (around ~15%), as this portion in ERβ is comparatively not longer than that of ERα [116, 117]. Both AF-1 and AF-2 are involved in regulating the transcriptional activities of ERs, where hormones and steroids regulate AF2 actions, but the hormone-independent function is only represented by AF1 [118, 119]. Interestingly, ERs regulate gene transcriptions in nuclear signaling, known via classical and non-nuclear signaling approaches, dependent on ligand-induced activation [120, 121].

Accumulating evidence represented that non-nuclear ER signaling maintains a critical role in modulating the brain's proteostasis network and functional integrity [122]. In the human brain, both ERα and ERβ are present and modulate a broad range of brain functions, such as neuronal defense, neurogenesis, synaptic plasticity, reproductive processes, learning, memory, mood, and behavior [123]. E2 protects neurons by modulating the following pathways; axonal sprouting, synaptic transmission, regenerative responses, neurotransmitter receptor function, phosphorylation cascades, kinase signaling pathways, *etc* [124, 125]. E2 controls cell proliferation, differentiation, and apoptosis occurring in the normal mammary gland at lactation/involution cycles [126]. ER signaling protects mammary cells from EnR stress by modulating the UPR, where the modulators are exerted during milk protein synthesis and secretion [127]. The mechanistic premise of ER in modulating diverse signalings of degeneration cascades is discussed in the subsequent sections.

4.1. In the Attenuation of Ca^{2+} Mediated Excitotoxicity

Calcium appears to have a major role in brain aging that contributes to Alzheimer's disease (AD), and dementia has been established by several lines of evidence [128, 129]. Although physiological activities are required for intracellular Ca^{2+}, neuronal dysfunction and cell death can be caused when the amount is excessive. There are a variety of enzymes, including proteases, endonucleases, phospholipases, and nitric oxide synthase (NOS), which can cause the elevation of Ca^{2+} level in the neuronal cell, thus there upregulated activity can be linked to neuronal cell death [130, 131]. In many neuronal signal transduction pathways, excessive intracellular calcium accumulation plays an essential role, where changes in the intracellular calcium homeostasis are crucial in brain aging, memory, and cell death. In such a case, one of the most common receptors, N-methyl-D-aspartic acid (NMDA), which regulates Ca^{2+} influx through glutamate-derived activation, triggers a broad range of cellular processes in the postsynaptic neuron, ranging from synaptic plasticity to cell death. Continuous activation of a high number of NMDA receptors causes a rise in intracellular calcium loading and catabolic enzyme activities, which can set off a chain of events that finally leads to apoptosis or necrosis. Excess glutamate levels in the CNS can produce an increase in intracellular Ca^{2+} levels, which causes an increase in Ca^{2+} concentration in sensitive organelles, such as mitochondria and the EnR [132]. Furthermore, increased Ca^{2+} entrance into the cytosol induced by NMDA activates calcineurin and causes death in rat hippocampus neurons and stable cell lines, such as HeLa cells [133, 134].

Accumulating studies evidenced that ER signaling regulates the expression of NMDA receptors, especially in the memory process. It was found that E2 enhances NR2B expression, a subunit of NMDAR, and accordingly enhances long-term potentiation (LTP) in the learning and memory process [135, 136]. Liu *et al.*, 2008 found that LTP enhancement was directly mediated through ERβ activation [137], and ERβ lacking mice (ERβ-/-) failed to show E2 mediated neuroprotection against NMDA-induced excitotoxicity [138]. The evidence further suggests that E2-mediated neuroprotection reduces ischemia-induced excitotoxicity through interaction with the NMDA receptor [139, 140]. Weiss *et al.* showed that treatment of E2 in ovariectomized Wistar female rats decreased the NMDA mediated cerebral oxygen consumption, and the effect deviated from a reduced number of NMDA receptors [141]. As cortical neurons in the female brain have more immunoreactive ER than males, as shown by *in vitro* in Bryant *et al.*, an ER-specific ligand propylpyrazoletriol (PPT) protected cortical neurons against glutamate-induced damage in females, while this effect was absent in males [142].

In ovariectomized rats, SERMs, such as tamoxifen, raloxifene, and bazedoxifene, protected neurons against kainic acid-induced hippocampus neuronal injury [143]. In ischemic rat brains, tamoxifen promoted neuroprotection against AMPA/NMDA receptor-mediated excitotoxicity caused by oxygen/glucose deprivation [144] and also against glutamate-induced excitotoxicity [145]. In the rat cerebral cortex, raloxifene, which acts as an ER agonist in the brain but an antagonist for the reproductive system [146], promoted neuroprotection against kainic acid-induced excitotoxicity as well as oxidative stress [147].

In addition to NMDA receptor modulation, ER can reduce calcium influx through L-type channels [148, 149]. As suggested by Zhao and Brinton [150], glutamate-mediated intracellular Ca^{2+} accumulation can be reduced by ER subtype-selective agonists PPT and diarylpropionitrile (DPN) through ERK/MAP kinase pathway, which was differentially regulated ERα and β in hippocampal neurons. Studies also suggested that ERα can interact with mGluR1 at the postsynaptic membrane of a hippocampal neuron when activated by E2 [151], and this interaction facilitates higher phosphorylation of the cAMP response element-binding protein (CREB) [152]. A similar phenomenon was also observed in the case of striatal neurons; however, the effect was mediated by the direct interaction of ERα to mGluR3 but not mGluR5 [153]. Both ERα and ERβ enhance mGluR2/3 activation and the

Gi/0 pathway, which lowers L-Ca^{2+} channel function by inhibiting PKA phosphorylation of CREB.

