Protective Mechanisms of Pomegranate Polyphenols in Neurodegenerative Diseases

Subjects: Integrative & Complementary Medicine

Contributor: Simona Aleksandrova, Ralitza Alexova, Stela Dragomanova, Reni Kalfin, Ferdinando Nicoletti, Paolo Fagone, Maria Cristina Petralia, Katia Mangano, Lyubka Tancheva

Pomegranate (*Punica granatum* L.) is a polyphenol-rich food and medicinal plant containing flavonols, anthocyanins, and tannins. Ellagitannins (ETs) are the most abundant polyphenols in pomegranate. A growing body of research shows that polyphenol-rich pomegranate extracts and their metabolites target multiple types of brain cell and support their redox balance, proliferation and survival, as well as cell signaling. Independent studies have demonstrated that the significant neuroprotective effects of ETs are mediated by their antioxidant and anti-inflammatory effects, their chelating properties, by their ability to activate various signaling pathways, as well as the ability to influence mitochondrial damage, thus regulating autophagy, apoptosis and neurotransmitter signaling.

Keywords: pomegranate ; antioxidants ; amyloid

1. Misfolded Protein Deposition

Small soluble Aβ oligomers play a crucial role in Alzheimer's disease (AD) pathogenesis, hence, selective inhibition of Aβ oligomer formation represents an optimal target for the development of innovative AD therapies. It is well known that an oxidative environment can promote protein misfolding. Glia is involved in clearing up protein fragments and toxic oligomers of the proteins, but if the process is inefficient, as occurs with cumulative stress and ageing, misfolded proteins can influence the integrity of neuronal cells, endothelial cells and the BBB [1]. Their accumulation can lead to deficits in cognition and altered behavior. Typical examples of misfolded protein in the brain include Aβ plaques and intracellular deposits of hyperphosphorylated Tau neurofibrillary tangles. These are believed to be late markers of disease, preceded by smaller but more neurotoxic oligomers. In Parkinson's disease (PD), aggregation of α-synuclein (αSyn) in Lewy bodies is also a feature. Ellagitannins (ETs) appear to be able to reduce the amount of misfolded protein in the CNS not only by their antioxidant activity, which will provide a better redox balance, but apparently also by direct interaction with the proteins themselves.

Pomegranate extract limits Aβ accumulation both in vivo and in vitro with a proposed involvement of β-secretase (BACE) pathway in amyloid processing in some studies [2][3]. This was also observed in transgenic mice supplemented with EA, where Aβ decreased along with the phosphorylated forms of BACE1, Amyloid Precursor Protein (APP) and Tau. Ellagic acid (EA) in vitro was able to decrease αSyn aggregation in a dose-dependent manner, to dissociate already formed aggregates and decrease their neurotoxicity. Researchers have shown that EA is able to restore the scopolamine-induced changes in the conformation of water-soluble proteins in the brain [4][5].

PUN and EA both have the capacity to disaggregate Aβ, perhaps through their direct interaction with the hydrophobic amino acids in the amyloid structure [5]. Each of the two polyphenols appeared to produce a different organization of the amyloid fiber, and therefore may interact with different regions of this polypeptide [5]. One study revealed that EA promotes Aβ42 fibrillization and inhibits Aβ42-induced neurotoxicity [6]. A dose-dependent decrease in levels of pathogenic Aβ oligomers and Aβ cytotoxicity has also been found. This is consistent with the hypothesis that plaques are actually a protective mechanism against toxic Aβ oligomers transformed into less toxic fibrils [7].

2. Oxidative Stress

The brain is particularly susceptible to oxidative stress due to its high O_2 consumption and low levels of endogenous antioxidants. Infection and ageing can further deplete its already low antioxidant pool [8][9]. Stress, both physical and emotional, depression and sleep deprivation can cause reactive oxygen and nitrogen species (RONS) formation at a rate that overwhelms the brain antioxidant defense [9]. Batandier et al. [10] showed that acute emotional stress can increase oxidative stress in the brain, and this is further modulated by the diet.

Oxidative stress in the CNS may lead to lipid peroxidation, which in turn could be responsible for Aβ fibrillization and neuronal death or demyelination, thus affecting the function of the brain [11].

Polyphenols are considered exogenous antioxidants that complement the endogenous antioxidant system (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glutathione, etc.) in order to maintain the cellular redox balance [9].

