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REVIEW ARTICLE

Phytochemicals Targeting Oxidative Stress, Interconnected Neuroinflammatory, and Neuroapoptotic Pathways Following Radiation

Sajad Fakhri[1,*], Sana Piri[1,#], Seyed Zachariah Moradi[1,2,#] and Haroon Khan[3,*]

[1]*Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah 6734667149, Iran;* [2]*Medical Biology Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah 6734667149, Iran;* [3]*Department of Pharmacy, Abdul Wali Khan University Mardan, 23200, Pakistan*

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Abstract: The radiation for therapeutic purposes has shown positive effects in different contexts; however, it can increase the risk of many age-related and neurodegenerative diseases such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and Parkinson's disease (PD). These different outcomes highlight a dose-response phenomenon called hormesis. Prevailing studies indicate that high doses of radiation could play several destructive roles in triggering oxidative stress, neuroapoptosis, and neuroinflammation in neurodegeneration. However, there is a lack of effective treatments in combating radiation-induced neurodegeneration, and the present drugs suffer from some drawbacks, including side effects and drug resistance. Among natural entities, polyphenols are suggested as multi-target agents affecting the dysregulated pathogenic mechanisms in neurodegenerative disease. This review discusses the destructive effects of radiation on the induction of neurodegenerative diseases by dysregulating oxidative stress, apoptosis, and inflammation. We also describe the promising effects of polyphenols and other candidate phytochemicals in preventing and treating radiation-induced neurodegenerative disorders, aiming to find novel/potential therapeutic compounds against such disorders.

Keywords: Neurodegeneration, polyphenols, phytochemicals, radiation, oxidative stress, inflammation, apoptosis.

1. INTRODUCTION

Neurodegenerative diseases are relatively well-known as progressive degeneration of the structure or dysfunction of central nervous system (CNS) neurons. Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and Parkinson's disease (PD) are amongst the most common neurodegenerative diseases [1] affected by radiation. Radiation has shown potential applications in various fields of science such as medicine [2]. Although high doses of radiation can exacerbate neurodegenerative diseases, there is no conclusive evidence that low doses in radiotherapy cause neurodegeneration. Besides, several studies have demonstrated the adverse effects of radiation on human health towards neurodegenerative diseases' progression. This procedure highlights the importance of a general biphasic dose-response relationship named hormesis, regarding arriving at suitable doses [3, 4].

From the mechanistic point of view, high doses of radiation induce oxidative stress, inflammation, apoptosis, and mitochondrial dysfunction, which play essential roles in the pathology of neurodegeneration [1, 5]. In this regard, radiation activates oxidative stress *via* an increase in the levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [6, 7]. The relationship between free radicals and radiation has been well-established, such that radiation-induced ROS production causes brain injury and neural cell apoptosis [5]. Apoptosis is yet another critical pathway interconnected with radiation. Radiation leads to cell apoptosis through modifying the caspase-3 and p53 activities during neurodegeneration. Consequently, p53, in turn, controls the levels of produced ROS *via* different mechanisms such as enhancing the expression of the superoxide dismutase (SOD) gene [8, 9]. The mediators involved in the inflammatory processes are among other pathways that may be stimulated by radiation. Radiation can cause an increase in the expression of tumor necrosis factor-α (TNF-α), intercellular adhesion molecule 1 (ICAM-1), interleukin-1 beta (IL-1β), and cyclooxygenase-2 (COX-2) [10].

Radiation also remarkably increases the concentration and activity of activator protein-1 (AP-1), cyclic adenosine monophosphate (cAMP), cAMP response element-binding protein (CREB), and nuclear factor kappa B (NF-κB). In this line, NF-κB was introduced as an important player in radiation-induced neuronal damage [11, 12].

*Address correspondence to these author at the Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah 6734667149, Iran; E-mail: Sajad.fakhri@kums.ac.ir
Department of Pharmacy, Abdul Wali Khan University Mardan, 23200, Pakistan; E-mail: haroonkhan@awkum.edu.pk
#*These authors have contributed equally to this work.*

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Nowadays, there are concerns over the effect of radiation on human health [13]. Fortunately, many natural products have shown anti-inflammatory, antioxidative, and anti-apoptotic effects [14-16].

Extensive experiments have introduced polyphenols and some candidate phytochemicals as hopeful radioprotective agents. From the mechanistic point, phytochemicals have shown protective properties in neuronal disorders by involving radical scavenging factors, iron-chelating activities, and anti-inflammatory properties. Besides, these secondary metabolites decline DNA lesions after gamma radiation, decreasing malondialdehyde (MDA) and suppressing caspase-3 activities. Inhibiting the radiation-induced apoptosis and ROS generation, as well as increasing the levels of antioxidant elements, such as glutathione peroxidase (GPx), catalase (CAT), and SOD, are amongst other mechanisms of action of candidate phytochemicals.

Several previous studies have shown miscellaneous radioprotective agents [17], traditional Chinese medicine [18], or natural products in combating radiation. However, there is no focus on the neuroprotective mechanisms of polyphenols and candidate phytochemicals against radiation. This review aims to show major dysregulated signaling pathways in neurodegenerative disorders induced by radiation. The current study also highlights advances in neuroprotective effects of polyphenols and candidate phytochemicals against radiation-induced neurodegeneration.

2. HORMETIC MECHANISMS AND RADIATION HORMESIS

Arriving at the right dose is a major key point towards a successful therapy against neurodegeneration; however, this procedure would be challenging due to human inter-individual variation affected by gender, age, diet, genetics, exercise, and health status [3, 4, 19]. As a general biphasic dose-response relationship, hormesis is a dose-response phenomenon known by low-dose stimulation and a high-dose inhibition of biological responses, represented by either graphical J/U-shaped or an inverted U-shaped dose-response curve [20]. Hormetic responses are triggered by various stimuli, including dietary restriction, chemical exposures, hypoxia, thermal/light/electricity extremes, physical stress, and ionizing radiation [21].

Accordingly, while high doses of radiation indicate cellular damage, decreased doses represent adaptive biological performance, including cognition, growth, longevity, bone density, and other biological activities. Following evaluating the effects of radiation and some other therapeutic agents, similar dose-response curves were reported by researchers. The hormetic dose-response confers a new set of interpretations for the dose-response [3]. Considering the hormetic responses, it would be more accessible to predict desirable drug-induced responses and prevent the associated side effects of therapies. On the other hand, ignoring hermetic responses could fail preclinical studies during the afterward clinical trials. Therefore, there is a need to develop hormetic dose-response for biological systems towards a desirable clinical effect [20].

Accordingly, researchers should modify the sensitivity or susceptibility of the individuals to therapeutic agents regarding the drawbacks of the limitations in hermetic curves. In this line, subjects with resistance to drug therapy encounter a right-shifted dose-response curve in hormetic response. In contrast, individuals with higher drug susceptibility would have hormetic response shifted to the left. Thus, hormetic dose-response could be a critical challenge, especially in the developments of those drugs with concerns of being extrapolated to clinical results.

In this regard, activating hormetic pathways by developing alternative agents without associated risks, as in radiation, could be considered a step forward. These neuroprotective responses of subtoxic doses are termed preconditioning [22] under the hormesis umbrella [23]. Consequently, exposure to low doses of toxicants could protect against the toxicity of subsequent high doses, such named hormesis or preconditioning [24]. Of other examples, exposure of cells to moderate transient stress protects them against more severe stresses [25]. According to that, radiation hormesis hypothesizes that low doses of ionization apply beneficial effects towards stimulating repair mechanisms. Therefore, multiple neuroprotective effects are mediated by pre- /post-conditioning induced by the quantitative features of the hormetic dose-response. The preconditioning concept is variously termed adaptive response in ionizing radiation and rebound effects in phytochemicals [19]. Thus, it has been increasingly clear that hormesis could affect several neurodegenerative endpoints through a direct stimulation of preconditioning [21].

