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### ► To cite this version:

Md. Sahab Uddin, Abdullah Al Mamun, Md. Tanvir Kabir, Jamil Ahmad, Philippe Jeandet, et al.. Neuroprotective role of polyphenols against oxidative stress-mediated neurodegeneration. *European Journal of Pharmacology*, 2020, 886, pp.173412. 10.1016/j.ejphar.2020.173412 . hal-02916840

**HAL Id: hal-02916840**

**<https://hal.science/hal-02916840>**

Submitted on 22 Aug 2022

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1 **Neuroprotective role of polyphenols against oxidative stress-mediated neurodegeneration**

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31 **Abstract**

32 Neurodegenerative diseases (NDs) are characterized by disorders with progressive deterioration  
33 of the structure and/or function of neurons. Genetic mutations can lead to many NDs.  
34 Nevertheless, neurodegeneration can also take place due to several biological processes. The  
35 pathogenesis of several NDs including Alzheimer's (AD), Parkinson's (PD), and Huntington's  
36 (HD) diseases are associated with oxidative stress (OS). In order to maintain the normal  
37 functions of neurons, lower levels of reactive oxygen species (ROS) and reactive nitrogen  
38 species (RNS) are important, since their increased levels can cause neuronal cell death. It has  
39 been found that OS-mediated neurodegeneration involves a number of events including  
40 mitochondrial dysfunction, Ca<sup>2+</sup> overload, and excitotoxicity. A growing number of studies are  
41 suggesting the benefit of using polyphenols for the treatment of neurodegenerative disorders.  
42 Indeed, in order to treat most of the NDs, synthetic drugs are extensively used which are found to  
43 exert side effects in the course of the treatment. There is mounting evidence that researchers have  
44 identified several naturally-occurring chemical compounds in plants, which are used for the  
45 management of NDs. Overall, polyphenolic phytochemicals are safer in nature and have  
46 negligible side effects. In this article, we have focused on the potential efficacy of polyphenols  
47 such as epigallocatechin-3-gallate, curcumin, resveratrol, quercetin and methylated polyphenols  
48 berberine against the most common neurodegenerative disorders.

49 **Keywords:** Neuroprotection, Polyphenols, Oxidative stress, Neurodegeneration, Neurotrophins

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## 58 **1. Introduction**

59 Over time, neurodegenerative diseases (NDs) have become a global threat. Presently, there is no  
60 available treatment that can cure these NDs. It has been found that NDs are most common  
61 among elderly people (Uddin et al., 2018). Globally, since there is a rise in the elderly  
62 population, therefore the number of people who are suffering from NDs is also increasing. Older  
63 people often develop NDs which ultimately can lead to death. Parkinson's disease (PD),  
64 Alzheimer's disease (AD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS)  
65 are the commonly seen NDs among elderly people (Islam et al., 2018; Sahab Uddin and Shah  
66 Amran, 2018; Uddin et al., 2017, 2019c). Indeed, movement disorders are linked with PD  
67 patients (Kaur et al., 2020), whereas dementia is most common among patients with AD (Uddin  
68 et al., 2020g). It is well-known that neurons of the brain are susceptible to oxidative stress (OS)  
69 (Sato et al., 1998) owing to high oxygen demand, low levels of glutathione, abundantly of  
70 redox-active metals (iron, copper), and high levels of polyunsaturated fatty acids (Geon Ha Kim  
71 et al., 2015). Furthermore, OS has the ability to disrupt the overall functions of the brain (Uddin  
72 and Kabir, 2019). At molecular and cellular levels, a number of processes exist that provide  
73 protection against oxidative toxicity. In the case of NDs, it has been found that disruptions take  
74 place in the defensive mechanisms which can trigger neurological impairments. It was suggested  
75 by various studies that OS may trigger cellular damage (Liguori et al., 2018), mitochondrial  
76 dysfunction (Van Houten et al., 2018) and impairment of the deoxyribonucleic acid repair  
77 system (Van Houten et al., 2018), all of these are crucial factors associated with multiple NDs  
78 including AD, PD, and HD (Andersen, 2004; Uddin and Upaganlawar, 2019). Increased  
79 generation of reactive oxygen species (ROS) inside mitochondria could lead to oxidative injury  
80 against mitochondrial membranes, mitochondrial DNA, and mitochondrial proteins, ultimately  
81 causing mitochondrial damage (Higgins et al., 2010). ROS affect the heme-comprising  
82 cytochrome c oxidase I (complex IV) of the respiratory chain and trigger further injury to the  
83 components of complexes I, II, and III (Lassmann, 2011). Oxidative injury in mitochondria plays  
84 a crucial role in the release of cytochrome c inside the cytosol causing apoptosis. Furthermore,  
85 the internal mitochondrial membrane displays higher penetrability to small molecules (Chen et  
86 al., 2012). It has indeed been found that several events such as the overproduction of ROS,  
87 mitochondrial dysfunction, as well as oxidative injury are accountable for neurodegeneration  
88 (Hroudová et al., 2014).

90 An association between aging and buildup of OS has also been confirmed (Castelli et al., 2019;  
91 Uddin et al., 2019a). Therefore, it is essential to elucidate the complete relationship between  
92 cellular damage and OS in the case of the aging process and NDs (Harman, 2006). Indeed, it is  
93 established that different cellular events such as mitochondrial dysfunction, an overload of  $\text{Ca}^{2+}$ ,  
94 excitotoxicity, and the induction of intracellular signaling mechanisms have significant  
95 contributions in the molecular and cellular processes underlying OS-stimulated cell death  
96 (Bossy-Wetzel et al., 2004; Liu et al., 2017). It has been found that the survival of neurons under  
97 OS is promoted by several polyphenols (Numakawa et al., 2011; Potì et al., 2019; Uddin et al.,  
98 2020b). Polyphenols are involved with a wide range of neuroprotective activities such as  
99 inhibiting neuroinflammation, providing protection to neurons against neurotoxin-induced injury,  
100 and improving cognitive function, learning, and memory (Choi et al., 2012; Uttara et al., 2009;  
101 Vauzour, 2012). Furthermore, phytosterols, for example, have important actions on the redox  
102 state. A study reported that  $\beta$ -sitosterol reversed the impaired ratio of glutathione/oxidized  
103 glutathione mediated via phorbol esters, in RAW 264.7 macrophage cultures. The findings of  
104 this study can be linked with the reduction in the activity of catalase and the rise in the activities  
105 of glutathione peroxidase and manganese superoxide dismutase (Vivancos and Moreno, 2005).

106 Currently available drugs only provide symptomatic treatment to the individuals with NDs,  
107 rather than preventing or curing neurodegeneration (Hossain et al., 2019; Kabir et al., 2019b,  
108 2019a). Therefore, effective therapeutic agents are still lacking to treat NDs (Mizuno, 2014). In  
109 this regard, it is essential to develop novel and more therapeutic approaches to fight against these  
110 NDs. In recent times, there is growing popularity in the use of polyphenols to treat against  
111 chronic diseases. Interestingly, polyphenols can also be used in association with other  
112 phytochemicals leading to both additive and synergistic actions as shown, for example, in the  
113 case of the combined effects of the polyphenol resveratrol, the monophenol tyrosol and the  
114 phytosterol  $\beta$ -sitosterol on oxidative stress in RAW 264.7 macrophages (Vivancos and Moreno,  
115 2008). Furthermore, a number of studies have been published regarding the use of dietary plant  
116 constituents in the treatment of NDs (Debnath et al., 2017; Hossain et al., 2017; Makkar et al.,

117 2020; Rahman et al., 2017; Venkatesan et al., 2015). In this article, we have focused on the  
118 mechanism of actions and the significance of some dietary polyphenols in neurodegenerative  
119 diseases.  
120

## 121 **2. Oxidative stress in neurodegenerative diseases**

122 In terms of cellular functions, low levels of RNS and ROS have a physiological role including  
123 neuronal plasticity (Kishida and Klann, 2007). Nevertheless, excessive RNS/ROS can cause  
124 nitrosylation/oxidation of nucleic acids, proteins, and lipids, which can ultimately lead to  
125 neuronal cell death (Meo et al., 2016). It has been observed that such damage can take place  
126 either due to the decreased activity of non-enzymatic and enzymatic antioxidants or owing to the  
127 excessive production of RNS/ROS. Therefore, an intricate balance is required between pro- and  
128 antioxidant reactions so as to maintain normal neuronal functions.  
129

130 It has been found that OS-mediated toxicity might be closely associated with the pathogenesis of  
131 NDs including HD, PD, AD, and ALS (Andersen, 2004; Uddin et al., 2020e) as shown in **Fig. 1**.  
132 In this regard, for instance, markers for DNA oxidation (8-hydroxy-2-deoxyguanine [8-  
133 OHdG]), lipid oxidation (4-hydroxy-2-nonenal [4-HNE]), and protein oxidation (protein  
134 carbonyls and 3-nitro-tyrosine [3-NT]) are found to be increased in AD brains (Butterfield et al.,  
135 2007). Amyloid beta (A $\beta$ ) buildup is regarded as an AD hallmark, which can trigger the  
136 production of ROS including hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) in the presence of Cu<sup>2+</sup> or Fe<sup>3+</sup> (Huang  
137 et al., 1999; Jiang et al., 2007; Xudong Huang et al., 1999). Unfortunately, a progressive and  
138 selective loss of dopamine (DA) neurons takes place in the substantia nigra pars compacta in the  
139 brains of individuals with PD. In addition to this, the levels of 8-OHdG, 3-NT, protein carbonyls,  
140 and 4-HNE are found to be elevated, while the level of glutathione (GSH, a major intracellular  
141 antioxidant) is reduced (Zhou et al., 2008). It has been observed that 4-HNE has the ability to  
142 covalently bind with the central protein in PD pathogenesis,  $\alpha$ -synuclein ( $\alpha$ -Syn), which  
143 eventually leads to neurotoxic actions on GABAergic and DAergic neuronal cultures (Qin et al.,  
144 2007). On the other hand, increased levels of 8-OHdG, malondialdehyde (a marker for lipid  
145 oxidation), lipofuscin (a product of unsaturated fatty acid peroxidation), and 3-NT have been  
146 observed in case of HD brains (Stack et al., 2008). Decreased GSH level has been observed in

147 cultured neurons obtained from mice that express mutant huntingtin protein (Htt140Q/140Q) (Li  
148 et al., 2010).