4.2. In the Regulation of Oxidative Stress

ERs play essential roles in maintaining redox balance and protecting cells from oxidative damage [111]. Studies evidenced that ER modulators, such as E2, can initiate a chemical antioxidant system and regulate ROS signaling [154-158] by regulating expressions of antioxidant enzymes. Evidence derived from *in vivo* studies dealing with rat brains lacking estrogen revealed that estrogen deficiency downregulates the expression of SOD, CAT, NADH, and GSH/GSSG ratio [159], thus elevating oxidative stress along with anxiety, memory loss, and learning disability [160]. While in a similar experimental model, treatment of E2 showed a withdrawal effect of brain oxidative stress [161]. A detailed analysis by Rao *et al.* [162] represented that E2 treatment upregulates SOD1 in cortical neurons, which is negatively associated with the progression of oxidative stress induced brain damage. Yang *et al.* reported that knockdown of ERβ from HT-22 cells showed resting mitochondrial membrane potential becoming resistant to oxidative stress, leading to increased ROS production [163], suggesting that ERβ is associated with regulation of ROS in mitochondria. Siriphorn *et al.* stated that Schwann cells expressed ERα and ERβ and treatment with E2 had a protective effect and survival mechanism against H_2O_2 exposure, which was validated by ICI182780, an ER antagonist [164]. E2 consists of hydroxyl group which usually acts as a chemical shield during the protection from free radical [165]. In the case of mitochondrial ROS, Stirone *et al.* reported that E2 reduced the formation of hydrogen peroxide (H_2O_2] in female cerebral blood vessels [166]. E2 decreased bain mitochondrial ROS generation in Fischer 344 rats, by increasing aconitase and manganese superoxide dismutase (MnSOD), where enzymes break superoxide radicals in the male and female rat [167] to reduce mitochondrial ROS production.

In nongenomic pathways, overexpression of ERα and ERβ activates some cytosolic signaling molecules, including ERK and MAPK, leading to attenuating amyloid β-related ROS in the HT22 hippocampus-derived cell line [168]. Tsialtas *et al.* reported that mitochondrial ERβ was involved in reducing H_2O_2 mediated apoptosis via suppressing caspase -9 and -3 activation in the N2A cells line [169]. Razmara *et al.* reported that the E2-mediated protective effect decreases ROS-related mRNA in human cerebral endothelium cells through ERα [170]. Furthermore, investigations found that E2 offered neuroprotection in the brain tissue of male mice following permanent blockage of the middle cerebral artery, as well as in primary neurons exposed to ROS *via* an ER-independent anti-oxidant mechanism [171].

4.3. In the Modulation of Neuroinflammation

Neuroinflammation is a response to specific CNS injuries [172], mediated by collaborative approaches of activated astrocytes and microglial cells that elevate pro-inflammatory mediators, such as ROS, chemokines, and pro-inflammatory cytokines, a vicious cycle that eventually causes neurodegeneration [173]. In such cases, ER signaling offers neuroprotection through the interactions with tissue and cell-specific co-regulators [2]. The neuromodulator causes the conformational change of ER and eventually causes receptor activations, and reduces neuroinflammation [2]. Interestingly, it is proved that all three ERs, ERα, ERβ, and GPR30, are involved in neuroprotection [174]. It is now evidenced that E2 inhibits the activation of NF-κB signaling [175]. NF-κB provokes the expression of several chemokines and cytokine-producing genes, including pro-inflammatory mediators [176]. The NF-κB family members (*e.g*. NF-κB1, NF-κB2, RelA, RelB, and c-Rel) facilitate around five hundred gene expressions, including iNOS, IL-1, IL-6, IL-8, TNF-α, which are responsible for inflammation [177]. The activated NF-κB signaling cascade is associated with many neurological disorders [176-178]. It is also found that ERK/MAP kinase activation is vital for E2-mediated neuroprotection [179]. Choi *et al.* showed that E2 activates PI3K/Akt signaling in cortical neurons [174, 180]. Xing *et al.* found that E2 activates ERβ, upregulates IκBα expression, and inhibits RelA (p65) binding to the inflammatory gene, which might reduce inflammation [181]. Tiwari-Woodruff showed that activation of ERα decreased the level of pro-inflammatory mediators TNF-α, IFN-γ, and IL-6 and upregulated the expression of anti-inflammatory cytokine IL-5 in EAE model animals [182]. Treatment with E2 led to reduced dendritic cell activation in the CNS of EAE mice and reduced the expression of IFN-γ, TNF-α, and IL-12 mRNA [183]. Remarkably, E2 also provides a neuroprotective effect through the activation of the GPR30 receptor [184]. The GPR30 agonist G-1 treatment also reduced CNS inflammation, axonal damage, and demyelination [185]. G-1 also reduced the number of macrophages in the CNS [186]. Blasko *et al.* showed that G-1 reduces the expression of chemokine and cytokine, including CCL2, CCL4, CCL5, TNF-α, IFN-γ, IL-17, and IL-23, [186]. Recently, Spence *et al.* have found that activation of ERα also declines the expression of chemokine CCL2 and CCL7 in EAE astrocytes [187].

4.4. In the Activation of Protein Clearance Systems

ER-mediated signaling is a complex process, and numerous anonymities need to be resolved. It is evidenced that ERα controls HSF1 signaling, the mediators which increase the expression of HSP70, HSP90, and HSP110 in stress conditions [188, 189]. Recently, Riar *et al.* have shown that activated ERα induces UPR^{mt} activation, raises NRF1, and increases cellular proteasome systems in the ALS model [190]. The first outcome of UPR is the activation of BiP (GRP78) with a subsequent reduction of protein production, ultimately reducing EnR stress [191]. On the other hand, mitochondrial UPR upregulates CHOP [192], and CHOP influences the expression of HSP10, HSP60, and proteases [190].

Chung *et al.* found that E2 treatment activates autophagy, resulting in a higher level of Atg12, LC3B-II/LC3B-I, HSP70, and HO-1 expression in ovariectomized rats [193]. Activated ERα was also shown to increase p62 and reduce Bcl-2 expression, provoking autophagy [194, 195]. Besides, activated ERβ influences autophagy by controlling the expression of autophagy-associated markers, including p62 and LC3-I/II activating AMPK signaling, modulating P13K/AKT/mTOR signaling [196], and detachment of BECN1-BCL2 complex [197, 198]. The mitochondrial ERα mediates autophagy by modulating p38 MAPK and ERK signaling

[199]. It is now clear that ERs regulate several autophagy-related transcription factors. Li *et al.* showed that E2 stimulates Nrf2-ARE signaling and the expression of autophagy proteins in the brain [200].

5. ESTROGEN REPLACEMENT THERAPY IN NEURODEGENERATION

Many etiological studies established a relationship between sex preference of AD development. They found that women during the age of eighty are more likely to have a higher incidence of AD development, which is double that of men, though having a protective measures, including education. This finding also suggests that E2 deprivation is linked to AD. Many studies have been conducted so far to ensure the benefits or risks of hormone replacement therapy (HRT) in patients with various NDDs, where therapy includes either only several categories of E2 or in combination with exogenous or synthetic or progestogen. However, the implication of estrogen replacement therapy (ERT) for neurological disorders is not beyond question, as some studies also suggested that this treatment method may not be beneficial [201].