Hormesis could provide central supports for neuroprotective responses by providing a dose-response relationship, mechanistic features, and associated relationship to biological plasticity and developing a bright insight for improving the dose accuracy within the heterogeneous population of humans. Overall, mechanistic details of hormetic dose-responses and endogenous cellular defence pathways integrate preconditioning and adaptive stress responses to prevent neurodegenerative diseases [26, 27]. Furthermore, these hormetic responses are mediated by activating antioxidant mediators (*e.g.*, Nrf2-Keap1/ARE) and inhibiting inflammation/apoptosis and other involved enzymes/mediators [28-30].

The current mechanistic review has highlighted the modulatory roles of phytochemicals against high hermetic doses of radiations.

3. RADIATION TRIGGERS OXIDATIVE STRESS

Extensive studies have indicated that radiation can lead to disturbances in learning, memory, and spatial information processing [31]. The injury could result from DNA damages in mammalian cells and the induction of oxidative responses. This response promotes CNS damage and triggers various mechanisms and signaling pathways such as apoptosis and inflammation [32-34] (Fig. **1**). Accordingly, radiation affects various signaling mediators such as diacylglycerol formation, protein kinases C (PKC), NF-κB, AP-1, and signal transducer and activator of transcription (STAT) [35]. Limoli *et al.* suggested ROS as a major key player during the procedure of radiation-induced responses in neural cells [31]. UVA radiation increased the generation of hydrogen peroxide (H_2O_2), superoxide anion ($O_2^{\cdot-}$), and hydroxyl anion

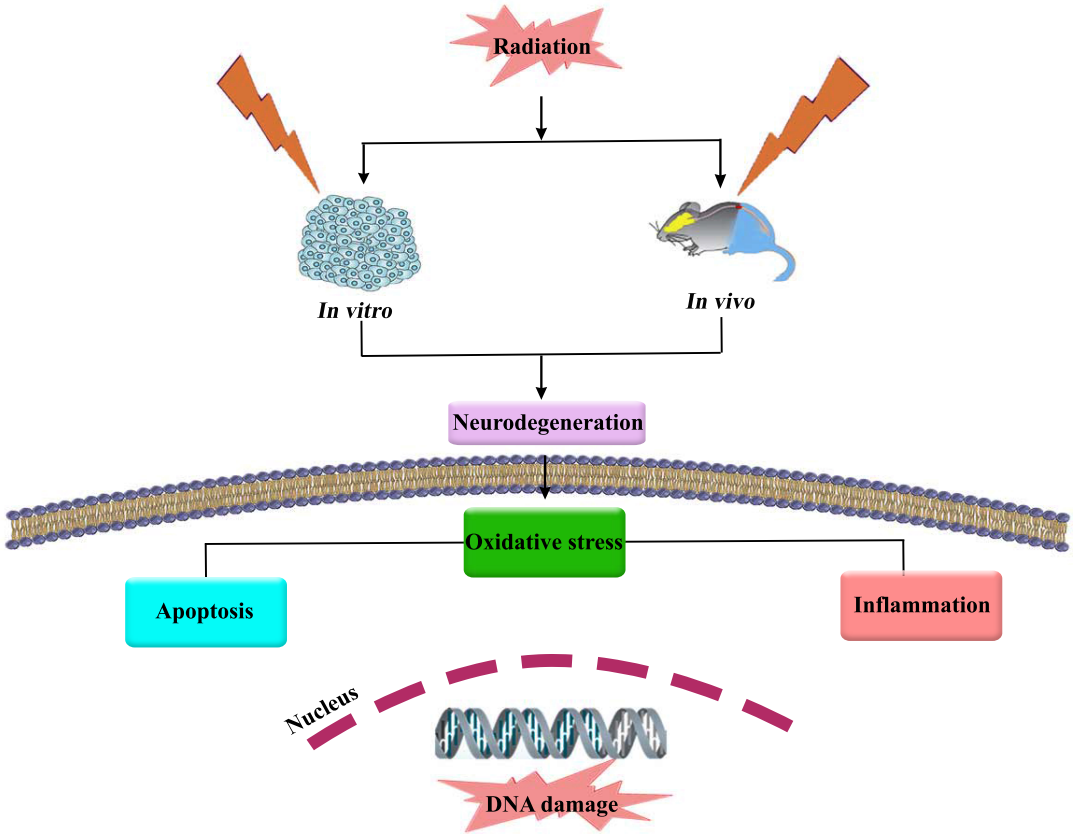

Fig. (1). Radiation causes neurodegeneration through oxidative stress, inflammation and apoptosis. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

(OH^-). The excessive ROS generation by UVA is undesirable and can damage several antioxidant enzymes like SOD, GPx, CAT, and glutathione (GSH) [36]. Furthermore, microwave radiation at 900, 1800, and 2450 megahertz (MHz) alters the levels of MDA, CAT, GSH, and SOD [2]. Bilgici *et al.* indicated that 900 MHz electromagnetic fields (EMF) increased oxidative stress, lipid peroxidation (LPO), and nitric oxide (NO) levels in serum, as well as a decreased level of SOD and GPx [37]. In a similar study, Heinloth *et al.* indicated that the mitogen-activated protein kinase (MAPK) pathway is affected by UV radiation [38]. Furthermore, it was observed that radiation had a critical role in precancerous skin lesions (or conditions) and skin cancers, possibly through induction of oxidative stress and apoptosis cross-talk [39]. Research has shown that gamma radiation influences the cell cycle phases by declining the expression of the genes involved in the cell cycle, such as *FEN1* (Flap endonuclase1), *RFC3* (replication factor C subunit 3), and *RFC4* (replication factor C subunit 4) [40]. Lee *et al.* indicated that ionizing radiation increased c-Jun levels by phosphorylating Ser63 and Ser73 residues [41]. High levels of polyunsaturated fatty acids (PUFAs), such as docosahexaenoic acid and eicosapentaenoic acid, as well as high iron content, increased O_2- content, and insufficient antioxidant defence system, cause damages in the brain [2, 42]. There are also close associations between radiation and PUFAs [43], as well as radiation and iron [44] in triggering oxidative damage. Several signaling pathways are activated in response to ionizing radiation, such as PKC, MAPK, p53, NF-κB, ataxia telangiectasia mutated (ATM), and DNA-dependent protein kinase (DNAPK) [45]. It has been observed that a low dose of radiation activates the PKC, thereby leading to increased expression of c-fos, c-jun, c-myc, and c-Ha-ras [46]. Moreover, ionizing radiation activates extracellular signal-regulated kinases (ERK1/2) by activating epidermal growth factor (EGF) receptors, mitogen-activated protein kinase kinase (MEK1), c-Jun N-terminal kinases (JNK), and p38 [46, 47]. Besides, ionizing radiation causes epigenetic changes by interfering with DNA methyltransferases and DNA histones and increasing the generation of ROS [48]. Researchers showed that 1800 MHz radiofrequency radiation-induced oxidative stress is followed by DNA damage. Oxidative stress induced by ionizing radiation, UV radiation, and pathogens promote the generation of ROS. ROS products (*e.g.*, peroxides, superoxide, hydroxyl radical, singlet oxygen, and α-oxygen) damage macromolecules, including lipids, proteins, and DNA, regarding contribution to neurodegenerative disorders [9, 48, 49]. Indeed, radiation induces ceramide (CER) production as one of the important mediators of oxidative stress and apoptosis in neuronal cells, thereby leading to the progression of neurodegenerative diseases [35]. Activation of NADPH oxidase is another mechanism of radiation-induced DNA injury [48, 50], interfering with the expression and function of NF-κB and c-Jun, consequently increasing the level of β-secretase by activated c-Jun amino-terminal kinase and p38MAPK [51-53].