149

150 **- Insert Figure 1-**

151

152 Oxidative toxicity has also been found to play a pivotal role in reperfusion injury/cerebral  
153 ischemia (Uddin et al., 2019b; Zaplatic et al., 2019). There are limited areas of brain and types of  
154 neurons that are susceptible to ischemia. Cerebral blood flow is regarded as the primary reason  
155 behind the aforesaid phenomenon since this flow is highly spatiotemporally regulated (Cremer  
156 and Seville, 1983). The phenomena outlined before may also reveal why certain neuron types of  
157 different brain areas are affected in each ND. It has been suggested by copious evidence that  
158 aggregation of OS-dependent damage can take place in the course of normal aging, which can  
159 further result in substantial impairment in cognitive function (Bishop et al., 2010; Harman, 2006;  
160 Jakaria et al., 2019).

161

162 In many NDs, cell death primarily takes place due to apoptosis (a form of programmed cell  
163 death). A number of processes usually contribute to apoptosis, such as OS, endoplasmic  
164 reticulum (ER) stress, mitochondrial dysfunction, Ca<sup>2+</sup> overload, and excitotoxicity (Bossy-  
165 Wetzel et al., 2004) as given in **Fig. 2**. It is known that via the electron transport chain (ETC),  
166 mitochondria generate a lower level of ROS in cellular respiration. There are five protein  
167 complexes (I–V) that comprise the ETC. It has been found that excess ROS production can occur  
168 due to the disruption of ETC (Nicholls, 2008). Various studies have indeed revealed that  
169 mitochondrial dysfunction (including the disrupted activity of the ETC) may be involved in AD  
170 animal models and patients with HD (Gil and Rego, 2008), PD (Henchcliffe and Beal, 2008),  
171 and AD (Adam-Vizi and Starkov, 2010).

172

173 Furthermore, mitochondria affect the homeostasis of Ca<sup>2+</sup> by sequestering superfluous cytosolic  
174 Ca<sup>2+</sup> within their matrix. However, neurodegeneration may occur through an uncontrolled Ca<sup>2+</sup>  
175 loading. According to the study of Oliveira et al. (Oliveira et al., 2007), disrupted Ca<sup>2+</sup>  
176 homeostasis was observed in striatal mitochondria of Hdh150 knock-in HD mice. It has been  
177 found that a lack of phosphatase and tensin homolog deleted on chromosome 10-mediated

178 putative kinase 1, causes mitochondrial aggregation of  $\text{Ca}^{2+}$  in cultured neurons (Gandhi et al.,  
179 2009). Moreover, ER controls intracellular levels of  $\text{Ca}^{2+}$  via ryanodine receptors as well as  
180 inositol-1,4,5-triphosphate receptors (InsP3Rs). Remarkably, presenilin (*PSEN*) 1 and 2 play a  
181 pivotal role in AD pathology, act as a passive ER  $\text{Ca}^{2+}$  channel to keep up the equilibrium state  
182 of  $\text{Ca}^{2+}$  levels that disrupts by mutant *PSEN2*-N141I and *PSEN1*-M146V (Tu et al., 2006; Zhang  
183 et al., 2010c). These *PSEN* mutants increased the gating of InsP3Rs activity, resulting in the  
184 aggregation of  $\text{A}\beta$  (Cheung et al., 2008). It has also been observed that  $\text{A}\beta$ -comprising senile  
185 plaques lead to  $\text{Ca}^{2+}$  overload (Kuchibhotla et al., 2008). Collectively, it is assumed that mutant  
186 *PSEN* as well as  $\text{A}\beta$  lead to the disturbance of  $\text{Ca}^{2+}$  homeostasis that might result in  
187 mitochondrial dysfunction causing neurodegeneration (Adam-Vizi and Starkov, 2010).

188

189 **- Insert Figure 2-**

190

### 191 **3. Polyphenols as antioxidative factors**

192 Since there is an involvement of OS in the pathogenesis of NDs, thus a crucial therapeutic  
193 approach can delay or block the OS through elevating the activity of endogenous antioxidants  
194 and/or inhibiting the generation of ROS. However, it is still elusive whether OS is a consequence  
195 or cause of ND (Andersen, 2004). It has been suggested by evidence that OS directly starts and  
196 progresses to neuronal cell death. Nevertheless, there is a chance that OS accumulation is easily  
197 stimulated in neurons that are damaged by other insults. Death signaling pathways can be  
198 activated in the apoptotic process through a number of cellular processes such as excitotoxicity,  
199  $\text{Ca}^{2+}$  overload, and mitochondrial dysfunction. In fact, cell viability may get affected by such  
200 negative feedback loops. The aforesaid processes can take place in parallel and have an additive  
201 action in case of stimulation of cell death. Henceforth, along with the blockage of OS  
202 accumulation, activating survival signaling and suppressing death-signaling cascades may also  
203 prove effective.

204

205 Some studies revealed that one or more mechanisms related to adaptive cellular stress responses  
206 might get activated by lower amounts of dietary polyphenols (Mandel et al., 2008; Schroeter et  
207 al., 2001, 2007; Vauzour et al., 2007). Activation of such hormetic signaling pathways in  
208 neurons can lead to the generation of various types of cytoprotective proteins such as anti-



209 apoptotic proteins, antioxidant and phase II enzymes, protein chaperones, and neurotrophic  
210 factors (Calabrese, 2008; Mattson and Cheng, 2006). There is a growing interest in the hermetic  
211 actions in neurons that involve nuclear factor erythroid 2-related factor 2 (Nrf2). It has indeed  
212 been reported that Nrf2 has the ability to bind with antioxidant-responsive element (ARE) with  
213 high affinity and has a significant contribution in the up-regulation of genes that are involved in  
214 the modulation of the cellular redox status and the protection of the cells from OS (Kraft et al.,  
215 2004; Lee and Johnson, 2004; Uddin et al., 2020h). Furthermore, Nrf2 can also interact with a  
216 cytosolic repressor protein Keap1 (Kelch ECH associating protein) limiting Nrf2-induced gene  
217 expression, under basal conditions (Itoh et al., 1999). Upon exposure to oxidative damage, Nrf2  
218 is released in cells from Keap1 and translocates to the nucleus, where it causes activation of  
219 ARE-dependent transcription of phase II and antioxidant defense enzymes including heme  
220 oxygenase-1 (HO-1), glutathione peroxidase (GPx), and glutathione-S-transferase (GST)  
221 (Nguyen et al., 2003).

222 A study by Calabrese et al. (Calabrese, 2008) demonstrated that most polyphenols responded in a  
223 bell-shaped dose-response mode, showed cellular toxicity at high concentrations whereas  
224 triggering light chemical stress at low doses with the initiation of physiological hormesis in cells,  
225 causing increased expression of protective genes including those initiated by Nrf2. Some studies  
226 revealed that resveratrol protected PC12 cells from H<sub>2</sub>O<sub>2</sub>-induced oxidative stress (Chen et al.,  
227 2005b) and attenuated cerebral ischemic injury in an animal model (Ren et al., 2011) through the  
228 initiation of Nrf2 as well as the upregulation of HO-1. Numerous upstream signaling pathways  
229 might activate Nrf2 either independently, or in a combined way. These have specific functions  
230 on several lipid and protein kinase signaling pathways including the mitogen-activated protein  
231 kinase (MAPK) and phosphoinositide 3-kinase (PI3k)/protein kinase B (Akt) cascades that  
232 control prosurvival transcription factors as well as the expression of the gene (Williams et al.,  
233 2004). Furthermore, activation of the extracellular signal-regulated kinase (ERK) plays an  
234 essential role in the initiation of cyclic adenosine monophosphate (cAMP)-response element-  
235 binding protein (CREB), a transcription factor that leads to the initiation of long-term alterations  
236 in memory and synaptic plasticity (Bourtchuladze et al., 1994; Impey et al., 1998). The  
237 activation of CREB also controls the expression of many essential genes, such as brain-derived  
238 neurotrophic factor (BDNF), consequently playing an important role in regulating synaptic  
239 activities and neuronal survival in the adult central nervous system (CNS) (Finkbeiner, 2000;

240 Tully et al., 2003). Besides, another polyphenol, fisetin, is commonly observed in strawberries,  
241 which has been revealed to enhance long-term potentiation as well as to improve object  
242 recognition in an animal model by the initiation of CREB and ERK (Kong et al., 2000).

243

#### 244 **4. Neuroprotective potential of polyphenols against neurodegenerative events**

245 NDs including multiple sclerosis (MS), HD, PD, and AD fall under the category of NDs along  
246 with neurotraumatic disorders (Helman and Murphy, 2016; Winner et al., 2011). Environmental  
247 and genetic factors also have a significant contribution to the progression of NDs.

248 Neuroinflammation, OS, and buildup of certain aggregated proteins are the common pathological  
249 characteristics of NDs (Farooqui, 2012; Uddin et al., 2020d, 2020f). These stimuli are embedded  
250 in the plasma membrane via extracellular receptors. Chronic inflammation is directly related to  
251 oxidative/nitrosative stress (Mitjavila and Moreno, 2012). Lipoxygenase (LOX), as well as  
252 cyclooxygenase (COX) cascades, are upregulated in chronic and age-related brain pathologies  
253 (Bishnoi et al., 2005; Vivancos and Moreno, 2002). The metabolism of polyunsaturated fatty  
254 acids (PUFAs) are impaired by COX. Furthermore, COX-1, COX-2 are accountable for the  
255 generation of many eicosanoids, as well as by LOXs that catalyze the addition of oxygen to  
256 docosahexaenoic linolenic, and arachidonic acids and other PUFA playing a crucial role in the  
257 generation of bioactive lipids, which considerably affects the event of neurodegeneration. Amid  
258 numerous isoforms, 12/15-LOX and 5-LOX are particularly significant in neuroinflammation or  
259 neurodegeneration (Czapski et al., 2016).