As E2 is predominately synthesized from the ovary and involved in many endocrine-related mechanisms of women, in the case of menopausal women, ERT has been applied and studied more extensively [202-204]. ERT could be beneficial in avoiding NDDs by boosting neuronal defense and memory systems based on E2-mediated neuroprotection [205]. Again, ERT can improve cognitive function performance in the aging brain [206]. A double-blind placebo-controlled clinical trial concluded that ERT would be an ineffective strategy for reversing the pathology of AD if it had already been initiated [207]. Another 12-week clinical trial investigation on 50 participants found that the E2 treatment group exhibited no significant improvement over the placebo group, indicating that ERT has limitations in treating AD [208]. In 2000, a clinical trial was conducted among mild to moderate AD patients. The study showed neither deterioration nor improvement in ERT patients [209]. It can, however, lessen the risk of AD or delay its development [210]. Numerous studies reported that ERT in older women showed improved cognitive function and memory. An early study conducted in 1952 showed ERT improved the verbal memory of old women patients compared to the placebo group [211]. In 1997, an investigation involving 472 perimenopausal women showed that ERT provided a protective action against AD progression compared to non-user of ERT [212]. Another clinical trial study conducted among 278 post-menopausal women patients (aged 55 to 93) showed an improved memory function after ERT.

The study showed significant improvement in proper name recall in the treatment group patients [213]. A clinical investigation with 46 postmenopausal women was done to examine how E2 affected brain activity patterns during a working memory task. The study discovered that E2 increases activity in the inferior parietal lobule during the storage of verbal information and decreases activation during the storage of nonverbal information [214]. A recent meta-analysis study summarized the existing research and clinical data and illustrated a dramatically lower risk of AD and PD by ERT compared to the control group [215]. In 1994, one clinical trial study reported that dementia with AD is significantly reduced by ERT [216]. Also, ERT may help to improve the efficacy of other clinical therapy for AD. In 1996 a 30-week-long clinical trial study was conducted with 318 subjects, which concluded that ERT enhanced the efficacy of Tracine, an AD medicine [217].

PD is a progressive movement disorder developed by the degeneration of the dopaminergic neurons. The risk of PD begins to develop in pre-menopausal women, reducing the effectiveness of their medications. Furthermore, post-menopausal women have a higher risk of developing PD, suggesting ERT might play a crucial role against PD symptoms. Additionally, E2 has a modulatory role in lessening the degradation of dopaminergic neurons [218].

Several studies have reported the beneficial effect of ERT on PD during the menstrual cycle. Recently, song *et al.* showed that HRT reduced the risk of PD significantly in postmenopausal women compared to the control by using a random-effects meta-analysis where the odds ratio value was 0.470; 95% CI: 0.368-0.600 [215]. Along with this, some clinical studies have reported the more significant impact of ERT on PD. In a double-blind, parallel-group study, administration of conjugated E2 (Premarin; 0.625 mg/day) over eight weeks showed the reduction of motor fluctuation and improvement “on” and “off” times in postmenopausal women patients of PD (n=20) compared to placebo-treated patients. However, a double-blind, placebo-controlled study reported a short-term anti-Parkinsonian effect with mild-to-moderate PD in 8 postmenopausal women without altering dyskinesia scores [219]. In another placebo-controlled, randomized, double-blind trial with postmenopausal patients (12 females), the dopaminergic effect of E2 was not significant [220]. Thus, the null findings concluded the attenuation of PD symptoms in the menopause stage of women by ERT.

Multiple sclerosis (MS) is a persistent demyelinating disease of the central nervous system (CNS), affecting eyesight and causing a significant decrease in relapses [221]. Pregnant women with MS have the beneficial effect of the pregnancy hormone estriol in reducing lesions. Therefore, one clinical study was conducted to observe the role of estrogen treatment in MS. Non-pregnant patients with MS were (aged from 18 to 50 years) examined after the oral administration of estriol (8mg/day) for six months, where a significant decrease in lesion numbers was found compared to the control group [222]. Soldan and the team reported that the levels of CD4+, CD8+ T cells, and CD4+ CD45Ro+ (memory T cells) were decreased significantly while the levels of IL-5 and IL-10 increased during estriol (8 mg/day, for six months) treatment in ten female patients with MS, suggesting the correlation with depletion of lesions improvement [223].

Huntington's disease (HD) is a well-known inherited NDDs that causes the deterioration of nerve cells. Several studies revealed both enhancement and blocking of dopaminergic activity by E2 in animal models, but the study of ERT on HD patients was minimal. However, one clinical study reported the improvement in lower than one-third of patients with chorea in HD patients together with tardive dyskinesia [224].

Amyotrophic lateral sclerosis (ALS) is a fatal nervous system disease with various phenotypes. A case-control study in Ireland, Italy, and the Netherlands was performed to observe the effect of HRT in 653 patients and 1,217 controls over four years. The exogenous E2s combined with progestogens were found to reduce ALS risk in women [225]. Another study on HRT failed to demonstrate the beneficial effect of E2 in ALS patients. There was no significant difference in neuroprotection between postmenopausal women with ALS treated and those not taking ERT [226].

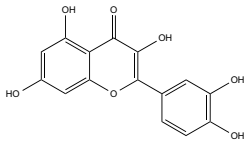
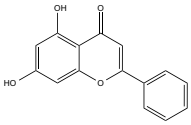
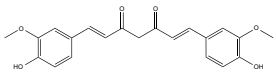
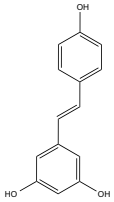
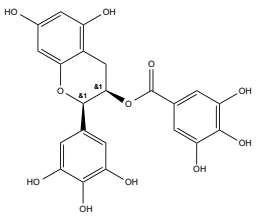
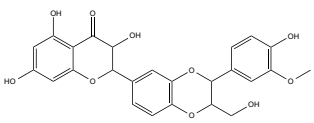
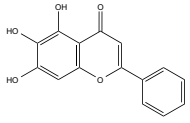
In brief, ERT is a newly established treatment that diminishes menopausal symptoms and the risk of postmenopausal diseases. The risk of NDDs, such as AD, PD, MS, HD, and ALS, might be lessened during the menopausal stages through ERT. Although several clinical studies were assessed, further studies are required with similar approaches to expand ERT-induced neuroprotection.