Pomegranate is able to reduce oxidized low-density lipoprotein levels and to inhibit oxidation caused by Cu^{2+} ions [12]. Pomegranate polyphenols and their metabolites can decrease lipid peroxidation in the nervous system in a variety of RONS-generating experimental setups. This effect is unlikely to be caused by urolithin metabolites of pomegranate, which showed 42-fold lower antioxidant activity than PUN [13].

Aqueous pomegranate extract had a protective effect against reactive oxygen species ROS production in brains, and simultaneously decreased lipid peroxidation [14]. The extract, along with purified PUN, was able to trap the OH radical and $ONOO^-$, in contrast to EA at the same concentrations. EA was also less effective at interacting with superoxide, but better at protecting against lipid peroxidation. PUN decreased lipid peroxidation after brain hemorrhage, as well as after ischemic stroke. Pomegranate extract prevented lipid peroxidation in the hypothalamus of spontaneously hypertensive rats [15]. In the hippocampus, pomegranate flower extract also decreased oxidized lipids. In the same brain region, in mice under chronic stress, pomegranate fruit extract decreased lipid peroxidation, as measured by malonyl dialdehyde (MDA). Pomegranate peel extract lowered oxidized lipids and NO (nitric oxide) accumulation not only in animals treated with oxidative stress-inducing aluminum, but also in untreated animals [16]. This change in the lipidome of healthy animals may be advantageous if they are subsequently exposed to oxidative stress.

As noted above, EA appears to be particularly efficient at preventing lipid oxidation. This was shown in researcher' studies on a rat PD model and on a mouse scopolamine-induced dementia [5][16], in the hippocampus of sleep deprived animals [17]. EA acted on a subcellular level in a Huntington's disease model, decreasing lipid peroxidation in brain mitochondria [18]. A specific property of UA but not EA is the stimulation of sphingolipid synthesis from palmitic acid, in oligodendrocytes [19]. In these cells, EA was also able to preserve demyelination but did not stimulate sphingolipid synthesis [20]. Many studies on the effect of pomegranate polyphenol supplementation have also measured either the expression levels or activity of the endogenous antioxidant enzymes: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione (GSH). A study conducted by researcher's group demonstrated that EA improved the antioxidant capacity of neurons in the 6-OHDA model of PD by increasing CAT, SOD and GSH activity [5]. However, unlike the case of decreased lipid peroxidation, healthy animals did not experience upregulation of antioxidant enzymes SOD, CAT, GPx, and GR when exposed to pomegranate polyphenols.

The beneficial effect of pomegranate extracts and active compounds seems to decrease at high concentrations, under which conditions the polyphenols may act as prooxidant [21]. Increased activity or expression of the endogenous antioxidant enzymes was observed in a variety of stress-inducing conditions [22][23][24][25] and brain regions, as well as in vitro, indicating a direct effect on neuronal cells. Even though similar effects were achieved for manganese-treated neurons with other well-known antioxidants, such as vitamin E and niacin, the greatest effect was observed with PUN [4]. This ET changed intracellular antioxidant levels dose dependently in human neuroblastoma culture [25], showing that pomegranate-derived substances modulate not only the antioxidant capacity of the extracellular milieu, but also intracellular redox balance.

In the process of respiration, mitochondria produce semi-reduced free radicals, superoxide and hydrogen peroxide, that cause oxidative stress [22][23][24][25][26][27]. In NDD, various oxidative reactions lead to neuronal death [28], and molecules such as vitamins, lipoic acid, and antioxidant enzymes, as well as redox-sensitive protein transcription factors, are able to alleviate the neuronal oxidative stress [29][30][31][32][33].

3. Inflammation

There is a vast amount of data confirming the role of inflammation in NDD, including AD and PD. Chronic inflammation can lead to neuronal loss, and the activation of microglia can contribute to the onset and progression of NDD including AD, PD, Amyotrophic Lateral Sclerosis (ALS) and MS. When macrophages are classically activated to M1 polarization, they induce a proinflammatory environment, while a shift to an M2 profile promotes neuroprotection [34][35]. UA is able to induce M2 polarization in bone marrow-derived macrophages (BMDM) and microglia, showing that it can elicit similar responses in both peripheral and resident immune cells [34][35].