260 In brain, increased levels of PUFAs including arachidonic acid and docosahexaenoic acid have  
261 been observed as compared to other organs. Since these fatty acids are extremely unsaturated,  
262 they are thus prone to OS-mediated lipid peroxidation, which has been found to be one of the  
263 major consequences of free radical-induced injury (Montine et al., 2002). Breakdown of  
264 neuronal membrane-associated PUFAs can lead to the release of increased concentrations of  
265 reactive electrophilic aldehydes, which can further covalently bind proteins to generate multiple  
266 adducts (Tramutola et al., 2017) including 4-HNE. Various studies have confirmed elevated  
267 levels of nitrosative stress and lipid peroxidation in the brains of individuals with AD and PD  
268 (Butterfield et al., 2006; Hardas et al., 2013; Yoritaka et al., 1996). Numerous studies have  
269 revealed an association between OS and protein homeostasis. Proteostasis network is essential

270 for the degradation of proteins that are irreversibly oxidized (Jung et al., 2009; Sahab Uddin and  
271 Ashraf, 2020; Tramutola et al., 2017). During aging, the ability of the cells to preserve  
272 proteostasis is reduced, which can make the organism vulnerable towards neurodegeneration  
273 (Uddin et al., 2020c). Furthermore, the main outcome of protein oxidation is the generation of  
274 large protein aggregates, whose buildup develops toxicity in cells. Insoluble aggregates can be  
275 generated due to covalent cross-links among peptide chains, as in the case of the mutant  
276 superoxide dismutase 1 in ALS,  $\alpha$ -synuclein in PD, and neurofibrillary tangles (NFTs) and A $\beta$  in  
277 AD (Kabir et al., 2020; Uddin et al., 2020a; Uddin and Kabir, 2019).

278

279 Furthermore, neurotrophins (NTs) can cause cellular stress and stimulate release and generation  
280 of the BDNF, and activation of the tropomyosin-related kinase B (TrkB) receptor family and  
281 other downstream protein kinases (**Fig. 3**) (Barbacid, 1994; Marini et al., 2004). In the brain,  
282 NTs play vital roles in the regeneration, survival, and maintenance of specific neuronal  
283 populations (Venkatesan et al., 2015). Moreover, the expression of NT has a strong association  
284 with the occurrence of ND (Cho et al., 2013). On the other hand, mammalian NTs including NT-  
285 3, BDNF, nerve growth factor (NGF), and NT-4/5 play a significant role in the maintenance of  
286 neurons of both central and peripheral nervous systems (Reichardt, 2006). Indeed, NTs have  
287 been identified as promoters of neuron survival. It was also suggested that the levels of NT drop  
288 drastically in the case of NDs (Dawbarn and Allen, 2003). Henceforth, NTs are regarded as vital  
289 targets for polyphenols that exert effects against ND. Through the binding and activation of Trk  
290 receptors (located in the plasma membrane), NTs avert neuronal degeneration as depicted in **Fig.**  
291 **3**.

292 **- Insert Figure 3-**

293 In addition, the aforesaid binding of NTs with Trk receptors ultimately helps in the establishment  
294 of a growth-encouraging microenvironment for neurons (Huang and Reichardt, 2001). Following  
295 this, several intracellular signaling processes occur including the ERK pathway and PI3k/Akt  
296 cascade which stimulate cell survival and help in protecting the neurons against  
297 neurodegeneration. Besides activation of the signaling pathway, expression of B-cell lymphoma  
298 2 (Bcl-2) genes (an inhibitor of intracellular apoptosis) can also be promoted by NT. On the  
299 other hand, gradual degeneration of neurons has been observed in the absence of binding of NTs

300 to the tropomyosin-related kinase (Trk) receptors. Therefore, the administration of NTs might be  
301 an effective way to combat neurodegeneration and ultimately overcome this disorder.  
302 Nevertheless, crossing the blood-brain barrier (BBB) is still a big challenge to treat CNS  
303 disorders. In order to reverse NT loss, an enhancer or modulator (i.e. therapeutic agent)  
304 particularly targeting the Trk receptor might be a good candidate (Reichardt, 2006). Moreover,  
305 due to the promising findings of several studies, there is a rise in the intake of certain plant  
306 ingredients for the treatment of NDs (Essa et al., 2012; Howes and Houghton, 2012).  
307 Polyphenols are most commonly found in vegetables, fruits, and natural products. Furthermore,  
308 polyphenols contain several hydroxyl groups on aromatic rings (Tresserra-Rimbau et al., 2018;  
309 Vauzour, 2012). Interestingly, *in vitro* studies have revealed that polyphenols exert their  
310 beneficial effects by directly scavenging free radicals and nitrogen species (Halliwell, 2006;  
311 Pannala et al., 1997; Russo et al., 2000; Visioli et al., 1998). Nonetheless, polyphenols are  
312 limitedly bioavailable and get extensively metabolized. These factors attenuate their antioxidant  
313 properties making it also difficult to estimate the *in vivo* concentrations at which they will exert  
314 them (Williams et al., 2004).

315

#### 316 **4.1. Epigallocatechin-3-gallate**

317 EGCG (**Fig. 4**) is the most common polyphenol found in tea. Because of its potential to delay  
318 neurodegeneration, this plant compound has drawn a lot of attention in the last few decades.  
319 Interestingly, it has been observed that the occurrence of NDs is inversely connected with the  
320 consumption of tea (Pervin et al., 2018). In AD models, several experiments have been carried  
321 out where EGCG was provided. Many studies have revealed that the administration of a drug  
322 named D-gal in AD models played a significant role in the reduction of A $\beta$  (Chan et al., 2016;  
323 Walker et al., 2015; Wobst et al., 2015). A study by Liu et al., showed that the administration of  
324 EGCG decreased the level of  $\beta$ - and  $\gamma$ -secretases [i.e. amyloid precursor protein (APP) cleaving  
325 enzyme] via suppression of the activity of nuclear factor kappa B (NF- $\kappa$ B) and ERK, which  
326 ultimately leads to the prevention of neuronal cell death (Liu et al., 2014b). It was also found that  
327 EGCG administration resulted in a reduced level of A $\beta$  due to the  $\alpha$ -secretase-mediated APP  
328 cleavage (Smith et al., 2010). On the other hand, Choi et al., (Choi et al., 2002) recommended

329 that consumption of three or more cups of tea containing high levels of EGCG led to a reduced  
330 risk of PD development.

331 It has been observed that there is a substantial loss of tyrosine hydroxylase (TH) positive cells in  
332 PD. Koh et al., (Koh et al., 2003) demonstrated that the concurrent consumption of EGCG and  
333 tea could help to prevent the loss of these cells in the substantia nigra. Collectively, these  
334 findings denote that the use of EGCG can be useful in the treatment of ND. Furthermore, by  
335 preventing the uptake of DA and by displaying neuroprotective effects, EGCG can inhibit  
336 neuronal cell death. EGCG exerts this aforesaid function through its activity on the catechol-*O*-  
337 methyltransferase (COMT) enzyme that blocks DA metabolism.  $\alpha$ -Syn accumulation is also  
338 observed in ND. It is supposed that EGCG regulates the proteolytic cleavage of  $\alpha$ -Syn converting  
339 it into a less toxic form (Koh et al., 2003; Liu et al., 2014b).

340 EGCG exerts neuroprotective effects on oxidative-stress-mediated apoptosis in neuronal-  
341 differentiated PC12 cells by downstream signaling via mitochondrial damage, poly(ADP-ribose)  
342 polymerase, and caspase (CASP)-3 as well as upstream signaling via the PI3K/Akt, and GSK-3  
343 cascades (Koh et al., 2003). Interestingly, EGCG also counteracts radicals and exerts antioxidant  
344 effects, since EGCG has a 3', 4', 5-trihydroxy B ring containing a member of the catechol family  
345 (Kalaiselvi et al., 2013). The Nrf2/ARE pathway outlined above plays an important role in  
346 mediating the antioxidant effects of EGCG (Han et al., 2014). In addition, catalase and  
347 superoxide dismutase (SOD) are the two radical scavenging enzymes that are typically activated  
348 by EGCG (Kalaiselvi et al., 2013; Srividhya et al., 2008).

349 Several properties of EGCG such as its BBB penetrating and metal chelating features make this  
350 plant compound a promising solution for neurodegenerative events. Numerous studies performed  
351 in animal models demonstrated the BBB permeability of EGCG and showed that it can prevent  
352 cognitive dysfunctions (Pervin et al., 2017; Wei et al., 2019) (**Table 1**). It has already been  
353 observed that EGCG restores DA neurons by preventing the aggregation of iron-dependent  $\alpha$ -  
354 Syn (Bieschke et al., 2010). A number of clinical studies have confirmed that EGCG suppresses  
355 the activity of cytochrome p450 and that this plant compound is also accountable for lipid  
356 peroxidation *in vitro* as well as *in vivo* (Mangialasche et al., 2010; Schneider et al., 2014). In  
357 their work, Castellano-González et al., (Castellano-González et al., 2016) observed that EGCG  
358 mediates oxidative phosphorylation via activating cytochrome c oxidase (CcO) in human

359 cultured astrocytes and neurons. Furthermore, they also noticed that there is an increased activity  
360 of CcO in 10  $\mu$ M EGCG-treated neurons as compared to the controls. However, the increased  
361 activity of CcO recorded in astrocytes was not statistically significant. EGCG treatments up to 50  
362  $\mu$ M did not elevate the generation of ROS in both human cultured neurons and astrocytes, while  
363 EGCG at 100  $\mu$ M elevated the generation of ROS in neurons. Over generation of ROS is found  
364 to be involved in the stimulation of apoptosis. The presence of CcO dysfunction has also been  
365 detected in individuals with NDs including AD (Castellano-González et al., 2016). Thus it is  
366 likely that treatment with EGCG may restore the functions of mitochondria and avert the  
367 following synaptic functional loss.