As mentioned earlier, oxidative stress, like neuroinflammation, is one of the most important mechanisms in neurodegeneration pathology. Also, extensive evidence shows the key role of radiation in the progress of AD through augmenting oxidative stress. Numerous studies have shown a link between amyloid-beta (Aβ) plaques in the brain and oxidative stress, inflammation, neuronal loss, and neurofibrillary tangles (NFT) formation, as well as increased level of MDA [54-58]. As synaptic flexibility is important and responsible for cognitive deficits resulting from neuron death, research has elucidated that oxidative stress lowers synaptic flexibility in neurodegenerative disorders [59]. Under oxidative stress conditions, as ROS production increases, it enhances the accumulation of Aβ peptides in AD. The resulting amyloid plaques can increase ROS production through the MAPK and result in pathological phenomena such as NFTs formation and enhanced oxidative stress [54-58]. Also, Aβ plaques can deplete the concentration of calcium ions in the endoplasmic reticulum, leading to reduced levels of GSH and increased ROS generation in the neurons. Besides, oxidative stress-activated N-methyl-D-aspartate-type glutamate receptors (NMDARs) lead to increased production of calcium ions, increased intracellular calcium, and instigate mitochondrial damage, which augments ROS production and activates caspases/proteases [60, 61]. Furthermore, ROS targets mitochondrial enzymes, for example, α-ketoglutarate dehydrogenase, aconitase, and JNK/stress-activated protein kinase pathway. This cascade plays a significant role in the phosphorylation of tau protein and Aβ peptides [60, 62]. Besides, it has been found that radiation can mitigate the density of dendritic spines and change spine structure. Also, it can increase amyloid protein precursor/presenilin1 and enhance abnormal tau phosphorylation, which contributes to amyloid-induced pathology in AD patients [63, 64]. It was shown that short and long radiation in different intervals remarkably increased ROS and RNS levels in neural cells. The generation of free radicals and enhanced ROS lead to dopaminergic neuronal loss in PD. It is due to the sensitivity of dopaminergic neurons to oxidative stress.

Mitochondria are amongst the key targets of low-dose radiations. It has been shown that after gamma radiation, antioxidant molecules are increased in PD [65-69]. Neuroepigenetic mechanisms could be viewed as key contributors to radiation-induced brain damage. For instance, increased expression of DNA methyltransferase 1 and 3a, as two associated epigenetic enzymes, can cause cognitive dysfunction and neurodegenerative disorders following radiation [70, 71].

The expression of various genes, such as ATP-binding cassette sub-family A member 7 (*ABCA7*), Apolipoprotein E (*APOE*), Myc box-dependent-interacting protein 1 (*BIN1*), CD2-associated protein (*CD2AP*), clusterin (*CLU*), complement receptor type 1 (CR1), membrane-spanning 4-domains A4E (*MS4A4E*), Membrane-Spanning 4-Domains A6A (*MS4A6A*), and phosphatidylinositol binding clathrin assembly protein (*PICALM*), are altered in AD. These genes could also be induced after radiation and activate troponin T1 gene (TNNT1) expression in CNS [72-76]. A similar study confirmed that radiation-induced oxidative stress leads to telomere shortening and an increased mortality rate in AD [77].

ALS is another neurodegenerative disease that results in mutations in SOD1 [78]. SOD is an important enzyme playing a role in various functions such as free radical scavenging, energy metabolism, and post-translational modifications [79]. Dučić and co-workers showed that in a rat model of ALS (hSOD1 G93A), LPO level, spotted SOD, and Copper, Zinc, and Nickle ion levels were increased. The aptitude of the ALS model astrocytes was enhanced to oxidative stress that indicates the particular metabolic changes in these cells, which may be relevant and effective in the progression of the disease [80]. Evidence also indicates that a low dose-radiation increases the levels of vascular endothelial growth factor (VEGF) and growth-associated protein 43 (GAP-43), while high dose-radiation induces demyelination [81]. In this regard, while low doses of radiation lead to cognitive dysfunction, high doses facilitate obvious microscopic alterations such as structural changes [67]. Extensive research has indicated that ionizing radiation can change the morphology of neurons and decrease the length, complexity, and density of dendritic spines, and change spine structure [59]. Belka and co-authors reported increased levels of interferon-gamma (IFN-γ), TNF-α, and adhesion molecules following ionizing radiation [82]. Dynamin-related protein-1 (Drp-1), as a mediator of mitochondrial fission, is implicated in apoptosis and accumulates in mitochondria after radiations [83]. The role of radiation in triggering the redox system, inflammation, and apoptosis has been provided in Fig. (**1**).

Evidence has also shown a close link between oxidative stress and inflammation/apoptotic pathways/mediators [84].

4. RADIATION CAUSES NEUROINFLAMMATION AND NEUROAPOPTOSIS

Growing reports are revealing the crucial role of radiation in triggering inflammatory/apoptotic pathways in the CNS. Evidence has shown that radiation can induce apoptosis, suppress the activation of caspase-3, and increase the levels/activity of platelet endothelial cell adhesion molecule (PECAM-1), E and P selectins, chemokine (C-X-C motif), ligand 1 (CXCL1), CXCL2, and ICAM-1 [85-89]. ICAM-1, also known as Cluster of Differentiation 54 (CD54), is an important protein with an undeniable role in the immune system in response to radiation [90, 91]. SOD can properly inhibit the radiation-induced inflammation response of other oxidative factors by decreasing oxidative stress and ICAM-1 [91]. Furthermore, protease-activated receptors (PARs), as G-protein coupled receptors, are increased after radiation [89]. In addition, Denning *et al.* found that UV radiation can activate the death receptors such as Fas (CD95/APO-1) and TNFR to activate caspase-8 and caspase-9 [92, 93]. Moreover, Bax and TNF-α are increased following radiation owing to the enhancement of early growth response protein 1 (EGR-1) [94, 95].

It also has been shown that UV radiation causes phosphorylation in several different serine and threonine residues of the p53 protein [96]. There are four critical phosphorylation sites in p53; Ser392, which is important for p53 oligomerization, Ser15, Ser20, and Ser37, which are important for p53 stabilization as well as the interaction of p53 serine residues with p300/CREB-binding protein (CBP), and P300/CBP-associated factor (PCAF) [96-99]. Studies have

indicated that radiation activates p53, stress-activated protein kinase (SAPKs), and the p38 kinase pathways [96]. Chen and colleagues found that two genes, *c-Ha-ras,* and *c-myc*, have impressive roles in radiation-induced apoptosis [100]. Also, irradiation increased the level of IFN-γ, an important cytokine with important roles in innate and adaptive immunity [101]. Evidence suggests that radiation enhances and accelerates the production of ROS/RNS, dependent on the modulation of mitochondrial functions or NADPH oxidase-1 (NOX-1) activity that has a key function in ROS generation post-radiation [102, 103]. Furthermore, it induces the expression of high mobility group protein 1 (HMGP1) that can lead to the activation of p53 and some proteins from the HSP70 family, protecting cells from stress in the extracellular space [104]. Researchers also have introduced the MAPK pathway as a critical player in radiation-induced apoptosis. Radiation can also induce apoptosis through the mitochondrial pathway and activation of JNK, increase the level of Bax, and decrease in the level of Bcl-2 [105, 106]. Also, ceramide production as a consequence of sphingomyelin hydrolysis after ionizing radiation can initiate apoptosis and facilitate PKC activation. It has been found that radiation inhibits anti-apoptotic enzymes such as phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt) pathway as well as SAPK or JNK and p38MAPK [107-110]. Results obtained from the study of Shan *et al.* emphasized that radiation increased the levels of toll-like receptor 4- myeloid differentiation factor 2 (TLR4-MD-2), cluster of differentiation 14 (CD14), and myeloid differentiation primary response 88 (MyD88) as well as pro-inflammatory cytokines [111, 112]. In a similar study, gamma radiation increased the levels of cyclin B1 protein, which regulates radiation-induced apoptosis [113]. Studies have elucidated that radiation could induce the transcription of some factors, including AP-1 and NF-κB, associated with p50, p52, RelA (p65), RelB, and c-Rel [114, 115].