6. ROLE OF SELECTIVE ESTROGEN RECEPTOR MODULATORS IN RADIATION-INDUCED BRAIN INJURY

Several selective ER modulators (SERMs) are currently available and are being used to manage postmenopausal symptoms, osteoporosis, and cancers like breast cancer, which because of their tissue selective behavior, act as both agonists and antagonists of ERs. The binding and activation mode of these modulators are briefly described elsewhere [227-230]. Among these SERMs, tamoxifen has been widely used and prescribed for many diseases for several decades as adjuvant endocrine therapy. In the case of radiation-induced brain injury, Liu *et al.* summarized that tamoxifen at a concentration of 1 μM reduces the radiation-induced microglial inflammatory response through the negative effect of irradiation in a murine microglial cell line, BV-2 cells. When radiation was applied to 10 Gy, the expression of TNF-α and IL-1β increased and promoted inflammatory responses, which were significantly reduced by tamoxifen. Notably, tamoxifen administration at a dose of 5 mg/kg decreased the tissue edema formation and blood brain barrier (BBB) breakdown, glial activation, and neuronal death, caused by total brain irradiation in the adult male Sprague–Dawley rats [231]. Another ER signaling modulator [232], lithium, is also reported to reverse radiation-induced cognitive impairment, as Zanni *et al.* [223] reported. It has been found that lithium treatment promoted hippocampal neurogenesis in C57BL/6J mice, even four weeks after whole-brain radiation (a single dose of 4 Gy). Earlier mechanistic analysis showed that pretreatment lithium could increase the proliferation of hippocampal neural progenitor cells and rescues radiation-induced (3.5 Gy) G1 and G2/M phases of cell cycle arrest without causing apoptosis [233].

In addition to synthetic SERMs, many naturally occurring SERM, known as phytoestrogen, are also reported to ameliorate radiation-induced brain injury (Table **1**). One of the popular phytoestrogens, quercetin, is a potential phytoestrogen that can protect against radiation-induced brain injury. Kale *et al.* found that quercetin treatment at 50 mg/kg can mitigate radiation-induced brain injury by altering antioxidant status, more explicitly regulating plasma total antioxidant status (TAS) and malondialdehyde (MDA) in male, Wistar-Albino rats [234]. Another experimental research, later on, revealed that quercetin (5-100 μM, 24 hrs) protected neurons against radiation (γ-ray, 2 Gy)-mediated EnR stress and inflammatory response through downregulating binding immunoglobulin protein (BiP) and C/EBP-homologous protein (CHOP), TNF-α, JNK, some EnR stress marker gene and upregulating Tuj1, a cytoskeletal protein with neurotrophin brain-derived neurotrophic factor, conducted by Chatterjee *et al.* [235]. Data obtained from a histopathological investigation of male Wister rats' brain tissues study, conducted by Mansour *et al.*, stated that 5, 7-Dihydroxyflavone (DHF) or chrysin (50 mg/kg, 21 days) could reverse acrylamide (ACR) or γ-irradiation-induced neurotoxicity attributing increased catecholamine level and brain-derived neurotrophic factor (BDNF), leading to increased serum activity of creatinine kinase-BB but decreased acetylcholinesterase and caspase-3 activities and MDA and β-amyloid level [236]. Furthermore, chrysin upregulates glutathione (GSH) with downregulating MDA and TNF-α levels in ACR-treated Male albino rats (140-160g) [237]. Flaxseed oil (FSO), which contains a high level of phytoestrogenic lignans, was found to have neuroprotective effects against 7 Gy γ-irradiation and CCl4-induced brain injury in the irradiated Swiss albino (6-8 weeks, 25±2 gm) mice model through improving the antioxidant status, suppressing the inflammatory responses, and regulating the trace elements at a dose of 100 μl/mice/day for 21 days [238, 239]. Learning and memory improvement against 4Gy radiation-induced cerebral injury of curcumin (200 mg/kg) was mediated via improving antioxidant status through the underlying mechanism of increasing antioxidant transcription factor, *i.e.* nuclear erythroid 2 related factor 2 (Nrf2) and its downstream gene *i.e.* NADPH quinine oxidoreductase 1 (NQQ1], heme oxygenase-1 (HO-1), and γ-glutamyl cysteine synthetase (γ-GCS) with a concomitant significant increase in superoxide dismutase (SOD) and cerebral malonaldehyde (MDA) activity in 6–7 weeks Kunming mice [240]. In addition to the brain, curcumin (150 mg/kg, seven days) reduced radiation-induced heart injury by increasing IL-4 along with its receptor IL4Ra1, infiltrating some immune cells, *i.e.*, lymphocytes and macrophages, and decreasing dual oxidase (Duox1 and Duox2) in γ-radiation (15 Gy) induced rat [241]. Resveratrol (5 and 10 mg/kg, 21 days) inhibits apoptosis induced by radiation and increases Sirt1 mRNA expression and activity with antagonizing oxidation and cellular ROS-scavenging effect in male Sprague-Dawley rats (200–220 g) [242]. Oral administration of epigallocatechin gallate (EGCG), with a dose of 2.5 and 5 mg/kg/d, significantly decreased amino acid homocysteine, immune molecules TNF-α and IL-6, and β amyloid with the simultaneous increase in the neurotransmitter dopamine, serotonin, and antioxidant status, including glutathione level, and the activities of glutathione peroxidase and glutathione reductase. They also found that EGCG prevents radiation-induced DNA damage to provide genomic stability and apoptosis *via* downregulating cyto-c, Bax, caspase-3, caspase-9, whereas upregulation of Bcl2 in the hippocampus [243]. Subsequently, silymarin (140 mg/kg/d) suppressed irradiation mediated damage that increased nucleic and

Table 1. Phytoestrogens conferring neuroprotection against radiation-induced neuronal injury *in vivo* and *in vitro*.