In peripheral macrophages, punicalin had the strongest effect in shifting the profile away from M1, stronger than pomegranate juice, EA or gallic acid [35]. UA, EA, and pomegranate flower extract decreased Glial fibrillary acidic protein (GFAP), a marker of astroglia activation. In a model of PD, both astrocyte and microglia activation were suppressed by UA [36] The EA effect was particularly strong in the astroglia-neuron, but not in the microglia-neuron coculture, even without direct contact between the different cell types [37].

Three proinflammatory cytokines, IL-1β, IL-6 and TNFα, were increased in response to multiple stressors but decreased in brain tissue in vivo and in vitro upon administration of pomegranate extracts and ET downstream metabolites [38][39][40][41]. EA has also been shown to affect neuroinflammation by suppressing the NLRP3 inflammasome, involved in the neuroinflammation process in PD. In in vitro studies, EA has been found to inhibit nigrostriatal dopaminergic neurons specifically by affecting NLRP3 function [42].

The levels of the anti-inflammatory IL-10 were also investigated, and were found to increase in parallel with the decrease in proinflammatory cytokines [2][15]. In some reports, the cytokine levels in serum changed as well, indicating a systemic inflammatory process not limited to the CNS, which nevertheless responded to the presence of pomegranate polyphenols [2][15].

IL-17 is a cytokine produced by Th17 cells that may be implicated in the pathogenesis of MS. It also mediates monocyte–endothelial interactions and passage through the BBB. Pomegranate extract dose-dependently suppressed IL-17 generation in CD4+ activated cells, without altering IL-17 levels in healthy rats [39]. Additionally, UA has been shown to decrease IL-17 production in and microglia [2].

Prostaglandins (e.g., PGE2), produced by cyclooxygenase (COX), contribute to the development of inflammation and pain perception. They may also be involved in creating an inflammatory environment that stimulates protein misfolding in AD [40]. Both amyloid formation and PGE2 synthesis in neuroblastoma cells stimulated with IL-1β were lowered upon the addition of pomegranate extract [40]. COX2 decreased with PUN treatment in manganese-induced stress [4]. Furthermore, PUN decreased not only COX2, but also mPGES1, as well as PGE2 levels in the supernatants of microglia cell culture and hippocampal slice culture [37]. Thus, pomegranate ETs are able to modulate prostaglandin synthesis in several CNS cell types.

It is likely that EA interacts with the Fe in the protoporphyrin active site of COX enzymes. This hypothesis is supported by the lack of an effect when competitive COX inhibitors are used in conjunction with EA treatment [41]. The effect is strongly dose dependent, with a bell-shaped curve of different concentrations of EA on PGE2 synthesis. Up to 1 µM EA, PGE2 synthesis was stimulated, and above 10 µM, it was slightly decreased [41]. At an oral dose of 6 mg/kg, EA also increased $[PGE]_{plasma}$ in rats [41].

Autophagy is linked to neuroinflammation and neurodegeneration [43]. Inefficient autophagy leads to the accumulation of debris, which in turn leads to apoptosis [44]. In chronic inflammation, it has been hypothesized that M2 polarization cannot be maintained due to insufficient or ineffective mitophagy and autophagosome flux. Both PUN and EA induce autophagy and improve autophagosome formation [35]. Toney et al. [45] reviewed the role of UA in different pathological scenarios, including neuropathology, and showed that UA is able to improve autophagy during inflammation and consequently, to increase cell viability, via the regulation of the mechanistic target of rapamycin (mTOR) pathway [46]. UA increased autophagy in microglia and its neuroprotective effects were lost when autophagy was blocked [43]. UA also increased autophagy in neurons following trauma [47].

Sun et al. observed that the regulator of mitophagy, Beclin1, was affected by exposure to pomegranate extract. This maintained mitochondrial clearance and mitochondrial biogenesis at appropriate levels [15]. Mitophagy was more effective when UA pretreatment was given to lipopolysaccharide (LPS)-stimulated microglia. When a mitophagy inhibitor was used, the UA suppression of NLRP3 inflammasome activation was abolished, suggesting that the urolithin acts by supporting the mitophagy flux in microglia [48]. If mitophagy is inefficient, ROS generation from mitochondria increases and can activate the inflammasome NLRP3, thereby linking oxidative stress and inflammation [49].

Whole pomegranate extracts, PUN, EA, and UA, administered by different routes in vivo, as well as in in vitro studies, revealed that such treatment decreases the pro-apoptotic Cas-3 and Bax and increases the antiapoptotic Bcl-2 at both the transcript and protein levels in neurons, microglia and oligodendrocytes.