368 EGCG exerts neuroprotective effects in SH-SY5Y cells by playing a significant role in the  
369 intracellular signaling mechanism of protein kinase C (PKC). It has been observed that inhibitors  
370 of PKC also take part in the neuroprotective mechanisms of EGCG. On the other hand, the  
371 neurotoxin, 6-hydroxydopamine (6-OHDA), was reported to be inhibited by EGCG through its  
372 activation of PKC phosphorylation (Koh et al., 2003). It has been found that EGCG not only  
373 activates the PKC signaling pathway, but also other pathways including the MAPK, PI3k/Akt,  
374 and pathways regulating calcium influxes (Chen et al., 2017; Ortiz-López et al., 2016).  
375 According to the study by Levites et al., (Levites et al., 2002) EGCG displayed a neuroprotective  
376 effect by restoring the reduced ERK1/2 and PKC phosphorylation levels induced by 6-OHDA,  
377 and by modulating of antiapoptotic-related genes. Furthermore, the study of Ding et al., (Ding et  
378 al., 2017) has demonstrated that EGCG was capable to efficiently suppress sevoflurane-induced  
379 neurodegeneration as well as enhance memory and learning retention of mice through the  
380 activation of CREB/BDNF/TrkB-PI3K/Akt signaling (**Table 2**).

381

382 **- Insert Figure 4-**

383

#### 384 **4.2. Berberine**

385 Berberine (**Fig. 4**), a naturally-occurring isoquinoline alkaloid, can be isolated from the stems,  
386 rhizome, roots, and bark of plants of the genus *Berberis* and also from plants including *Hydrastis*  
387 *canadensis* and *Coptis chinensis* (Koppen et al., 2017). Berberine also crosses BBB, exerts a  
388 direct action on neurons and accumulates in the hippocampus in several brain diseases (Wang et

389 al., 2005). According to the study of Zhang et al., (Zhang et al., 2012d) berberine improves BBB  
390 permeability and displays its neuroprotective effects through the activation of Akt/glycogen  
391 synthase kinase (GSK) signaling, downregulation of NF- $\kappa$ B nuclear transposition, and  
392 upregulation of phosphorylated cyclic AMP response element binding protein (pCREB) (**Table**  
393 **1**). On the other hand, berberine has the ability to stop the activity of a number of enzymes that  
394 are associated with AD progression (Hsu et al., 2013a). According to the study of Hsu et al.,  
395 (Hsu et al., 2013a) berberine demonstrates neuroprotective effects by activating Akt/GSK-  
396 3 $\beta$ /Nrf2-mediated regulation, triggers NGF and BDNF secretion and suppresses tumor necrosis  
397 factor alpha (TNF- $\alpha$ ), cyclooxygenase-2 (COX-2), interleukin 1 $\beta$  (IL-1 $\beta$ ), and nuclear factor-  
398 kappa B (NF- $\kappa$ B) levels (**Table 2**). A number of *in vitro* studies have revealed that H<sub>2</sub>O<sub>2</sub> and  
399 glutamate can induce neurotoxicity. In addition, it was found that cobalt chloride can facilitate a  
400 decreased oxygen environment that connected with neurotoxicity, as well. It was also established  
401 in these *in vitro* studies that berberine has the ability to protect neuronal cells from H<sub>2</sub>O<sub>2</sub>,  
402 glutamate and cobalt chloride-induced neurotoxicity (Cui et al., 2009; Hsu et al., 2013a; Simões  
403 Pires et al., 2014). Furthermore, berberine is useful in the treatment of cobalt chloride-induced  
404 hypoxia. In this regard, berberine plays a key role as a scavenger of ROS (i.e. which can inhibit  
405 multiple apoptosis-promoting agents) produced upon hypoxic conditions, therefore providing  
406 neuroprotective effects (Zhang et al., 2012c). Nevertheless, a study by Kwon et al. (Kwon et al.,  
407 2010) showed that berberine could exert substantial side effects including a fall in the level of  
408 DA neurons as a result of the cytotoxicity of 6-hydroxydopamine.

409 Berberine exerts its neuroprotective properties through activating the PI3K/Akt/Nrf2 pathway by  
410 scavenging radicals. Additionally, berberine exerts anti-apoptotic effects by decreasing the  
411 expression of CASP-1 and -3, Bax along with Bcl-2 upregulation (Asai et al., 2007). Another  
412 study by Hsu et al., (Hsu et al., 2012) revealed that the administration of berberine can prevent  
413 H<sub>2</sub>O<sub>2</sub>-stimulated neurotoxicity by decreasing the expression of cyclin D1, CASP, p53 and  
414 elevating the expression of Bcl-2 associated agonist of cell death (BAD). It has been observed  
415 that at a nanomolar concentration, berberine reduced OS and promoted cell survival via the  
416 downregulation of multiple factors including CASP, Bax, and cytochrome c (Maleki et al.,  
417 2018).

418 Zhang et al. (Zhang et al., 2009) demonstrated that the administration of berberine reduced the  
419 decrease of choline acetyltransferase and SOD activities in an aluminum-induced rat model of  
420 NDs. Interestingly, it has been observed that berberine provides protection against ischemic  
421 stroke by decreasing OS (Kim et al., 2014). Berberine administration can restore memory  
422 function and BDNF levels maintains cholinergic enzyme activity and reduces the expression of  
423 inflammatory molecules (Durairajan et al., 2012).

424 On the other hand, numerous studies have revealed that chronic administration of berberine can  
425 lead to loss of dopaminergic substantia nigra neurons (Kim et al., 2014; Kwon et al., 2010; Shin  
426 et al., 2013). Individuals receiving chronic therapy with levodopa might require the use of  
427 neurotoxic isoquinoline agents along with berberine, though they should be monitored for  
428 adverse reactions (Shin et al., 2013). Berberine exerts anti-apoptotic effects by reducing the  
429 hypoxia-inducible factor 1 $\alpha$  and p53 expression, which are both regarded as the major processes  
430 in order to avert apoptosis via berberine administration (Zhang et al., 2012c). Moreover,  
431 berberine is also believed to reduce ischemic stroke-caused damages via reducing the activity of  
432 gelatinase and by decreasing the expression of the matrix metalloproteinase-9, laminin, and that  
433 of neuronal nuclear protein (Hong et al., 2012). As berberine was reported to solubilize A $\beta$   
434 plaques in mouse models, this compound can thus be useful in the AD treatment (Asai et al.,  
435 2007). It has also been suggested that berberine binds with the N-methyl-D-aspartate (NMDA)  
436 receptor in order to exert its neuroprotective effects. In a caspase-independent manner, berberine  
437 exceeding 1  $\mu$ M decreased the viability of neurons through early changes of mitochondrial  
438 morphology and function. According to the study of Kysenius et al., (Kysenius et al., 2014)  
439 MK-801 and memantine played a significant role in the inhibition of NMDA receptors, which  
440 totally blocked berberine-mediated neurotoxicity.

441 There are still some concerns related to the safety profile of berberine, since some studies  
442 reported that bradycardia and exacerbation of neurodegeneration can take place owing to the use  
443 of berberine. In the study of Kysenius et al. (Kysenius et al., 2014), it was revealed that at  
444 micromolar level, berberine can cause rapid mitochondria-dependent toxicity in primary neurons  
445 and this toxicity was characterized by elevated OS, mitochondrial swelling, reduced  
446 mitochondrial membrane potential and depleted ATP content. Activation of caspase-3 is not  
447 induced by berberine and the resultant neurotoxicity stays unchanged due to the treatment with



448 pan-caspase inhibitor. MK-801 and memantine inhibited the NMDA receptors, which eventually  
449 leads to the complete blockage of berberine-mediated neurotoxicity. In addition, subtoxic  
450 nanomolar berberine concentrations were sufficient to cause sensitization of neurons to rotenone  
451 injury and glutamate excitotoxicity. Nevertheless, more studies are required on the safety profile  
452 of berberine, mainly because of its propensity to gather in the CNS and due to the potential risk  
453 of neurotoxicity linked to its increasing bioavailability.

454 **-Insert Table 1-**

455 **-Insert Table 2-**

456

### 457 **4.3. Curcumin**

458 One of the significant constituents of turmeric is curcumin (**Fig. 4**). A proposed mechanism of  
459 action for curcumin in AD is that it can bind to A $\beta$  by suppressing NF- $\kappa$ B, conferring this  
460 polyphenol the potential to reduce AD pathogenesis (Nam et al., 2014). A study by Kim et al.,  
461 (Kim et al., 2005) reported that out of about 214 compounds possessing anti-oxidant effects,  
462 curcumin exhibited the highest affinity towards A $\beta$ . In aged mice, upon administration of  
463 curcumin, cognitive deficits were ameliorated because of the rise in the levels of BDNF and  
464 CREB (Nam et al., 2014). Furthermore, in a PD model, it has been observed that curcumin can  
465 aid in the regeneration of neurons via activating Trk/PI3K signaling pathways which eventually  
466 increase the levels of BDNF (**Table 2**) (Yang et al., 2014). A study by Hoppe et al., (Hoppe et  
467 al., 2013) exposed that nanoparticles of curcumin can improve cognitive deficit through  
468 recovering the levels of BDNF by activating Akt/GSK-3 $\beta$  signaling pathways. Indeed, curcumin  
469 plays a crucial role in several aspects of NDs. Therefore, curcumin can be used as a cheap and  
470 safe preventive measure in NDs.