Compound	Structure	Treatment (Dose and Duration)	Experimental Model	Radiation (Type, Dose)	Major Outcomes	Mechanism	References
Quercetin		50 mg/kg	Male Wistar-Albino rats, 300–350 g	20 Gy	↑ Neuroprotection ↑ Antioxidant activity	↑Regulate plasma MDA, TAS	[234]
		5-100 μM, 24 hrs	Dorsal root ganglion (DRG) neurons	γ-ray, 2 Gy	↓ Inflammatory responses, ER stress,	↓ BiP and C/EBP ↓ TNF-α, JNK ↑Tuj1, BDNF	[235]
Chrysin		-	Male albino rats, 140-160 g	5 Gy	↓Oxidative damage	↑ GSH,BDNF ↓MDA, TNF-A, GABA	[237]
		50 mg/kg 21days	Male Wister rats, 120–150 g	γ-ray,5 Gy	↓Oxidative damage	↑Catecholamine content' creatinine kinase-BB ↓ MDA, β-amyloid, acetylcholinesterase and caspase-3	[236]
Curcumin		200 mg/kg	Kunming mice, 6–7 weeks	Heavy-ion radiation, 4 Gy.	↑ Cognitive functions	↑SOD, MDA ↓ NAD(P)H, NQO1, HO-1, γ-GCS	[240]
		150 mg/kg, 7 days	-	γ-ray, 15 Gy	↓ Heart injury	↑IL-4 ↓ Duox1 and Duox2	[246]
Flaxseed oil	--	100 μl/mice/day (21days)	Swiss albino 6-8 weeks, 25±2 gm	7 Gy	↓ Oxidative damage	↓ Lipid peroxidation (LPO), ↑ Glutathione (GSH)	[238]
Resveratrol		5 -10 mg/kg, 21 days	Male Sprague Dawley rats, 200-220 g	γ-ray, 4-Gy	↑ Apoptosis ↑ Oxidative damage	↑ Sirt1 mRNA ↑ ROS-scavenging	[242]
Epigallocatechin gallate (EGCG)		2.5-5 mg/kg/d	Male Wister rats	γ-ray, 4 Gy	↓DNA damage and apoptosis	↓ Homocysteine, ↓ Amyloid β, TNF-α, IL-6 levels ↑ Dopamine and serotonin ↓ Cytochrome-c, Bax, and caspase-3 and 9 ↑ Bcl-2	[243]
Silymarin		140 mg/kg/d	Rat model	γ-ray, 0.2-0.6 Gy	↑ Repair DNA damage	↑Nucleic acids, histone proteins stability ↓Free radical generation ↓Lipid peroxidation	[244]
Baicalein		10 mg/kg/d	C57BL/6 mice	γ-ray, 5 Gy	↑ Neurogenesis regulation	↑BDNF-pCREB	[245]

histone protein stability and inhibited radiation-induced free radical production with lipid peroxidation against γ-ray (0.2 and 0.6 Gy/d) induced brain damage in the rat [244]. Baicalein protected neural progenitor cells in male C57BL/6 mice against γ-ray (5 Gy) -induced necrotic cell death. The author found that baicalein (10 mg/kg/d) alters neurogenesis by modulating oxidative stress and elevating BDNF-pCREB signaling, improving learning and memory capacity [245].

Table 2. Neuroprotective activities of phytoestrogens against neurodegenerative hallmarks.

Compound	Estrogen Receptor Preference	Effect on Neurodegeneration				References
		Dose	Experimental Model	Cellular Mechanism	Molecular Mechanism	
Quercetin	ERβ-selective agonist	0-150 μM	P19 neurons	↓Oxidative injury	↓ROS production ↑Caspase-3/7	[265]
			RSC96 and rat Schwann cells	↓Autophagy	↑Beclin-1 ↑LC3	[266]
		0-25 μM	HT22 cell	↓Ca^{2+} excitotoxicity	↓Glutamate-mediated Ca^{2+} influx ↓Bid and Bax, and Cyt-c release	[267]
Chrysin	ERα, ERβ-selective agonist [268]	100 mg/kg, p.o.	Male Wistar rats	↓Neuroinflammation	↓Pro-inflammatory markers, *i.e*, TNF-α, IL-1β, IL-6, NF-κB, iNOS and COX-2	[269]
		5 and 10 μg/ml	Wistar rats	↓Oxidative stress	↑NRF2/HO-1 pathway activation	[270]
Resveratrol	ERα, ERβ-selective agonist [271]	10 and 50 μg/ml	NMDA induced neuronal injury	↓Neuronal death	↑Intracellular calcium ↑ROS generation	[272]
		20 μM	SH-SY5Y cells	↓Autophagic flux	↑LC3-II ↑HO-1 expression.	[273]
Epigallocatechin gallate (EGCG)	ERα-selective agonist [274]	1.5 or 3 mg/kg	PS2 transgenic mice model	↓Protein aggregation	↑Memory function ↑α-secretase activity ↓β- and γ-secretase activities	[275]
		25-100 μM	GO induced neurotoxicity in H 19-7 cells	↓Oxidative stress	↑Nrf2 activation	[276]

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Alongside regulating sexual behavior and reproductive functions, ER signaling has been renowned for its diverse functions in the CNS, including neurogenesis, synaptic plasticity, and neuroprotection, and eventually affecting motor activities, learning, cognition, and behavior [247-249]. Considering the substantial evidence highlighted in this review, it is inevitable that E2 or ER targeting modulators might hold the potential to delay the development and progression of various NDDs. Interestingly, it is evidenced that E2 or ER targeting modulators could successfully revert the expected pathological consequences in radiation-induced brain injury, including BBB breakdown, pro-inflammatory responses, and loss of hippocampal neurogenesis, where tamoxifen could be an example. Studies other than on radiation-induced injury revealed that the treatment of tamoxifen is effective in the brain and spinal cord injuries [250-252], promoting neuronal differentiation, preventing demyelination in the cerebral cortex [253], and providing neuroprotection against MS [254], stroke [255], PD [256], and dementia [257]. Nevertheless, other studies established that the use of tamoxifen failed to induce cognitive function when used as hormonal adjuvant therapy in breast cancer patients [258-260] and concluded that this drug could act like E2 only in the ovariectomized animals [261]. In the case of radiation-induced brain injury, Liu *et al.* observed a neuroprotective effect in the regular mice model [231], suggesting the importance of additional studies in different animal models to confirm the effectiveness and safety of radiation-induced neurodegeneration.