It has been shown that ASK1-JNK/p38MAPK signaling pathways have essential roles in response to UV radiation, cytokines, heat shock, hyperosmotic and ionizing stressors [114, 116, 117]. In addition, evidence has shown that radiation facilitates apoptosis and inflammation processes and induces apoptotic mediators such as caspases through intrinsic and extrinsic pathways [118]. Mitogen-activated protein kinase-4 (MKK4/SEK1), JNK, and AP-1 signaling pathway, as well as caspase-9, caspase-3, Bcl-2, Fas-L, and cytokines such as monocyte chemoattractant protein 1 (MCP-1), and IL-6, are some of the other critical signaling pathways and proteins which may undergo changes and play a role following radiation [119-121]. Radiation can activate NF-κB through MEK/extracellular signal-regulated kinase (ERK)/P90 signaling pathway. Besides, it induces COX-2, TNF-α, IL-1α, IL-1β, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-4, IL-5, IL-10, IL-12, IL-18, and transforming growth factor-beta (TGF-β) [122]. Previous studies have suggested that low-intensity radiation remarkably increases IL-2, IL-6, TNF-α, and IFN-γ [2]. In addition, IL-1β leads to activation of matrix metalloproteinases (MMPs), a group of zinc-dependent enzymes that regulate extracellular matrix (ECM) components. MMP-9 is one of the most important members of the MMP family, which has an essential role in neuroinflammation *via* the activation of several cytokines and chemokines [123-125]. Evidence has shown that inflammatory cells such as macrophages, lymphocytes, astrocytes, and microglia express and release chemokines, neurotransmitters, cytokines, and ROS, leading to neuronal damage, thereby accelerating the progression of neurodegenerative diseases [123, 126-129].

Studies have suggested that neuroinflammation and neuroapoptosis play important roles in neuronal injury in the context of neurodegenerative diseases [130-132]. Reports have shown that microglia play a prominent role in the pathology of neurodegenerative disorders such as PD, ALS, and AD [133]. Indeed, microglia, activated neurotoxic microenvironment, excitatory amino acids, quinolinic acid, complement proteins, reactive oxygen intermediates, and NO lead to AD progression [130, 131, 134-137]. Activated microglia causes the upregulation of various cell surface markers allegorically macrophage antigen complex-1 (MAC-1). This procedure promotes phagocytosis and the generation of cytotoxic molecules, including ROS, nitric oxide (NO), and several pro-inflammatory cytokines. On such a basis, activated microglia can bring about considerable cell damages with an outstanding role in the pathogenesis of neuronal diseases. Inhibition of microglial activation can prevent dopaminergic neuronal loss and could be considered a treatment option for PD [138, 139]. Additionally, it has been observed that the IL-1/IL-10 ratio is remarkably increased in AD patients [130]. In AD, death receptor 4 (DR 4) and DR5 can be induced by oligomeric Aβ peptides and trigger caspase-3-dependent apoptosis [140]. Investigations have demonstrated that Aβ binds to inflammatory receptors such as TLR-2, TLR-4 for advanced glycation end products (RAGE), NF-κB, TNF-α, COX-2, and inducible nitric oxide synthase (iNOS) [141].

From the mitochondrial point of view, PTEN-induced kinase 1 (PIKN1) is a mitochondrial kinase involved in Ca^{2+} efflux from mitochondria. Dysfunction of this protein can result in the accumulation of Ca^{2+} and increased ROS levels, followed by apoptosis *in vivo* and *in vitro* [142-145]. Gelders *et al.* observed that the levels of IL-6, IL-12, and IL-15 were increased during PD. Furthermore, α-synuclein expression was induced in PD *via* NF-κB, TNF-α, and IL-β [132, 146, 147].

As another inflammatory mediator, C-reactive protein (CRP) is an acute-phase protein augmented at the sites of inflammation/infection. It plays key roles in the inflammatory and related processes such as phagocytosis, apoptosis, NO release, and the production of cytokines, especially IL-6 and TNF-α, during neurodegeneration [148, 149]. In addition to its role in mitochondrial dysfunction, glutamate mediates excitotoxicity, free radical-mediated oxidative cytotoxicity, and neuroinflammation in the pathology of neurodegenerative disorders. The endoplasmic reticulum is also a key factor [150]. It has been found that endoplasmic reticulum stress can induce apoptosis in the microglia and astrocytes and facilities the gliosis reactive that have an important role in the pathology of neurodegenerative diseases [151-153]. The levels of ROS, COX-2, IL-1β, IL-6, and TNF-α are increased with caspases and mutant SOD1/Bcl-2 aggregation [153, 154]. A unique apoptotic pathway in the motor neurons known as Fas-associated protein with death domain

(FADD)/caspase-8 pathway has been detected that is activated by FAS receptors and Daxx [155]. A correlation between Daxx and MAPK (ASK1) has been observed in motoneuron cell death. Indeed, ASK1 regulates p38 kinase that increases NO level [156]. Necroptosis pathway is described as a particular type of programmed necrosis whose initiation by death receptors requires receptor-interacting serine/threonine kinase 1 (RIP1) and RIP3. Necroptosis takes part in the pathogenesis of various diseases, such as neurodegenerative disorders, ischemic injury, and viral infection. Thus, it may be an attractive/effective target to prevent unwarranted cell death. Extensive studies highlight the activation of necroptosis pathways in the motor neurons. RIP1, RIP3, and mixed lineage kinase domain-like pseudokinase (MLKL) are other important factors in ALS pathology [157]. Studies also have illustrated that Nod-like receptor family pyrin domain 3 (NLRP3), IL-18, and ASC play a role in neurodegeneration conditions such as ALS [158].

Radiation induces inflammation *via* upregulating proinflammatory molecules such as MCP1, chemokine (C-C motif), ligand 2 (CCL2), and CXCL1 [159]. Also, the expression of several chemokine receptors such as chemokine (C-C motif) ligand 7 (CCL7), CCL8, CCL12, CXCL4, C-C chemokine receptor type 1 (CCR1), and CCR2 are increased after radiation [160]. Radiation also enhances inflammatory gene expression, including IL-6, IL-1β, TNF-α, COX-2, and TGF-β [132]. Low dose radiation induces apoptosis in neuron and glial cells in the subventricular zone covering the olfactory bulbs, neocortex, dentate gyrus, striatum, thalamus, amygdala, brain stem, and the cerebral white matter [159]. It has been found that radiation raises the secretion of chemoattractant molecules and migration of monocytes and enhances BBB permeability [160]. NF-κB, as a transcription factor, has important functions and responds to various stimuli such as cytokines, free radicals, UV, and bacterial or viral antigens [161]. It has been demonstrated that cyclin-dependent kinase 5 (Cdk5) is a proline-directed serine-threonine kinase. It plays a fundamental role in memory formation, hippocampal apoptosis, synaptic flexibility, and adult neurogenesis in neurodegenerative diseases. Thus, the level of Cdk5 is increased after radiation and could be proposed as an important target of radiation-induced damage [162, 163]. Unfolded protein response (UPR) is another cellular stress response that induces apoptosis in neurodegenerative disorders. UPR signaling is mediated by protein kinase RNA-activated (PKR)-like ER kinase (PERK), activating transcription factor 6 (ATF6), and IRE1a [164]. Functional experiments show that Aβ and α-Syn activate the UPR signaling in PD, AD, and ALS [164]. Inositol requiring enzyme 1 alpha (IRE1a), JNK, NF-κB or p38, thioredoxin-interacting protein (TXNIP), and transmembrane E3 ligase RNF183 are a number of the most important factors involved in this pathway [164].

5. NATURAL PRODUCTS TARGET OXIDATIVE STRESS, INFLAMMATION, AND APOPTOSIS INDUCED BY RADIATION IN NEURODEGENERATIVE DISEASES

As mentioned in the previous sections, radiation alters cellular antioxidant capacity leading to oxidative stress, increased rate of point mutations, and chromosomal rearrangements [165]. A great deal of evidence has shown that there are different natural products such as polyphenols and candidate phytochemicals with important roles and beneficial effects in preventing, treating, or delaying the progression of neurodegenerative disorders. This event could be induced by radiation exposure by interfering with oxidative stress and other related mechanisms [166]. Besides, inflammation and apoptosis, as two crucial phenomena in close interconnections with oxidative stress, play essential roles in post-radiation neurodegenerative processes. Nowadays, studies have introduced phenolic compounds and other candidate phytochemicals as promising antioxidant, anti-apoptotic, and anti-inflammatory agents in neurodegeneration [167-169]. Fig. (**2**) illustrates selected polyphenols and candidate phytochemicals against radiation-induced neurodegeneration.