From the above, it may seem that an antiapoptotic effect, such as the one observed for CNS tissues and stressed neuronal and glial cells is the default response to pomegranate ETs. However, Venusova et al. [49] reviewed the immune and physiological functions of PUN, which in cancer cells increased Bax and decreased Bcl-2 and Bcl-XL to stimulate

apoptosis, release of mitochondrial cytochrome c, and activation of Cas-9 and Cas-3. In Herpes simplex virus 1 (HSV-1)-infected microglia, the ET corilagin had a pro-apoptotic effect [50]. This occurred despite the parallel anti-inflammatory response that it elicited (lower TNFα, NO and IL-1β) and showed that ETs act on apoptosis selectively and in concert with other signals to achieve a response relevant to the current stress that cells are experiencing.

4. Neurogenesis

Neurogenesis is a process that occurs in several regions of the healthy mature brain: the olfactory bulbs, the ventricular region, and the dentate gyrus of the hippocampus. Neurogenesis is a multistep process that includes proliferation, migration, differentiation, and maturation, with the final step of synapse formation [51]. Mood disorders, chronic stress, and neurodegeneration may reduce neurogenesis. A measure of neurogenesis is represented by the levels of BDNF. This molecule is active in the hippocampus, cortex, and basal nuclei of the forebrain and contributes to cognitive performance, learning and memory. BDNF levels increase following antidepressant treatment and are depleted during chronic stress [52].

Research studies on AD have shown a link between impaired neurogenesis and neurodegeneration, but the interrelated factors underlying the two processes are not fully understood [51]. Modulation of neurogenesis could be considered a potential therapeutic approach for the treatment of AD and other NDD. In a study conducted by Tabopda et al. on neural stem cells, EA demonstrated an effect on neurodegeneration by a not fully understood mechanism [53]. The authors used methanolic extracts of tree bark and EA, with two EA derivatives isolated (3,3′di-O-methylellagic acid and 3,3′-di-O-methylellagic acid-4-O-beta-D-xylopyranoside). Both showed potential to induce neuronal differentiation without cytotoxic effect. This makes the derivatives potential candidates for pharmacological agents.

5. Blood–Brain Barrier Integrity

The BBB is a system of interacting cells including neurons, astrocytes, pericytes, and endothelial cells [54]. In order for the pomegranate ETs to interact directly with misfolded proteins in vivo, they need to access the brain tissue from the systemic circulation. EA and its metabolites cross the blood–brain barrier, which is confirmed by several studies demonstrating the effects of EA on the CNS. Indeed, isotopically labeled EA was identified in the brain of mice after i.p. administration at very low concentrations of 5–8 nmol/g [55]. In another study, EA appeared in the brain at the ng/g level within 0.5–4 h after a single dose of 50 mg/kg orally [17]. Kujawska et al. [5] measured UA at 1.68 ng/g tissue in the brain, about 10-fold less than that in the plasma. This confirmed that metabolites from the intragastric administration of pomegranate juice were able to eventually reach the brain. In an in vitro transwell culture of neuroblastoma, endothelial and astrocyte cells, PUN and EA were able to pass through the model barrier with more EA passing through compared to PUN [34].

The urolithins (the active metabolites of EA) are considered lipophilic enough to be able to cross biological barriers, and low-molecular-weight polyphenols are more bioavailable in general [54][55][56]. However, the BBB is less permeable to sulfate and glucuronide conjugates [54]. This may account for the varying activity of urolithins and their conjugates. For example, Urolithin A (UA) and its methylated conjugate (mUA) had the strongest neuroprotective effect on differentiated neurons after coculture with activated microglia. Conjugated urolithins were more active in the inhibition of nuclear factor kappa B (NFκB), an important regulator of inflammation and oxidative stress, while free UA was more efficient at inhibiting the proinflammatory TNFα production and reducing iNOS expression [56]. The response of activated microglia to urolithins and their methyl-conjugates was also explored by Xu et al. [36] and free UA was found to be the most potent.

One possibility is that inflammation increases the leakiness of the BBB, allowing larger polyphenols to pass through more easily [54]. This would explain why pomegranate polyphenols have an effect on CNS during inflammation or oxidative stress, but exert no or limited effects on a healthy CNS.