471 Current studies are mainly focusing on the discovery of curcumin derivatives which possess  
472 more lipophilic properties helping them to penetrate BBB more easily and thus providing them  
473 more affinity towards A $\beta$  (Mourtas et al., 2011). A study of Garcia-Alloza et al., (Garcia-Alloza  
474 et al., 2007) demonstrated that curcumin could permeate the BBB and labeled senile plaques and  
475 ultimately ameliorates existing plaques in AD (**Table 1**). Present studies carried out in cell  
476 cultures and *in vivo* have also shown that the formation of A $\beta$  plaques can be reduced by  
477 curcumin (Wang et al., 2018). Zhang et al. reported that the activity of curcumin is not only

478 limited to disruption of A $\beta$  levels but also averts APP maturation in mouse neurons (Zhang et al.,  
479 2010a). Indeed, NF- $\kappa$ B inhibition is the main mechanism by which curcumin protects from A $\beta$   
480 plaques. Curcumin can provide protection against the PD through  $\alpha$ -Syn destabilization, as well  
481 (Liu et al., 2014a).

482 Studies have revealed that A $\beta$  plaques in AD individuals possess iron and the presence of this  
483 metal is also accountable for the production of free radicals, lipid peroxidation, advanced  
484 glycation end-products (AGEs), oxidation of DNA and proteins. Interestingly, *in vitro* studies  
485 have revealed that curcumin exhibits an affinity for iron (Liu et al., 2014a). Many works have  
486 reported that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-OHDA can be used to  
487 generate PD models and curcumin was shown to exert neuroprotective effects in these models  
488 through ROS inhibition (Yang et al., 2014; Zbarsky et al., 2005). According to the study of Yu et  
489 al., curcumin suppresses the c-Jun N-terminal kinase (JNK) pathway in MPTP- and 1-methyl-4-  
490 phenylpyridinium (MPP)-induced neurotoxicity in mice models (Yu et al., 2010). It has also  
491 been found that curcumin ameliorates locomotion and lifespan in different fruit fly AD models  
492 (Caesar et al., 2012).

493 In mammals, prepared A $\beta$ -expressing mice were administered with curcumin (Lim et al., 2001),  
494 resulting in curcumin-improved NDs by scavenging ROS, disrupting A $\beta$  plaques, and showing  
495 anti-apoptotic and anti-inflammatory properties (Hoppe et al., 2013). In a recent animal study,  
496 administration of curcumin at a dose of 500 ppm inhibited the aggregation of Huntingtin protein  
497 (Frautschy et al.). Curcumin has also shown various beneficial effects *in vitro*, for example  
498 enhancing the lifespan in *Caenorhabditis elegans* and *Drosophila*, though no improvement in  
499 mice was observed (Liao et al., 2011; Strong et al., 2013). Poor bioavailability of curcumin is  
500 one of the main issues associated with it, however, it can be managed by conjugating curcumin  
501 with lipophilic compounds or by changing its chemical structure (Purpura et al., 2018).

502

#### 503 **4.4. Resveratrol**

504 Resveratrol (**Fig. 4**) is a type of polyphenol found in peanuts, grapes, wine, and tea displaying  
505 numerous biological activities (Jeandet et al., 2018, 2019; Storniolo and Moreno, 2019). A lot of  
506 *in vitro* as well as *in vivo* investigations have shown the potential neuroprotective properties of  
507 resveratrol. For example, copious studies have revealed that resveratrol provides cytoprotective

508 activity in cells exposed to A $\beta$  and/or A $\beta$  -metal complex through sirtuin-3 (SIRT3)-mediated  
509 mechanisms (Granzotto and Zatta, 2011; Yan et al., 2018). In a study of mice with cerebral A $\beta$   
510 deposition, oral administration of resveratrol decreased the activation of microglia associated  
511 with the formation of cortical A $\beta$  plaques (Capiralla et al., 2012). Moreover, long-term  
512 consumption of dietary resveratrol has shown a neuroprotective role of this compound together  
513 with reduced cognitive impairment, tau hyperphosphorylation, and amyloid burden in age-related  
514 AD (SAMP8) mice (Porquet et al., 2013). In addition, increasing scientific evidence suggests  
515 that resveratrol can provide beneficial effects in cells or animals representing PD. For example,  
516 in primary midbrain neuron-glia cultures of rat, resveratrol has been shown to protect against  
517 lipopolysaccharide-induced neurotoxic dopaminergic neurons in a time- and dose-dependent  
518 way, by inhibiting the activation of microglia and the resultant reduction in the release of pro-  
519 inflammatory factors (Zhang et al., 2010b). In a clinical study, resveratrol also improved  
520 pathological changes and motor deficits in MPTP-treated mice by activating Sirtuin-1 (SIRT1)  
521 and the resultant light chain 3 (LC3) deacetylation-mediated autophagic degradation of  $\alpha$ -Syn  
522 (Guo et al., 2016). All of the above investigations have proposed that resveratrol is likely to be a  
523 possible therapeutic or prophylactic solution for NDs.

524  
525 The anti-oxidative activities of resveratrol have comprehensively been reported since the past  
526 years (Chen et al., 2005a; de Sá Coutinho et al., 2018; Wang et al., 2001; Zhang et al., 2008), but  
527 the recent popular discovery of the activation of vitagenes and SIRT1 by resveratrol, has caught  
528 fire (Yazir et al., 2015). Timmers et al., (Timmers et al., 2011) demonstrated that both resveratrol  
529 and energy restriction work in a similar way in increasing life expectancy. The possible  
530 mechanism of resveratrol includes the activation of peroxisome proliferator-activated receptor  
531 (PPAR) and the deacetylation of PGC-1 $\alpha$  (PPAR $\gamma$  coactivator-1) (Zhang et al., 2012a). PPAR  
532 activation can consecutively activate the catalase gene by PI3K/Nrf/Keap pathway (Rubiolo et  
533 al., 2008). Moreover, resveratrol provides neuroprotection by encouraging mitochondrial  
534 biogenesis through adenosine monophosphate (AMP)-activated protein kinase (AMPK)  
535 activation (Wu et al., 2011). The study by Anastácio et al., (Anastácio et al., 2014) reported that  
536 resveratrol exhibits neuroprotective effects by activating ERK-induced CREB regulation,  
537 triggers BDNF, NGF, and glial cell-derived neurotrophic factor (GDNF) secretion, and  
538 suppresses IL10, IL-1 $\beta$ , and NF- $\kappa$ B levels (**Table 2**). One of the main reasons for

539 neurodegeneration is ROS, which is caused by mitochondrial dysfunction and the nicotinamide  
540 adenine dinucleotide phosphate (NADPH) oxidases (Zhang et al., 2010b). All of the above  
541 studies afford evidence that resveratrol provides a favorable solution for neurodegenerative  
542 diseases. Resveratrol is also effective in preventing BBB impairment and inhibiting A $\beta$ 1–42  
543 from crossing the BBB and accumulating in the hippocampus (Omar, 2017; Zhao et al., 2015).  
544 According to the study of Wang et al., (Wang et al., 2002) resveratrol could cross the BBB and  
545 demonstrate protective effects against cerebral ischemic injury (**Table 1**).

546

547

548

#### 549 **4.5. Quercetin**

550 Flavonoids are widely known for their anti-oxidant activities and quercetin, one member of the  
551 flavonoid group (**Fig. 4**), has been extensively investigated for its anti-proliferative properties  
552 (Lesjak et al., 2018). Heo and Lee (Heo and Lee, 2004) reported the protective activities of  
553 quercetin on H<sub>2</sub>O<sub>2</sub>-mediated neurodegeneration in pheochromocytoma cells (PC12) cells.  
554 Findings also revealed that quercetin treatment convincingly ameliorates cell viability. In  
555 addition to this, quercetin exhibited an increased antioxidant protective activity as compared to  
556 vitamin C. Indeed, 10  $\mu$ M quercetin exerted protective activities in neurons and also exhibited a  
557 superior cell viability effect over 30  $\mu$ M (Heo and Lee, 2004). It has been shown to cross the  
558 BBB and prevents H<sub>2</sub>O<sub>2</sub>-induced cytotoxicity, as well (Heo and Lee, 2004). According to the  
559 study of Ishisaka et al., (Ishisaka et al., 2011) quercetin could permeate the BBB and protect it  
560 from disorders connected with oxidative stress in an animal model (**Table 1**).

561 Quercetin regulates the activity of kinases that consecutively modulate gene expression and  
562 cellular function. The arrangement of the functional groups also plays an important role in the  
563 properties of quercetin (Barreca et al., 2016). The activity of quercetin is influenced by some  
564 factors including time exposure and cell type, and at higher doses (>100  $\mu$ M) it shows cytotoxic,  
565 apoptotic, genotoxic, and anti-proliferative properties. Dajas et al., (Dajas et al., 2015)  
566 demonstrated that quercetin regulated NF- $\kappa$ B which could consecutively improve inflammatory  
567 processes associated with neurodegenerative diseases. Numerous studies (Liu et al., 2013, 2015;  
568 Suganthy et al., 2016) have reported that quercetin demonstrates neuroprotective activity by

569 regulating synaptic plasticity, learning, and neuronal adaptation through signaling pathways of  
570 the PI3K/Akt/Nrf2, ERK/CREB/BDNF, PGC-1 $\alpha$ /fibronectin type III domain containing 5  
571 (FNDC5)/BDNF, and activation of SIRT1 (**Table 2**).

572 Quercetin has also been found to modulate protein kinases, lipid kinases including the PI3k,  
573 tyrosine kinases, Akt/PKB, MAP kinases, and PKC (Dajas et al., 2015). This is useful as it  
574 modifies the state of phosphorylation of the target molecules hence deciding the cellular fate.  
575 Moreover, quercetin has been shown to activate pro-apoptotic as well as anti-apoptotic pathways  
576 (Bournival et al., 2009). Quercetin also plays an important role in increasing the biogenesis of  
577 mitochondria and this is an essential feature as mitochondrial dysfunction results in degenerating  
578 neurons by depleting adenosine triphosphate levels and generating ROS. Therefore, quercetin  
579 has the potential to protect from NDs through mitochondria-targeted activities (Dajas et al.,  
580 2015). Nonetheless, before the clinical trials of quercetin, there is a need for more evidence about  
581 the absorption and metabolism of quercetin after its oral administration (Moreno et al., 2017).