5.1. Curcumin

Over the past decade, evidence has revealed that curcumin possesses various biological effects such as antioxidant, anti-inflammatory, antimicrobial, antimutagenic, and anticarcinogenic activities [166, 170]. Rane *et al.* showed that curcumin properly reduces oxidative damage and amyloid-mediated pathological symptoms in AD and inhibits the oligomerization/fibrilization of Aβ protein while inducing Aβ disaggregation [171, 172]. In addition, curcumin binds tau protein and inhibits the aggregation of this protein [171].

From a mechanistic point of view, curcumin has shown an inhibitory effect on ionizing radiation-induced NF-κB signaling pathway and decreased various cytokines such as IL-6, IL-1β, and TNF-α. Accordingly, while radiation reduces the levels of glucocorticoid receptor (GR), CAT, and glutathione S-transferase (GST) [36], curcumin increases concentrations and activities of these antioxidative enzymes, including epoxide hydrolase (EH), SOD, heme oxygenase (HO-1), NAD(P)H Quinone Dehydrogenase 1 (NQO1), and other antioxidant enzymes [168, 173-176]. Soltani *et al*. investigated the beneficial effects of curcumin on the irradiated THP-1 cells. Data points to the improving effects of curcumin on antioxidant defence. It hinders ionizing radiation-induced necrosis by decreasing ROS and LPO levels and increasing CAT and GPx [177]. Besides, curcumin protects against radiation-induced acute/chronic cutaneous toxicity *in vivo*. This effect is applied through diminishing mRNA and protein expression of inflammatory cytokines, including TNF-α, IL-1, IL-6, IL-18, TGF-β, and lymphotoxin-β [178].

As mentioned earlier, radiation augments ROS generation [48], while curcumin decreases ROS in ALS and other brain damage and inhibits inflammatory mediators such as cytokines, chemokines, and oxidative stress in AD [179]. Additionally, curcumin activates nuclear factor-erythroid factor 2-related factor 2 (Nrf2) and suppresses apoptotic mediators (*e.g.*, Bax, Bcl-2, caspase-3, and caspase-9). Altogether, curcumin could be introduced as a promising radioprotective agent against neurodegenerative diseases.

5.2. Resveratrol

Substantial evidence has corroborated that resveratrol has beneficial effects on AD and other neurodegenerative diseases. Resveratrol exerts its neuroprotective effects *via* downregulating inflammation/apoptosis, Aβ aggregation, sirtuin 1 (sirt1), and NF-κB. It also decreases ROS, RNS, IFN-γ,

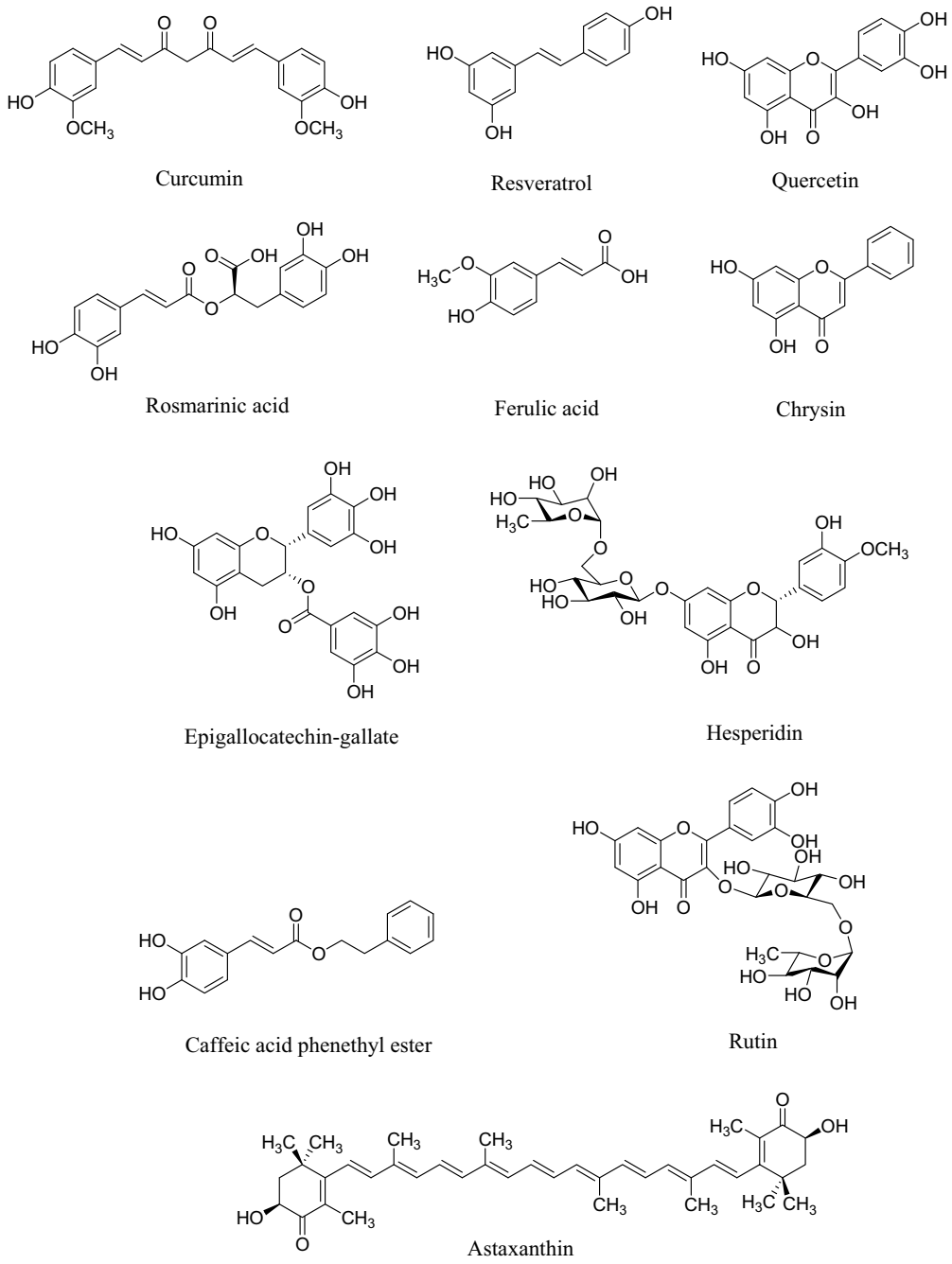

Fig. (2). Chemical structures of selected polyphenols and candidate phytochemicals against radiation-induced neurodegeneration.

TNF-α, IL-6, and IL-1β towards neuroprotective responses [180-183]. As stated, resveratrol inhibits Aβ as one of the inducers of apoptosis in neurons which precipitates neurotoxicity events [184]. Li *et al.* have shown that resveratrol suppresses apoptosis *via* activating Sirt1 through Sirt1/PGC-1α in neurological disorders [185]. In several studies, radiation has been shown to upregulate inflammatory mediators [11]. Accordingly, resveratrol inhibits these mediators, including NO, TNF-α, IL-1β, IL-6 [186], MCP-1, and diminishes the production of IL-12 p40 and IL-23 in neurodegenerative disorders [178]. Resveratrol also raises the levels of GSH, SOD, CAT, GPx, and HO-1 and reduces LPO [187] as dysregulated factors following radiation exposure.