As both tumor radiosensitization and reduced toxicities in non-cancer cells are equally important goals in RT, ER signaling modulating agents from natural sources could be an attractive option to have the dual ability to enhance radiation damage in the malignancy, simultaneously protecting the normal cell from radiation injury [262, 263]. As highlighted in Table **1**, several studies reported the potential of phytoestrogens in the neuroprotection against the radiation-induced brain or neuronal injury, where most of them are reported to increase radiosensitivity in conventional RT. For example,

quercetin is reported to potentiate radiosensitivity against tumor cells *in vivo* and *in vitro* by regulating ATM-mediated pathways and acting as a radioprotective agent when used systemically [253]. A similar impression is also applied to curcumin, which also proved to increase radiosensitizing in various *in vitro* and *in vivo* cancer models [254, 255], while other studies suggested curcumin as a radioprotector [256-261].

Interestingly, all of the natural modulators listed in this study provide cumulative neuronal protection, acting on the multiple pathways of NDDs, including antioxidant defense systems, calcium excitotoxicity, proteostasis modulation, and neuroinflammation, as highlighted in Table **2**. Since radiation exposure caused multi-path derived changes in brain signaling and function, the pharmacological modulation by these pleiotropic natural ER modulators compounds could open avenues to develop strategies for protecting brains against radiation-related incidents [264].

As their effects have only been recorded in pre-clinical investigations, the pharmacological potentials of the natural ER modulators remain somewhat imperceptible. In reality, no clinical trial has yet been carried out to assess their impact on radiation-derived brain injury; therefore, implementation of high-quality trials is essential to confirm these preventive effects in the various aspect of brain injury following RT. Unfortunately, the efficacy data highlighted in the present review only emphasized the single preclinical model focusing on specific signaling pathways. Thus, more mechanistic-based studies focusing on multiple pathways are needed to reveal the unknown mechanism of these modulators by emphasizing radiation-induced side effects.

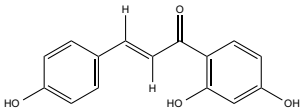
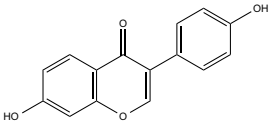
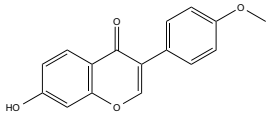
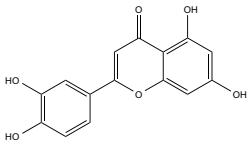
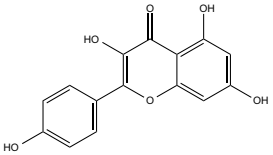
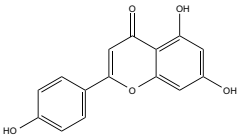
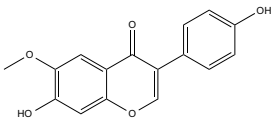
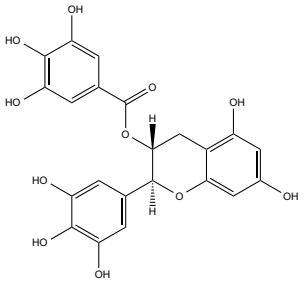
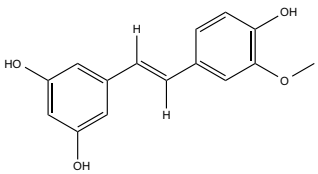
In addition to regulating oxidative imbalance, ER signaling can also be targeted for mitochondrial stress adaption. Mitochondrial dysfunction has long been known to play a critical role in tumor growth and has been linked to the expression of hormone receptors in several kinds of malignancies [277]. Studies showed that higher intracellular ROS and Ca^{2+} caused by mitochondrial stress adaptation are linked to AREG expression and secretion, where upregulated AREG further activates ERα through PI3K/Akt/mTOR and ERK pathways [278]. As a result, mitochondrial stress adaption through ER signaling could be a potential therapeutic target for the treatment of drug resistance [279].

Given the therapeutic benefits of HRT in neuroprotection [180, 280-283], various animal studies and a randomized controlled trial by the Women's Health Initiative (WHI) evidenced increased ischemic lesions in HRT [284-287], albeit the E2 on stroke have been mainly remaining contradictory. Other studies have described this effect of E2 on stroke as hormesis [288], a biphasic dose-response relationship, in which cellular exposure to a particular toxin at low concentrations develops resistance to future interactions with more significant concentrations, which might be described as an adaptive response to ongoing cellular stressors [289-292]. It is evident that ER signaling has hormetic phenomena, as a single receptor regulates multiple complex pathways [293], and thus studies evidenced the detrimental effect of E2 because of prolonged and higher concentrations on stroke models, while physiological concentrations are protective [284-287]. While describing the hormesis regulation by E2, other studies implied that higher concentrations of the female hormone are anti-inflammatory; on the contrary, low concentrations showed pro-inflammatory action [283, 294-296].

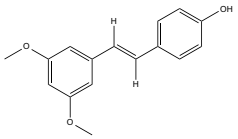
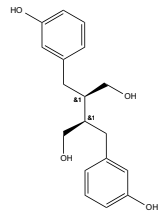
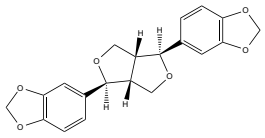
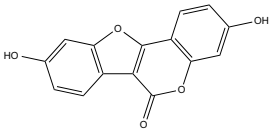
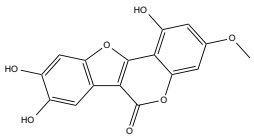
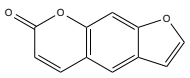
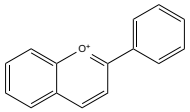
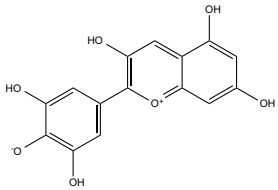
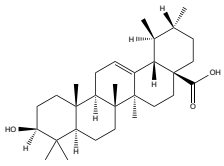
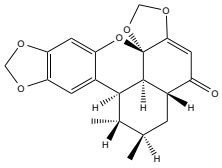
Again, hormetic pathways activation is regulated by vitagene brain axis activation that encodes several protein systems, including molecular chaperons (HSPs), sirtuin, and thioredoxin, which are essential redox-dependent regulators of ROS that exert effects ranging from physiological signaling to physiopathological consequences [283, 297, 298]. As described earlier, both E2 and natural antioxidants, including phytoestrogens, have been neuroprotective by activating hormetic pathways regulated by the vitagene protein network [299]. Unless used as dietary supplements, phytoestrogens are generally present in the food in chemical combinations. While large amounts of phytoestrogens may have no deleterious impact on an adult, they may negatively affect infant growth [299]. As both E2 and phytoestrogens exhibit non-monotonic and hormetic dosage responses, the design of pre-clinical and clinical trials, as well as approaches for optimum patient dosing in the treatment of neurodegeneration, are more challenging [300]. These conflicting findings of whether concentration ranges of E2s are neurotoxic or neuroprotective may be due to organ variations or inconsistencies in the measured end-points. Thus bearing hormesis in mind, experiments aimed to reveal the appropriate biological and therapeutic effects of E2 should thus be designed and conducted with a broad range of dosages. The biological relevance of these doses should be evaluated by blood hormone readings and subsequent comparison with the desired biological/clinical scenario [301].