582

## 583 **5. Conclusion**

584 At the molecular and cellular levels, an increased level of neuronal damage might be associated  
585 with the pathogenesis of NDs. Possibly, OS can cause neuronal cell death by elevating the  
586 concentration of intracellular Ca<sup>2+</sup>, glutamate-mediated excitotoxicity, reducing overall survival  
587 signaling, activation of death-signaling cascades, and mitochondrial dysfunction. Polyphenols  
588 indeed provide protection against neuronal damage and this article elucidates the multiple  
589 mechanisms by which they can act against NDs. Although a number of studies have revealed  
590 their potential benefits, more extensive studies are required to establish the efficacy and long-  
591 term effects of using polyphenols as therapeutics for NDs.

592

593

## 594 **Author contributions**

595 MSU conceived the original idea and designed the outlines of the study. MSU, AAM, MTK, and  
596 JA wrote the draft of the manuscript. MSU and AAM prepared the figures for the manuscript. PJ  
597 edited the whole manuscript. MSS, GMA, and LA performed the literature review and aided in  
598 revising the manuscript. All authors have read and approved the final manuscript.

599

600 **Acknowledgments**

601 The authors concede the support by the Pharmakon Neuroscience Research Network, Dhaka,  
602 Bangladesh.

603

604 **Conflict of interests**

605 The authors proclaim no conflict of interest.

606

607 **Funding**

608 This project was supported by the Pharmakon Neuroscience Research Network, Dhaka,  
609 Bangladesh.

610

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1329

1330 **Figure Legends**

1331 **Figure 1: The role of oxidative stress in the pathogenesis of neurodegenerative diseases.**

1332 Several events like environmental factors, mitochondrial dysfunction as well as cellular  
1333 metabolic process are responsible for oxidative stress. Protein misfolding and aggregation are  
1334 common hallmarks of several neurodegenerative disorders. Oxidative stress activates PP2A,  
1335 p38MAPK, and JNK that lead to increase expression of neurotoxic A $\beta$  and tau (hallmarks of  
1336 Alzheimer's disease) that further increase cellular levels of ROS and RNS and results in  
1337 neurodegeneration. Furthermore, oxidative stress causes neuronal dysfunction by atypical  
1338 misfolding and aggregation of  $\alpha$ -synuclein (for Parkinson's disease), mHtt (for Huntington's  
1339 disease), and TDP-43 for (amyotrophic lateral sclerosis) by augmenting ROS and RNS levels.  
1340 ROS, reactive oxygen species; RNS, reactive nitrogen species; PP2, protein phosphatase 2;  
1341 p38MAPK, mitogen-activated protein kinase p38; JNK, c-Jun N-terminal kinase; mHtt, mutant  
1342 huntingtin; TDP-43, TAR DNA binding protein 43; NOX, NADPH oxidase; NFTs,  
1343 neurofibrillary tangles.

1344

1345 **Figure 2: Mechanism of oxidative stress-mediated neuronal apoptosis and**

1346 **neurodegeneration.** A number of pathogenic intracellular events like endoplasmic reticulum  
1347 stress and mitochondrial dysfunction cause oxidative stress by increasing Ca<sup>2+</sup> influx and  
1348 subsequent neuronal excitotoxicity. Excessive production of reactive species causes oxidation of  
1349 proteins, lipids, and nucleic acids that lead to neurodegeneration. Oxidative stress causes  
1350 activation of the p53 apoptotic pathway leads to the expression of Noxa, Bax, and Puma. The  
1351 expression of Puma causes the release of cytosolic p53 that held inactive by binding with Bcl-xL.  
1352 P53 and Bcl-xL complex cause Bax oligomerization and mitochondrial translocation.  
1353 Accumulation of intracellular p53 serves as a major source of mitochondrial p53 that induces  
1354 Bax and Bak oligomerization as well as antagonize the antiapoptotic effect of Bcl-2 and Bcl-xL  
1355 in the mitochondria. As a result, mitochondrial cytochrome c is released that stimulates the  
1356 activation of caspase pathways that lead to neuronal apoptosis and finally neurodegeneration.  
1357 p53, tumor suppressor protein p53; 8-OHG, 8-hydroxyguanosine; 8-OHdG, 8-hydroxy-2'-  
1358 deoxyguanosine; 4-HNE, 4-hydroxy-2-nonenal; MDA, malondialdehyde; Noxa, phorbol-12-  
1359 myristate-13-acetate-induced protein 1; Puma, p53 upregulated modulator of apoptosis; Bax,

1360 Bcl-2-associated X protein, Bak, Bcl-2 antagonist/killer; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-  
1361 cell lymphoma-extra-large.

1362

1363 **Figure 3: Role of polyphenols involved with neurotrophins to alleviate the progression of**  
1364 **neurodegenerative diseases by activating the TrkB receptor.** Polyphenols or neurotrophins  
1365 especially BDNF binds to the TrkB receptor, which activates PI3K/Akt, Ras/ERK 1/2 and PL-C $\gamma$   
1366 pathways and eventually phosphorylates CREB protein. Subsequently, CREB increases the  
1367 transcription of target genes coding NTFs, Bcl-2 and antioxidant genes that regulate cell survival  
1368 and ultimately inhibit neurodegeneration. Polyphenols also trigger Keap-Nrf2-ARE cascade and  
1369 increase the expression of antioxidant enzymes and proteins, which play an essential role in  
1370 increasing the neuroprotective activity. In addition, polyphenols also inhibit the ROS and GSK3 $\beta$   
1371 that leads to neurodegeneration. Trk, tropomyosin-related kinase; BDNF, brain-derived  
1372 neurotrophic factor; PI3K, phosphatidylinositol-3-kinase; MEK, MAP kinase kinase; MAPK,  
1373 mitogen-activated protein kinase; ERK, extracellular signal-regulated kinases; PL-C $\gamma$ ,  
1374 phospholipase C $\gamma$ ; PKC, protein kinase C; CaMKII/IV, Ca<sup>2+</sup>-calmodulin kinase II/IV; Nfr2,  
1375 nuclear factor erythroid 2-related factor 2; CREB, cyclic adenosine monophosphate response  
1376 element-binding protein; CRE, cyclic adenosine monophosphate response elements; GSK3 $\beta$ ,  
1377 glucose synthase kinase-3 $\beta$ ; ROS, reactive oxygen species; Akt, protein kinase B; Ras, a small  
1378 GTPase; Keap1, Kelch-like ECH associated protein; ARE, antioxidant response element; NTFs,  
1379 neurotrophic factors; Bcl-2, B-cell lymphoma 2.