Resveratrol has shown a protective function against the cell death triggered by α-syn in PD [187]. Besides, resveratrol meaningfully alleviated DNA damages and cytotoxic effects of megavoltage radiation in the glioblastoma cell line [188]. Studies indicated the inhibitory effects of radiations on the PI3K/Akt pathway [185], while evidence indicated resveratrol as a neuroprotective agent by activating PI3K/Akt/mTOR pathway and inhibiting the apoptosis of neurons [189]. As mentioned above, resveratrol has neuroprotective properties by reducing radiation-induced Bax elevation. Furthermore, it can diminish the *in vivo* salivary gland dysfunction induced by radiation *via* enhancing the activity of SOD and reducing the level of MDA [190]. To improve the pharmacokinetics and bioavailability of resvera-

trol, Yin *et al*. developed a new nanoformulation of resveratrol that could decrease Aβ or radiation-induced oxidative stress [191]. Reducing Bax, MMP-9, accumulation of tau, BACE1A, amyloidogenic processing and apoptosis of neurons, as well as increasing Sirt-1, AMP-activated protein kinase (AMPK), Bcl-2, claudin 5, and mitochondrial biogenesis are some of the other neuroprotective mechanisms of resveratrol [192].

5.3. Quercetin

Quercetin is a natural flavonoid abundant in many plants possessing pivotal properties, including antioxidant, anti-inflammatory, radical scavenging, antidiabetic, and anticancer activities. It has also shown therapeutic potentials in neurodegenerative disorders [193, 194]. It has been shown that quercetin reduces intracellular tau and gliosis in the amygdala and hippocampus during AD [195]. As mentioned earlier, radiation elevates inflammatory and apoptotic mediators [57], while quercetin ameliorates astrogliosis in AD by inhibiting COX-2, iNOS, NO, IL-1β, TNF-α, and prostaglandin E2. Quercetin also ameliorated the expression of Bax/Bcl-2, SOD, GPx, and CAT in neuronal damages [196, 197]. Kale *et al.* implemented a study to investigate the *in vivo* neuroprotective potential of quercetin against radiation-induced brain injury. Findings have demonstrated that quercetin can significantly protect the nervous system against radiation and decrease plasma and tissue concentrations of MDA [198]. Also, quercetin exerts its neuroprotective effects against radiation-induced neuronal endoplasmic reticulum stress by reducing the expression of stress marker genes, C/EBP-homologous protein, TNF-α, JNK, and enhancing the cytoskeletal protein Tuj1 [199].

According to the aforementioned data, quercetin is of potential interest in combating neurodegeneration induced by radiation.

5.4. Ferulic Acid/Hesperidin

Studies have introduced ferulic acid (FA) as a phenolic compound with diverse biological activities, including neuroprotective, anti-inflammatory, antioxidant, antidiabetic, antiaging, and anticancer effects. It has been shown that FA can scavenge or capture free radicals and ROS as well as decrease ERK and p53 levels [200]. Considering the crucial role of radiation in ROS production in CNS [36], FA possesses a notable neuroprotective activity against the Aβ protein. It was reported to decrease the levels of ROS and LPO and increase HO-1, GSH, SOD, and CAT, and heat shock protein (HSP72), leading to the modulation of neuroinflammatory responses [165].

Hesperidin is another polyphenolic compound with significant neuroprotective properties that can considerably modulate brain damages induced by radiation. Hesperidin restored diminished levels/activities of antioxidant enzymes and the parameters such as CAT, GSH, GPx, and SOD, which were decreased in the rats exposed to γ-rays [201]. Furthermore, hesperidin alleviated mitochondrial damage, oxidative stress, and monoamine neurotransmitter alterations in irradiated rats' brains [202]. Moreover, hesperidin exhibited remarkable neuroprotective activities and improved neurological outcomes of radiation-induced brain injury in the rats exposed to a dose of 20 gray (Gy) [203].

Hence, FA and hesperidin employ neuroprotective mechanisms to combat radiation-induced neurodegeneration.

5.5. Other Polyphenols

Evidence has shown that rutin possesses neuroprotective effects *via* activating PI3K/Akt/glycogen synthase kinase 3 beta (GSK-3β)/Nrf2 and lowering the xanthine oxidase level (XO) that reduces O_2^-, H_2O_2, and MDA generation in the brain [204]. Furthermore, monoglucosyl-rutin has been reported to increase cell survival and exhibit *in vitro* radioprotective activity by attenuating radiation-induced DNA damage in mammalian cells [205]. Oral rutin in Swiss albino rats exposed to irradiation considerably reduced dicentric formation and reduced micronucleated polychromatic, normochromatic erythrocytes [206]. As mentioned earlier, radiation exerts cytogenetic effects, while rutin mitigates DNA damages, a feature that could be attributed to its antioxidant and free radical scavenging properties [207].

Investigations have shown that radiation induces COX-2 mRNA expression in microglia and astrocytes [107], but polyphenolic constituents such as 6-gingerol, zerumbone, 6-shogaol and dehydrozingerone, have shown significant radioprotective activities *via* inhibition of UVB-induced COX-2 expression and NF-κB, as well as reducing cell apoptosis and DNA damage by activation of Nrf2/keap1/antioxidant response element (ARE) signaling pathway [208-213]. Also, irradiation-induced apoptosis was inhibited by zingerone by reducing Bax and caspase-3 activity and increasing Bcl-2, GST, GSH, SOD, and CAT [214]. In another study, zingerone showed significant *in vitro* protective advantages against radiation-induced apoptosis, DNA damage, and genotoxicity on the human lymphocytes. Scavenging free radicals and suppressing oxidative stress can also be regarded as other major radioprotective mechanisms of zingerone [215].

As radiation triggers apoptosis, oxidative stress, and inflammation [26], considerable evidence indicates that flavonoids have an important function in preventing and treating neurodegenerative diseases. These compounds reduce iNOS, COX-2, TNF-α, IL-6, IL-1β, iNOS, MMP-9, and COX-2, as well as apoptosis mediators [216]. Besides, evidence has shown that the major flavonoid of *Scutellaria baicaleins*, baicalein, diminishes DNA damages in humans after gamma radiation [217]. As another flavonoid found in propolis, honey, and other plants, chrysin has also shown advantageous features such as antioxidant activity by reducing MDA and lowering caspase-3 activity post-irradiation [218]. Mansour *et al*. investigated 5, 7-dihydroxyflavone as a natural flavonoid against gamma irradiation and acrylamide-induced neurotoxicity in rats. Their results demonstrated that 5, 7-dihydroxyflavone could reduce the levels/activities of Aβ, caspase-3, BDNF, MDA, and acetylcholine esterase (AChE) [218]. As demonstrated by investigations, radiation inhibits PI3K/Akt, PKC, MEK1/2-ERK1/2 [107] and increases NF-κB**,** TNF-α, IL-6, and IL-1β [186]. In this regard, Rehman *et al.* reported that kaempferol is a natural flavonol capable of inhibiting brain lesion and neuroinflammation by inhibiting STAT3 and NF-κB, as well as alleviating cognitive impairment through increasing the ERK1/2-CREB signaling pathway [219].

Epigallocatechin 3-gallate (EGCG) is another polyphenolic compound with considerable neuroprotective effects

inhibiting radiation-induced injuries [220]. EGCG supply this effect *via* downregulating IL-1β, IL-6, IFN-γ, TNF-α, NF-κB levels, and disaggregation of Aβ protein [221]. In addition, EGCG increases cell survival and preserves human retinal pigment epithelial cells against damages induced by UV irradiation [222]. Epicatechin could properly decline the phosphorylation of MEK1/2, ERK1/2, and c-Jun as well as reduce the expression of p-JNK, p38, and ROS generation after radiation [167]. As mentioned above, EGCG has radioprotective effects through the scavenging of superoxide anions, hydroxyl radicals, and hydrogen peroxide [223, 224]. This phenolic compound can also bind free radicals to intercalate with DNA and inhibit the proteasome as a regulator of inflammation [225].

Furthermore, propolis and its phenolic chemical compound, caffeic acid phenethyl ester (CAPE), could meaningfully increase the activity of SOD and decrease the levels of MDA in the brain of rats exposed to ionizing radiation compared to the control group [226]. CAPE is another flavonoid with anti-inflammatory, immunomodulatory, and free radical scavenging properties [227]. In addition, It has shown radioprotective effects against oxidative damage [228]. While radiation activates oxidative stress through an increase in ROS and RNS levels [36], apigenin, as another phenolic compound [206], was shown to reduce oxidative stress *via* inhibiting and decreasing iNOS, IL-6, COX-2, and TNF-α [229]. Also, apigenin exhibited cytoprotection as evidenced by its antioxidant and free radical-scavenging activities [230], as well as reduced the number of micronuclei in gamma-irradiation [231].