A subsequent question still remains regarding the bioavailability of natural products when the compounds are targeted for CNS diseases. Collecting evidence suggested that natural products generally fail to acquire adequate levels in the brain due to the poor bioavailability and BBB crossing ability. As poor bioavailabilities share the reason for clinical failure, more care should be taken when considering the natural products in clinical settings, emphasizing tolerances, safety, effectiveness, bioavailabilities, and biodistributions. Treatment with curcumin, for example, is challenging due to its instability, poor bioavailability, and instant body clearance [302]. In a clinical trial setting with Alzheimer's patients, curcumin was unsuccessful in reversing cognitive impairment and discontinued due to gastrointestinal issues [303]. Nevertheless, many efforts have improved curcumin bioavailability by applying different drug delivery approaches [304-307]. Hu *et al.* found that curcumin has minor impacts on cognition and mood in aged people and changes plasma biomarkers in a population of middle-aged people when administrated at 400 mg per day as a solid nanoparticle-based preparation, which ensured adequate plasma curcumin levels [308]. Chen *et al.* confirmed that mesoporous polydopamine nanoparticles loaded with curcumin enhance radioprotection in BEAS-2B cells and radiation pneumonitis rat model by increasing the anti-oxidant system, downregulating proinflammatory cytokines, and reducing apoptosis and tissue damages [309]. This novel observation calls for an extensive study to design a new delivery approach for natural ER modulators to prevent age-related diseases induced by radiation.

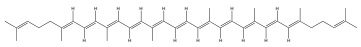
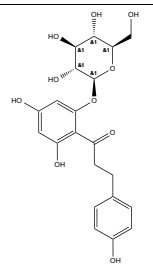
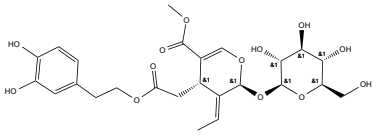
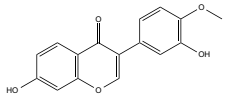
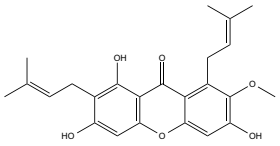
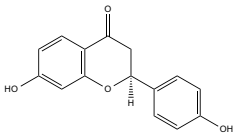
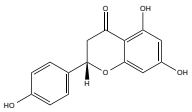
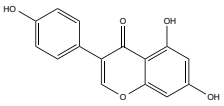
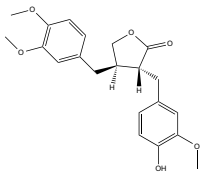
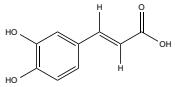
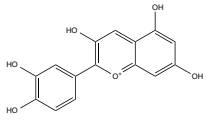
Table 3. List of phytoestrogens and their biological functions in numerous study models.

Compound	Chemical Structure	ER Pharmacology	Treatment (dose)	Experimental Model	Cellular Functions	References
Isoliquiritigenin		ERα	25-50 mM	*In vitro* (MDA-MB-231, MCF-7)	↓MMP-2 and MMP-9, PI3K expression ↑p38 phosphorylation ↓NF-κB DNA binding and Akt kinase activity	[321, 322]
Daidzein		ERα	0- 100 μM	*In vitro* (MCF-7)	↑ ROS generation, ↑ Bax, cyt-c. ↑ Caspase-9 and caspase-7, ↓ Bcl-2 protein level	[323, 324]
Formononetin		ERβ	30–100 μM	*In vitro* and in *vivo* (MCF-7)	↓p-IGF-1 R, p-Akt, cyclin D1 protein and cyclin D1 mRNA expression ↑G0/G1 phase arrest ↓IGF1/IGF1R-PI3K/Akt pathways	[325, 326]
Luteolin		ERα	40 μmol/L	*In vitro* (MCF-7)	↓pIGF-1 and PI3K-Akt pathway.	[327, 328]
Kaempferol		ERα		*In vitro* (MDA-MB-231and BT474)	↑ DNA damage ↑ Arrest at G_1, G_2 and G_2/M phase ↑ Expression of γH2AX, ↓ Caspase 3 and 9	[329, 330]
Apigenin		ERα	5–20 μM	*In vitro* and *in vivo* (MDA-MB231)	↓Pro-intravasation trigger factors and MMP1 expression ↓ CYP1A1 activity	[329, 331]
Glycitein		ERα	10-100 mg/ml	*In vitro* SKBR-3 cells	↑ Membrane permeability ↓ DNA synthesis	[323, 332]
Gallocatechin-3-gallate		ERα	20 μg/ml	*in vitro* and *in vivo*	↓ miR-25 expression ↑Pro-caspase-3 and pro-caspase-9 and PARP. ↑ Arrest G2/M phase	[274, 333]
Isorhapontigenin (ISO)		ERα		*In vitro* (MCF7, T47D)	↑ SPHK/tubulin destabilization ↑ ROS Production ↑ Cleaved PARP, cytoplasmic Cytochrome-C, cleaved caspase-3, and cleaved caspase-9	[334, 335]

(Table 3) contd….