1380

1381 **Figure 4: Chemical structures of several neuroprotective polyphenols.**

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1383

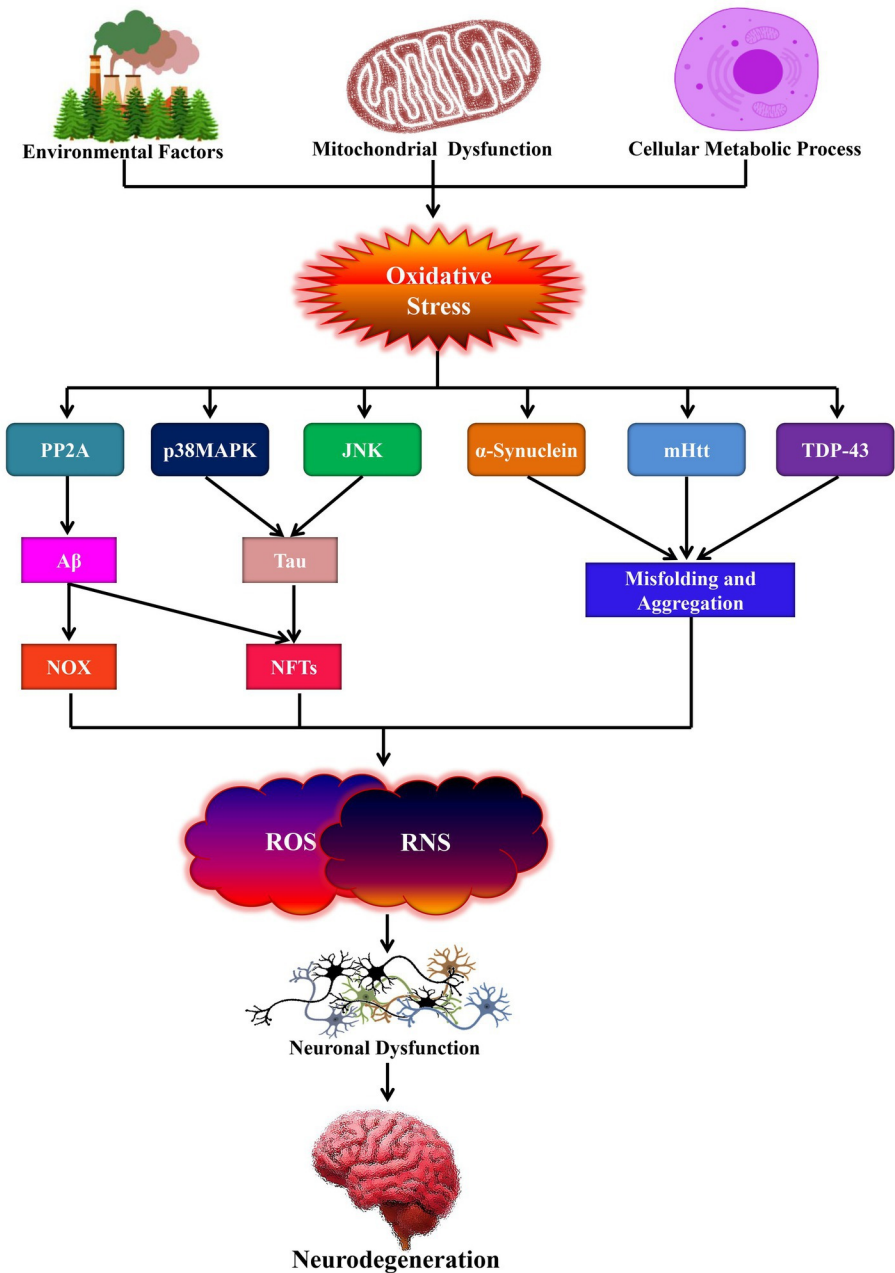
1384 **Tables**

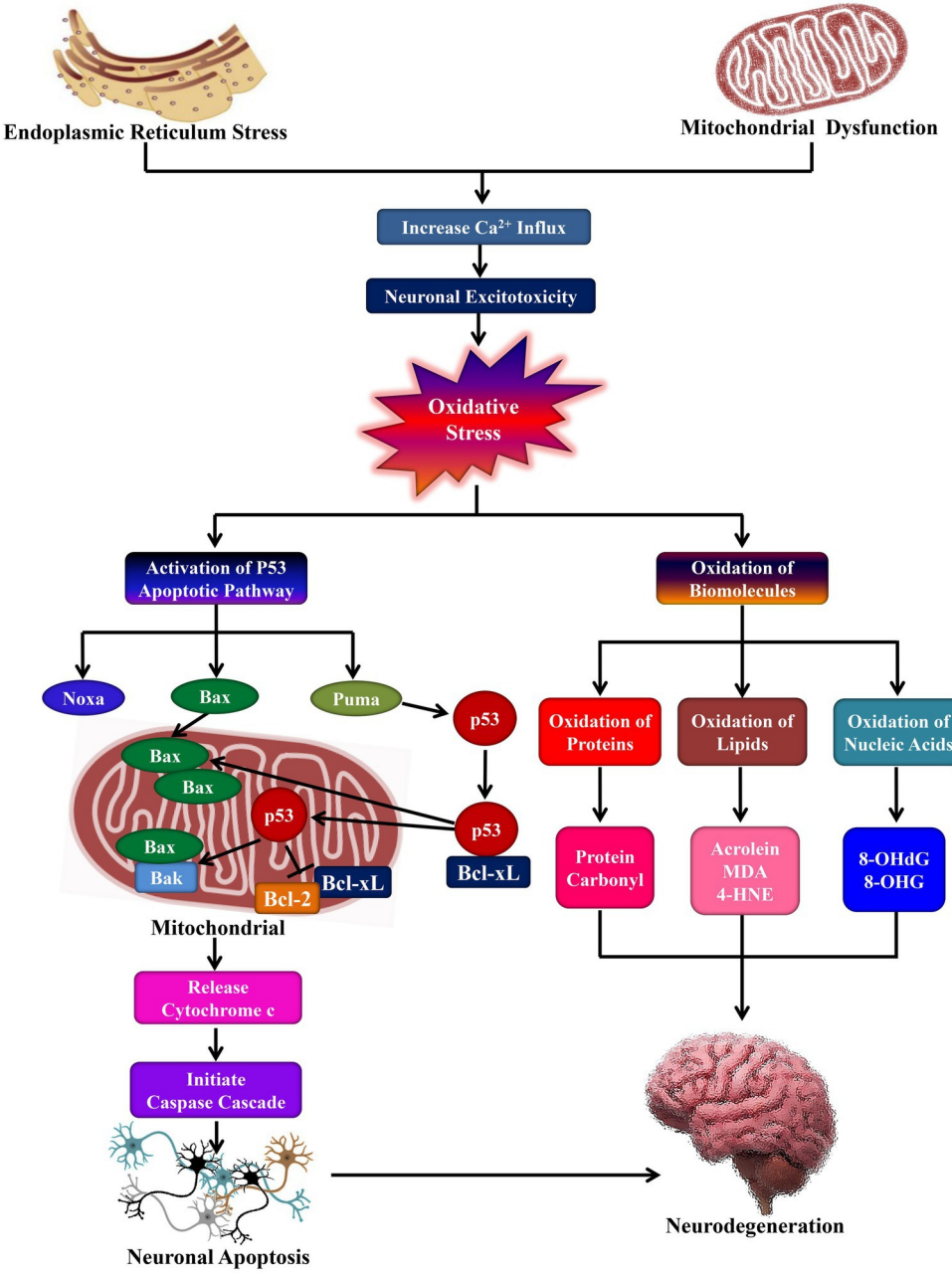
1385 **Table 1: The blood-brain barrier permeability of different polyphenols for**  
1386 **neuroprotection.**

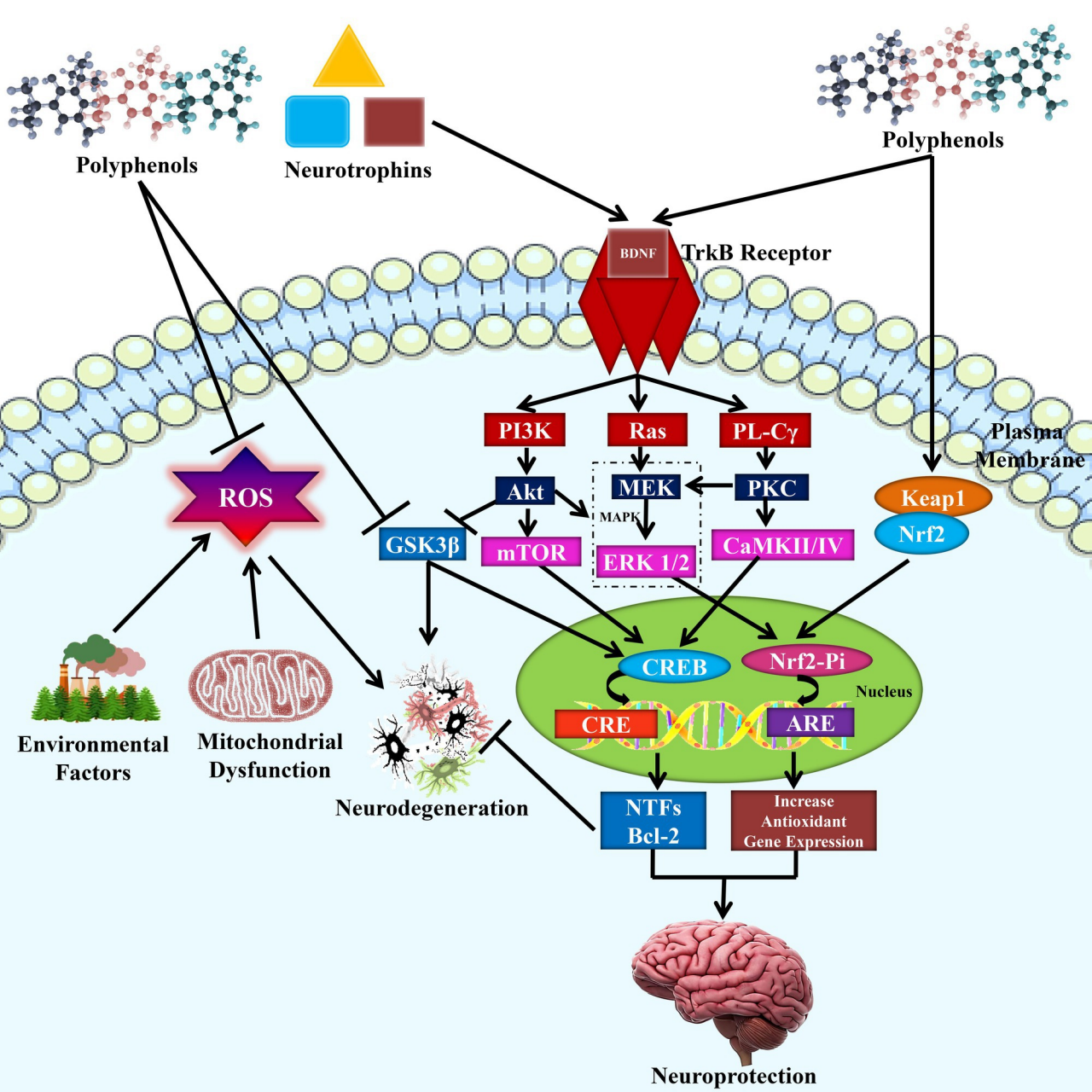
1387

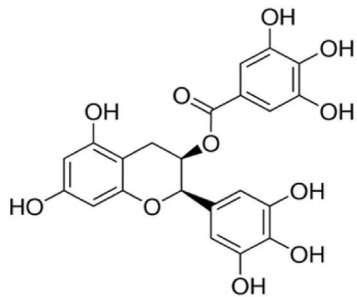
1388 **Table 2: The effects of different polyphenols on neurotrophin factors to combat**  
1389 **neurodegeneration.**

1390

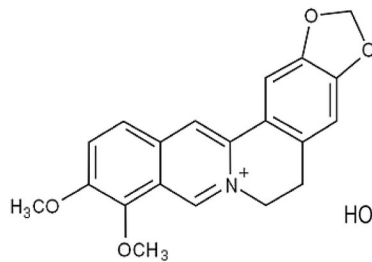




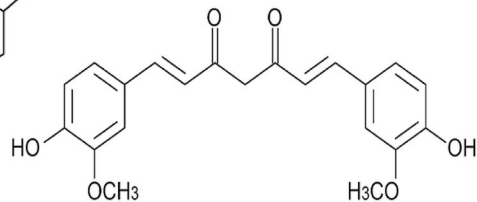




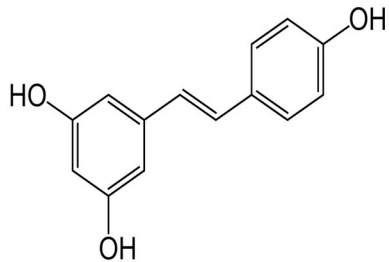
**Epigallocatechin-3-Gallate**



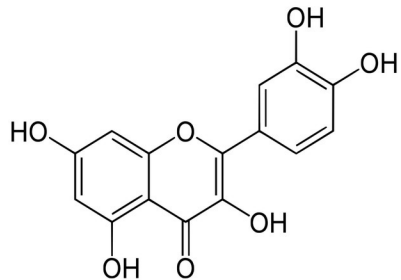
**Berberine**



**Curcumin**



**Resveratrol**



**Quercetin**

**Table 1: The blood-brain barrier permeability of different polyphenols for neuroprotection.**

Phytochemicals	Species/Studied Materials	Dose	Route of Administration	Neuroprotective Effects	BBB Permeability	References
	Male SAMP10/TaSlc (SAMP10) mice and human neuroblastoma SH-SY5Y cells	20 mg/kg	Oral	Ameliorates cognitive dysfunction by increasing brain plasticity	EGCG crosses the blood-brain barrier (BBB) and reaches the brain parenchyma at a very low concentration	(Pervin et al., 2017)
Epigallocatechin-3-gallate (EGCG)	Male pathogen-free Sprague-Dawley rats	100 mg/kg	Oral	Improves learning and memory dysfunctions	Different pharmacokinetic and tissue distribution patterns confirm the BBB permeability of EGCG	(Wei et al., 2019)
	Male Wistar rats	0.1% (w/v)	-	Inhibits neuronal stem cell death by free radicals and ameliorates traumatic brain injury	EGCG crosses the BBB due to its lipophilicity	(Itoh et al., 2012)
Berberine	Male Sprague-Dawley rats	10 and 40 mg/kg	Intraperitoneal injection	Exerts neuroprotective effect through activation of the Akt/GSK signaling pathway, upregulation of pCREB, downregulation of NF-κB nuclear transposition	Berberine ameliorates BBB permeability	(Zhang et al., 2012d)