While radiation induces the expression of COX-2 mRNA [108], silymarin meaningfully declines COX-2 and 5-Lipooxygenase (LOX). Besides, silymarin increases IL-10 toward neuroprotective potentials following radiation [232, 233]. Silymarin also protected the male Balb/c mice exposed to lethal 9 Gy γ-irradiation *via* increasing the CAT, GPx, glutathione reductase, and SOD activities [234]. In the same way, the neuroprotective potentials of silybin and its analogs (*e.g.*, naringin, naringenin, and hesperetin) have been addressed against X-ray radiation-induced DNA breaks [235]. As previously mentioned, radiation induces oxidative stress [36], and naringin has shown substantial biological effects such as anti-inflammatory, anticarcinogenic, and antioxidant activities leading to a reduction in ROS and an increase in Nrf2/HO-1, and SOD2 levels [236, 237]. Naringin also lowered the expression of several inflammatory proteins and genes like IL-1β, IL-6, cytoplasmic cytochrome C, TNF-α, Bax, p53, caspase-9, caspase-8, caspase-3, Bak, Fas, and FasL [236], thereby alleviating radiation-induced neuroinflammation/neuroapoptosis [186].

As another natural phenol, thymol showed radioprotective activities against ionizing radiation-induced salivary gland dysfunction in a rat model. It has been demonstrated that thymol reduces *in vitro* gamma ray-induced genotoxicity *via* decreasing free radicals and inhibiting oxidative stress [238, 239]. Additionally, modulation of the expression of Bax, Bcl-2, and survivin, as well as other apoptotic regulatory molecules, has been proposed as the main radioprotective mechanisms of plumbagin in C33A cells exposed to 2 Gy of radiation. Consequently, gallic acid as another phenolic compound has shown radioprotective properties by reducing radiation-induced DNA damages [240, 241]. Hence, phenolic compounds are of potential importance in combating radiation-induced neurodegeneration. Table **1** provides the radioprotective effects of the selected phenolic compound against neurodegeneration.

Hydroxytyrosol and oleuropein aglycone are other emerging phenolic compounds. They are mainly extracted from olive oil with potential antioxidant effects against radiation-induced neuronal damage. These compounds have shown the potential of reducing α-synuclein accumulation in PD models. Hormesis, antioxidative responses, and activating proteasome/phase II detoxifying enzymes are considered potential underlying mechanisms [242]. In a research study, hydroxytyrosol prevented protein damage induced by long-wave UV radiation through increasing antioxidant responses [243].

5.6. Miscellaneous Candidate Phytochemicals

In addition to polyphenols, other phytochemicals, including alkaloids, terpenes/terpenoids, carotenoids, and organosulfide compounds, also have shown neuroprotective effects [244]. Furthermore, other phytochemicals like phytoestrogens have also shown several useful effects such as neuroprotective, osteoporosis-preventive, antiacne, and anticancer activities. Phytoestrogens like progesterone and 17β-estradiol exert their neuroprotective/radioprotective activities *via* activation of receptors like estrogen receptors-α (ER-α), ER-β or G-protein coupled receptor-1, ERK1/2, PI3K/Akt, and c-Jun [219]. ER-α can bind to IGF-1 and regulate the signaling cascades involved in neuroprotection as PI3K/Akt/GSK-3β, and upregulate the levels of anti-apoptotic proteins such as Bcl-2, Bcl-xL, and Bcl-W. ER-α could downregulate the levels of Bcl-2-like protein 4 (BCL2L4) and Bcl-2 associated cell death (BAD) as proapoptotic mediators [219].

It has been shown that leafy vegetables rich in alkaloids have beneficial effects on CNS and its related disorders both *in vivo* and *in vitro* [245]. Oboh and co-authors have shown that bitter leaf alkaloid-rich extract (BLAE) has several beneficial effects through antioxidant effect and inhibiting the monoamine oxidase (MAO), angiotensin-1 converting enzyme (ACE), ATPdase, and ADPdase [245]. Huperzine is another alkaloid with neuroprotective properties against AD by inhibiting AChE and reducing oxidative stress [246]. In this phytochemical class, kukoamine A also inhibits oxidative stress and apoptosis [247]. Studies have shown that NF-κB and AP-1 trigger radiation side effects; therefore, inhibition of these factors may protect neuronal cells against radiation [247-249]. In the study of Zhang *et al.,* Kukoamine A declined the expression of Bax, and caspase-3 reduced the release of cytochrome C and increased the expression of Bcl-2 [250].

Amongst carotenoids, astaxanthin is a potent antioxidant compound with diverse biological properties. It suppressed radiation-induced cytogenetic impacts and reduced *in vivo* irradiation-induced hematopoietic system injuries by reducing apoptosis and oxidative stress pathways [251-253]. As stated, radiation increases ROS, oxidative stress, and inflammation [48], while lycopene (a carotenoid) has significant antioxidant, anti-apoptotic and anti-inflammatory effects. In this line, curcumin reduces ROS/LPO and increases the levels of antioxidant enzymes such as SOD and GSH [254], thereby exerting radioprotective responses. It has been

Table 1. Radioprotective effects of selected phytochemicals against neurodegeneration.

Compounds	Type of Study	Radiation Source	Cell Line/Animal Model	Mechanism of Action	References
Ferulic acid	*In vivo*	Gamma irradiation	Male albino rats	↑CAT, ↑GST, ↑SOD	[165]
Rosmarinic acid	*In vivo*	Wi-Fi radiation	Wistar strain male rats	↓NO, ↓protein carbonylation, ↓MDA, ↑total antioxidant capacity, ↑GPx, ↑SOD, ↑CAT, ↑GSH	[169]
Curcumin	*In vivo*	Various sources	Microglia	↑CAT, ↑GST, ↑SOD, ↓Oxidative damage, ↓IL-1β, ↓IL-6, ↓TNF-α	[18, 259].
Resveratrol	*In vivo*	Gamma irradiation	Sprague-Dawley rats	↑Sirt1/PGC-1α, ↓ apoptosis, ↓ ROS production	[185]
Quercetin	*In vivo*	NR	Male Wistar-Albino rats	↓MDA, ↓LPO	[198]
Hesperidin	*In vivo*	Gamma irradiation	Male albino rats	↑CAT, ↑GSH, ↑GPx, ↑SOD	[201]
Rutin	*In vivo*	Gamma irradiation	Transgenic mice (APPswe/PS1dE9)	↑SOD, ↑GSSG, ↓MDA, ↓IL-1β, ↓IL-6 , ↓Aβ	[204]
Zingerone	*In vivo*	Gamma irradiation	Microglia and astro-cytes	↑CAT, ↑GST, ↑SOD, ↑GSH, ↓caspase-3, ↑Bcl-2 ↓Bax	[214]
Chrysin	*In vivo*	Gamma irradiation	Male Wister rats	↓NF-κB, ↓TNF-α, ↓IL-1β, ↓IL-6, ↓NOS, ↓NO, ↓ROS, ↓COX-2, ↓caspase-3	[218]
5, 7-Dihydroxyflavone				↓β-amyloid, ↓caspase-3, ↓BDNF, ↓MDA, ↓AChE	
EGCG	*In vivo*	Various sources	Cerebellar granule neurons	↓ROS, ↓IL-1β, ↓IL-6, ↓IFN-γ, ↓TNF-α, ↓NF-κB, ↓p-JNK, ↓p-38,	[221]
Caffeic acid phenethyl ester	*In vivo*	Gamma irradiation	Male albino Sprague-Dawley rats	↑SOD, ↓MDA, ↑GPx	[226]
Silymarin	*In vivo*	Gamma irradiation	BALB/c mice	↑CAT, ↑GPx, ↑Glutathione reductase, ↑SOD	[234]
Ursolic acid	*In vivo*	Gamma irradiation	BALB/c mice	Improves contextual learning and memory, ↑neurogenesis	[260]

Abbreviations: AChE: acetylcholinesterase, BDNF: brain-derived neurotrophic factor, CAT: catalase, COX: cyclooxygenase, EGCG: epigallocatechin 3-gallate, GPx: glutathione peroxidase, GSH: glutathione, GSSG: glutathione disulfide, GST: glutathione S-transferases, IFN-γ: interferon-gamma, IL: interleukin, MDA: malondialdehyde, LPO: lipid peroxidation, NF-κB: nuclear factor-κB, NO: nitric oxide, NOS: nitric oxide synthase, NR: not-reported, p-JNK: phosphor c-Jun N-terminal kinase, SOD: superoxide dismutase, Sirt1/PGC-1α: sirtuin 1/peroxisome proliferator-activated receptor-γ coactivator-1alpha, TNF-α: tumor necrosis factor-alpha

shown that p53, as an important factor in the intrinsic apoptotic pathway (Bax/Bcl-2 ratio), is activated by DNA damage [255]. In this line, Cao *et al.* found that lycopene increased Bcl-2 and decreased p53, Bax, cytochrome C, and caspase-3 [254].