Compound	Chemical Structure	ER Pharmacology	Treatment (dose)	Experimental Model	Cellular Functions	References
Pterostilbene		ERα	50-75 μmol/L	*In vitro* (MCF-7 and MDA-MB-231)	↑Cytosolic Smac/DIABLO expression ↑MnSOD activity ↑Cytosolic calcium concentrations	[336, 337]
Enterodiol		ERα, ERβ	25- 75 μM	*In vitro* (MDA-MB-231)	↓ MAPK-p38 ↓ERK-1/2, NF-Kb ↓ Snail (mRNA & protein)	[338, 339]
Sesamin		ERα	12.5-100 μM	*In vitro* (MCF-7)	↑ Phosphorylation of RB and ↑Degradation of cyclin D1	[340, 341]
Coumestrol		ERα, ERβ	50 μM	*In vitro* (MCF-7)	↑ ROS production ↑ p53 and p21Cip1/WAF1 activity	[342, 343]
Wedelolactone		ERα, ERβ	12.78- 27.8 μM	*In vitro* (MDA-MB-231, MDA-MB-468 and T47D)	↑ Chymotrypsin-like activity	[344, 345]
Psoralen		ERα	0–65 μg/ml	*In vitro and in vivo* (MCF-7 & MDA-MB-231)	↑ G0/G1 & G2/M phase arrest ↓ Fra-1 & β-catenin expression ↑ Axin2 & phospho-(Y142) β-catenin expression	[346, 347]
Anthocyanin		ERα		*In vitro and vivo*N202/1A and N202/1E	↑Oxidative stress ↑AMPK signalling pathway	[348, 349]
Delphinidin		ERα	25–1000 μg/ml	*In vitro* (MDA-MB-453)	↑ Cell cycle arrests the G1 phase.	[350, 351]
Ursolic acid		ERα	≥10 μM	*In vitro* (MDA-MB-231)	↓ Nrf2 expression ↓ Keap1/Nrf2 pathway and EGFR/Nrf2 pathway	[352, 353]
Sauchinone		ERα	50 g/ml	*In vitro* (MCF-7)	↓VEGF, cyclin D1, and Bcl-2 gene products ↑Activate caspase ↑ ERK signalling pathway	[354, 355]

(Table 3) contd….

Compound	Chemical Structure	ER Pharmacology	Treatment (dose)	Experimental Model	Cellular Functions	References
Lycopene		ERα, ERβ	50 μM	*In vitro* (MDA-MB-468 c)	↑G0/G1 phase arrest ↑Activation of the ERK1/2 ↑p21 upregulation and Bax ↑Akt and mTOR activation	[356, 357]
Phloridzin		ERs	10-150 μM	*In vitro* (MDA-MB-231)	↓Paxillin/FAK, Src, and α-Sma expression. ↑p53, p21, and E-cadherin ↓Type 2 glucose trans-porter.	[358]
Oleuropein		ERα	100-200 μg/ml	*In vitro* (MCF-7)	↑Blocks G_1 to S ↑G_0/G_1 phase stability	[359, 360]
Calycosin		ERα, ERβ	0-150 μM	*In vitro* (MDA-MB-231)	↓Rab27B-dependent signaling ↑β-catenin and VEGF modulation	[361, 362]
α-Mangostin		ERα	10 μM	*In vitro* (MCF-7)	↑Activate-7, -8 and -9, Bax, p53, cytosolic cyto-chrome c and induced PARP cleavage ↓Bid and Bcl-2	[363]
Liquiritigenin		ERβ	50 μM	*In vitro* (HT22 cell)	↓Ca^{2}+ influx, ↓ROS production ↓Lipid peroxidation ↓Mitochondrial stress ↓MAPKs, ERK, c-JNK signaling pathways	[364, 365]
Naringenin		Partial ER ago-nist	25-100 mg/kg/b.wt,	*In vivo* C57BL/6J mice	↓Lipid peroxidation ↑Glutathione reductase and catalase ↓iNOS expression	[366, 367]
Genistein		SERM	0.01-1 uM	*In vivo* Sprague–Dawley rat embryos	↓Bcl-2/Bax ↓Caspase-9 and caspase-3 activities ↓NF-κB/p65, phosphorylation of p65 and IκB, ↓MAPK JNK and ERK signaling	[368, 369]
Arctigenin		ERβ agonist		*In vitro* (H89, SH-SY5Y cell)	↓Aβdeposition, p-CREB. ↓Presenilin 1(PS1]	[370], [312]
Caffeic acid		ERα	10 μmol/kg (7 days)	Male Sprague-Dawley rats, 9–10 weeks, 110–120	↓ MDA, XO and ADA ↑ NO(x) and SOD	[371, 372]
Cyanidin		ERβ	50-200, mg/kg/d	Kunming mice	Not mentioned	[348, 373]

The therapeutic benefits of phytoestrogenic substances and the molecular processes underpinning their positive effects in reducing inflammation, oxidative stress, and neuronal loss after menopause are well documented [307]. These advantages might also explain why they influence cognitive deficiencies in animal models of different NDDs. Remarkably, a combination of herbal supplements (a mixture of estrogenic substances) in a recent clinical study is found to be beneficial and safe to reduce menopausal symptoms [310]. As phytoestrogens and their derivatives can replicate the therapeutic consequence of natural E2, targeting ER signaling with phytoestrogen is seen as a viable way to avoid the onset and progression of NDDs [307]. There has also been a growing interest in phytoestrogens as a radioprotective agent in other organ-specific damages. For instance, genistein is an isoflavone phytoestrogen [311], and is considered a potent SERM due to having a binding affinity with ERα [312], ERβ [313], and GPR30 [314]. This phytoestrogen was trialed clinically and could attenuate the adverse effects of chemotherapy and RT [315, 316]. Moreover, genistein provides protection against radiation-induced bone marrow [317, 318], lung damage [319], and DNA damage in several types of cells [320]. However, the therapeutic activities of genistein against radiation-induced brain damage are still unknown. Similarly, many potential phytoestrogens are already identified to modulate ER signaling (Table **3**); some of them might provide cytoprotection against radiation-induced injury, while detailed information regarding the mechanism is scarce. As a result, this review recommends a high-throughput screening for the radiation-induced NDDs, along with pre-clinical and clinical studies to disclose the novel mechanisms of these phytoestrogens, which may yield promising pharmacological leads for the treatment of various NDDs.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This work was supported by the National Research Foundation of Korea (NRF) grant (No. NRF-2021R1A2C1008564) to ISM, funded by the Korean Ministry of Science and ICT.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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