	Male Wistar rats	3 mg/kg	Intravenous injection	Directly acts on neuron and accumulate in the hippocampus	Berberine penetrates the BBB to reach the hippocampus	(Wang et al., 2005)
	Male Wistar rats	187.75 mg/kg/day		Enhances spatial learning memory impairment	Berberine can cross the BBB and improves APP misprocessing in the hippocampus	(Wang et al., 2019)
	Adult male C57BL/6 mice	100 mg/kg	Intraperitoneal injection	Improves neurologic outcomes and attenuates brain edema by preserving BBB integrity	BBB permeability of curcumin was increased in the left hemisphere, right hemisphere, cerebellum, and brain stem	(Yuan et al., 2017)
Curcumin	Human Alzheimer's and Tg2576 Mouse Brain	500 ppm	Injected peripherally into the carotid artery of aged mice	Attenuates amyloid in Alzheimer's disease	Curcumin crosses the BBB and labels plaques and reduced amyloid levels	(Yang et al., 2005)
	Adult male and female APPswe/PS1dE9 mice	7.5 mg/kg/day	Intravenous injection	Attenuates existing plaques in Alzheimer's disease	Curcumin crosses the BBB and labels senile plaques	(Garcia-Alloza et al., 2007)
	Chinese Kun Ming mouse	Up to 2000 mg/kg	Oral	Effective in the treatment of Alzheimer's disease	Derivative of resveratrol crosses the BBB <i>in vitro</i>	(Lu et al., 2013)
Resveratrol	Adult male Mongolian gerbils	30 mg/kg	Intraperitoneal injection	Neuroprotective effects against cerebral ischemic injury	Resveratrol in the brain reached a peak at 4 h	(Wang et al., 2002)



	Male Wistar rats	12.5 mg/kg	Intraperitoneal injection	Neuroprotective effects by up regulating several detoxifying enzymes	Resveratrol crosses the BBB and modifies antioxidant isoenzyme patterns	(Mokni et al., 2007)
	Male Wistar rats	50 and 200 mg/kg	Oral	Inhibits oxidative stress and protects from disorders connected with oxidative stress	Quercetin can access the brain and reduces the increased oxidative stress in the hippocampus	(Ishisaka et al., 2011)
Quercetin	Male Sprague Dawley rats	2.7 mg/kg	Oral gavage	Exerts neuroprotective effects by maintaining antioxidant levels	Nano-encapsulated quercetin can access in different brain regions	(Ghosh et al., 2013)
	Male Sprague-Dawley (SD) rats	25 $\mu$ mol/kg	-	Reduces brain edema and BBB leakage, and enhances BBB dysfunction via Wnt signaling pathway	Quercetin crosses the BBB	(Jin et al., 2019)

**Table 2: The effects of different polyphenols on neurotrophin factors to combat neurodegeneration.**

Phytochemicals	Species/Study Material	Experimental Model	Effects	Mechanisms	Induced Neurotrophins	References
Epigallocatechin-3-gallate	Pregnant C57BL/6 mice	Sevoflurane-induced neurotoxicity	Improve learning and memory retention	Activates cyclic AMP response element binding protein (CREB)/ brain-derived neurotrophic factor (BDNF)/ tropomyosin receptor kinase B (TrkB)-phosphoinositide 3-kinase (PI3K)/ protein kinase B (Akt) signaling pathway	Brain-derived neurotrophic factor (BDNF)	(Ding et al., 2017)
	PC12 cells	Oxidative-radical-stress-induced apoptosis	Neurodegenerative diseases	Activates PI3K/Akt and inhibits glycogen synthase kinase (GSK)-3	Nerve growth factor (NGF)	(Koh et al., 2003)
	Rats	Acrylamide-treated	Attenuates cerebral cortex damage and enhances brain regeneration	Increases acetylcholinesterase activity and decreases the expression of inducible nitric oxide and cyclooxygenase-2 (COX-2) level	BDNF	(He et al., 2017)
Berberine	SH-SY5Y cells	Glucose-induced neurotoxicity	Neuritogenesis, neuroinflammation, and neuroprotection	Activates Akt/GSK-3 $\beta$ / nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated regulation,	BDNF, NGF	(Hsu et al., 2013b)

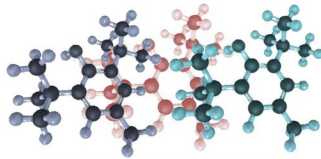
				cholinergic activity-induced neurite outgrowth, and inhibits COX-2, tumor necrosis factor- $\alpha$ (TNF- $\alpha$ ), nuclear factor-kappa B (NF- $\kappa$ B), and interleukin (IL)-1 $\beta$ levels		
	Rats	Middle cerebral artery occlusion model	Neuroprotection	Reduction of striatum apoptosis via the BDNF-TrkB-PI3K/Akt signaling pathway	BDNF	(Yang et al., 2018)
	CD1 and C57 mice	chronic social defeat stress model	Ameliorates depressive-like behaviors	Upregulation of neuronal per-arnt-sim domain protein 4 and BDNF expressions in hippocampus	BDNF	(Deng et al., 2018)
Curcumin	Male Sprague-Dawley (SD) rats	6-hydroxydopamine-induced Parkinson's disease	Neural regeneration and neuroprotection	Activates Trk/PI3K signaling pathways	BDNF	(Yang et al., 2014)
	Rats	$\beta$ -amyloid-induced cognitive impairments	Improves cognitive deficit and neuroprotection	Activates PI3K/Akt signaling pathways and inhibits GSK-3	BDNF	(Hoppe et al., 2013)
	Rodent cortical neurons	-	Neuroprotection	Mediates through BDNF/TrkB-mitogen-activated protein kinase (MAPK)/PI3K-cyclic AMP response element binding protein (CREB) signaling	BDNF	(Wang et al., 2010)

pathway						
Resveratrol	Adult Wistar rats	Two-vessel occlusion	Neuritogenesis, neuroinflammation, and neuroprotection	Activates extracellular signal-regulated kinase (ERK)-mediated CREB regulation and inhibits IL-10, IL-1 $\beta$ , and NF- $\kappa$ B levels	BDNF, glial cell-derived neurotrophic factor (GDNF), NGF	(Anastácio et al., 2014)
	Female Wistar rats	-	Neurological diseases	Induces the phosphorylation of ERK1/2 and CREB in astroglia	BDNF, GDNF	(Zhang et al., 2012b)
	Male Wistar rats	Phenylephrine-induced contraction of vascular smooth muscle cells	Neuroprotection	Increases BDNF serum concentrations and reduces the contractility of resistance arteries via nitric oxide synthase-independent mechanisms	BDNF	(Wiciński et al., 2017)
Quercetin	Male Chinese Kunming mice	High fat diet	Ameliorates cognitive impairment	Modulates PI3K/Akt/Nrf2 pathway and activates CREB pathway	BDNF	(Xia et al., 2015)
	Male Wistar albino rats	Streptozotocin-induced diabetes model	Neuroprotection	Activates Akt survival pathway, increases the level of TrkB and Bcl-2 and decreases the level of both caspase-3 and cytochrome c	BDNF, NGF	(Ola et al., 2017)

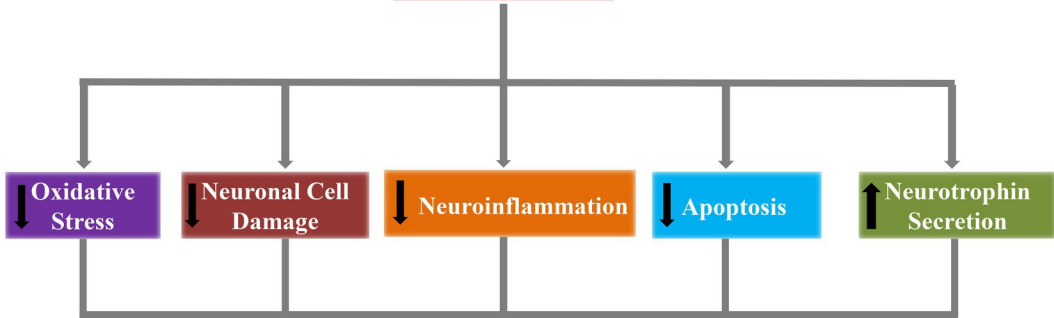
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Adult male albino rats	Polychlorinated biphenyls-induced neurotoxicity	Protects and prevents neuronal damage	Prevents transmembrane tight junctional proteins, cytoplasmic accessory tight junctional proteins in the hippocampus as well as maintains the level of estradiol	BDNF	(Selvakumar et al., 2019)
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**Polyphenols**



**Neuroprotection**