As another emerging miscellaneous phytochemical, sulforaphane induced hormetic activation of Nrf2 to reduce the occurrence and severity of a wide range of human-related pathologies, including PD, AD, stroke, and other age-related damages, while also enhancing stem cell proliferation. Besides, sulforaphane was a wide chemoprotective agent within a hormetic dose-response context. It potentially acts through increasing cell proliferation/viability at low concentrations in multiple tumor cell lines. Interestingly, the mechanistic profile of sulforaphane is similar to that of numerous other hormetic agents in protecting neurons, including activation of Nrf2 and AREs [26]. Of AREs, CAT, SOD, HO-1, NQO1, and GST are predominantly upregulated by sulforaphane to prevent the progression of neurodegeneration [26, 256, 257]. Sulforaphane is also a potential neuroprotective phytochemical acting through suppressing neuroinflammatory mediators (*e.g.*, IL-6, TNF-α, COX-2). So, sulforaphane could be a promising protective agent against high doses of radiation [258].

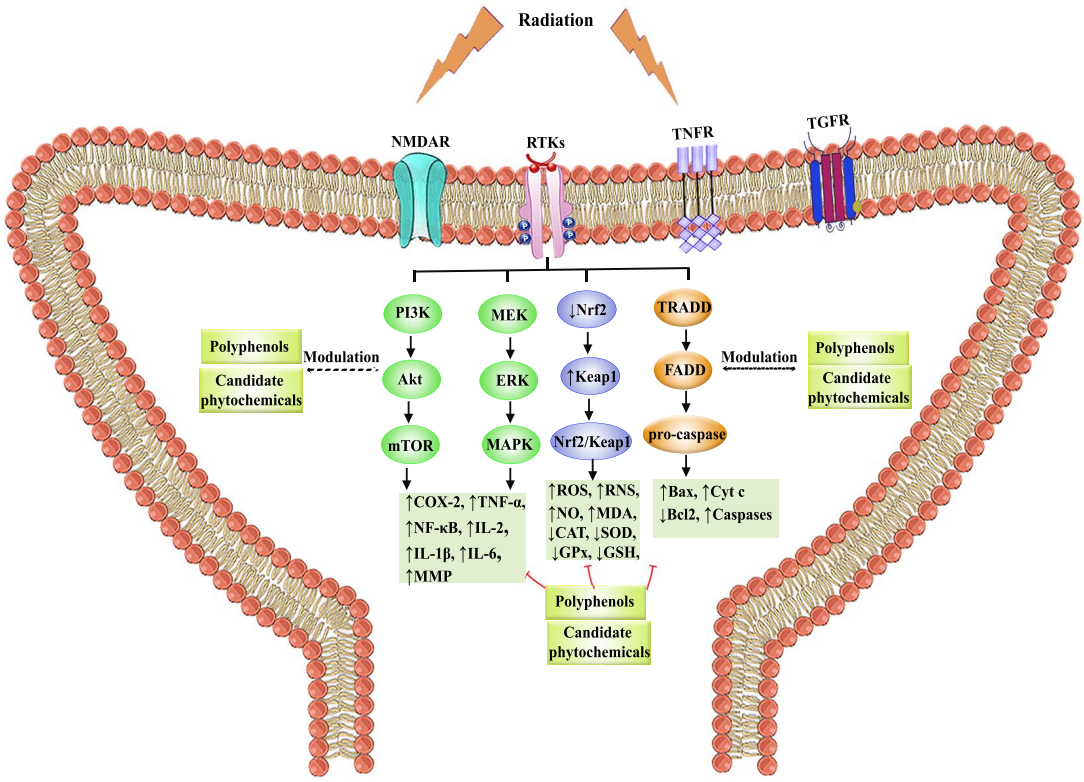

Fig. (3). The role of polyphenols in modulating neurodegeneration-induced oxidative stress and cross-talking inflammatory/apoptotic mediators. **Abbreviations:** CAT: catalase, COX: cyclooxygenase, Cyt C: cytochrome C, ERK: extracellular signal-regulated kinase, FADD: Fas Associated Via Death Domain, GLUTR: glutamate receptor, GPx: glutathione peroxidase, GSH: glutathione, IFN γ: interferon-gamma, IL: interleukin, Keap1: Kelch-like ECH-associated protein 1, LPO: lipid peroxidation, MAPK: mitogen-activated protein kinase, MDA: malondialdehyde, MEK: mitogen-activated protein kinase/ERK kinase, MMP: matrix metalloproteinase, mTOR: mammalian target of rapamycin, NF-κB: nuclear factor-κB, NMDAR: N-methyl-D-aspartate receptor, NO: nitric oxide, NOS: nitric oxide synthase, Nrf2: nuclear factor erythroid 2–related factor 2, PI3K: phosphoinositide 3-kinases, RNS: reactive nitrogen species, ROS: reactive oxygen species, RTKs: receptor tyrosine kinases, SOD: superoxide dismutase, TGFR: transforming growth factor-beta receptor, TNF-α: tumor necrosis factor-alpha, TNFR: tumor necrosis factor receptor, TRADD: TNFR1-associated death domain protein. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

The schematic roles of polyphenols and candidate phytochemicals against radiation-induced neurodegeneration are presented in Fig. (**3**).

CONCLUSION

Despite substantial progress in treating neurodegenerative diseases, they have remained a global challenge and a primary cause of disability and death worldwide. Several factors are behind the causative agents of neurodegeneration, among which radiation plays an unavoidable role. Radiation triggers several dysregulated signaling pathways in oxidative stress, inflammation, and apoptosis towards neurodegenerative disorders. Accordingly, there are several signaling pathways behind neurodegeneration, including PI3K/Akt/mTOR, MEK/ERK/MAPK, Nrf2-Keap1, and their cross-talk mediators seem to be of great importance. The complex pathophysiological mechanisms behind radiation-induced neurodegeneration raise the need for providing potential multi-target agents to pave the way in combating radiation-induced neurodegeneration. Nowadays, the plant kingdom is a prominent source of multi-target compounds. Among natural entities, polyphenols and some candidate phytochemicals potentially modulate radiation-induced dysregulated mediators for the treatment/prevention of neurodegeneration. These phytochemicals potentially target multiple neuronal dysregulated pathways following radiation (Fig. **3**), thereby envisioning a bright future in the prevention/treatment of neurodegeneration.

Further reports on the destructive mechanisms of radiation-induced neurodegeneration will help to provide related clinical therapies. Future studies should cover wide *in vitro* and *in vivo* experiments with regard to hormesis dose-response, related signaling pathways, preconditioning, and revealing radioprotective potentials of phytochemicals against neurodegeneration, followed by well-controlled clinical studies. Such studies play crucial roles in providing more potential therapeutic agents in the prevention, management, and treatment of radiation-induced neurodegeneration.

AUTHORS' CONTRIBUTIONS

Conceptualization, S.F., and H.K.; software, S.F., drafting the manuscript, S.F., S.P, and S.Z.M; review, editing, and revising the paper: S.F., and H.K.

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