A key player in determining the availability of free UA and other low molecular weight polyphenol metabolites in the CNS may be the activity of β-glucuronidase, released from neutrophil granules at the site of inflammation [56]. This enzyme hydrolyses less active conjugates to their free form [57][58][59]. A study showed that LPS stimulation of a pro-inflammatory response increased deconjugation of UA-glucuronide in several organs (liver, lung, spleen, and bladder), and thus increased the concentration of free UA in organs. On the other hand, higher levels of UA-glucuronide were detected in plasma and may serve to increase UA delivery to inflammatory hotspots in the body [59].

The urolithins are also capable of preventing the release of granules from primary human neutrophils [56]. This could serve as a negative feedback response, controlling neutrophil degranulation in inflamed tissue and limiting free UA production

when concentrations of the deconjugated metabolite are already high in situ.

Once present in their bioactive form in the brain, free urolithins may limit inflammation by improving the integrity of the BBB. For example, after traumatic brain injury, UA was able to reduce BBB permeability, increase the expression of tight junction proteins and close gaps in the barrier that formed after the injury [43]. In a model of intracerebral hemorrhage in rats, PUN treatment reduced the infiltration of immune cells and improved barrier function. This occurred only when the brain was experiencing injury and not in healthy animals [19]. Barrier function was also improved after ischemic stroke where PUN was used as pretreatment [18]. Similarly, corilagin was effective in preventing infiltration of inflammatory cells and interstitial edema in HSV-1 infected mice brains [50]. UA was also effective at preventing infiltration of dendritic cells and Th1/ Th17 cells into the CNS in a MS model [60]. EA did not prevent the infiltration of perivascular spaces with immune cells or the number of activated microglia, in an experimental autoimmune encephalitis (EAE) model, but in another study, EA reduced CD45 levels in the brain in both young and old animals, used as a measure for the amount of infiltrating immune cells. Animals treated with pomegranate peel extract and the oxidative-stress-generating aluminum had lower levels of aluminum in the brain [61]. This may be indicative of a better barrier function, or, as the authors hypothesized, a complex forming between the large ET PUN and the metal ions, making them too big to pass through the BBB. The improved barrier function by pomegranate polyphenols is not specific to the BBB and in the study by Singh et al. [62], gut barrier integrity was improved though reduced permeability and increased tight junctions.

6. Neurotransmitter Interactions

The proper functioning of the CNS depends on a fine balance of correct synthesis, sensing, recycling, and removal of neurotransmitters by neurons and glia. Disturbances in this process can lead to a decline in mental health and CNS function [63]. The pomegranate ETs have been shown to affect the levels of a multitude of neurotransmitters. This is not a universal effect of ETs, since depending on the experimental setup and the stress induced in the CNS, one or more neurotransmitters may be affected, while the others remain unchanged.

Dopamine (DA) levels were restored by pretreatment with EA, and UA was able to protect the dopaminergic neurons in vivo [4]. Importantly, EA does not seem to directly protect dopaminergic neurons from 6-OHDA toxicity in vitro, even though oral gavage in vivo prevented dopaminergic loss in the striatum [4]. In a study of scopolamine-induced dementia by Tancheva et al. [64], researchers showed that DA uptake increased by oral EA supplementation. This protection may be driven by astroglia, as shown by Wei et al. [65]. DA released in the extracellular space can lead to oxidative stress, and can be neurotoxic if not controlled. In astroglia, oxidative stress activates Nrf2 signaling, which releases GSH to support antioxidant levels for neurons [65].

Cholinergic neurons, important for memory and learning, also appeared to be subject to pomegranate polyphenol protection. One of the typical hallmarks of AD is the loss of cholinergic neurons, along with the accumulation of beta-amyloid and hyperphosphorylated tau protein [66][67][68], as well as the increased activity of enzymes that hydrolyze acetylcholine in the synapses of cholinergic neurons—butyrylcholinesterase and acetylcholinesterase [69]. This pathogenetic mechanism of AD has been studied since the 1980s [70][71], and resulted in the introduction of cholinesterase inhibitors as the first class of medicinal products for the treatment of AD, led by the plant-derived galantamin. Oral supplementation of EA in mice with scopolamine-induced dementia (to mimic AD) showed that this pomegranate metabolite reduced AChE activity. Methylated conjugates of EA appeared more effective in inhibiting AChE than EA itself, acting as reversible competitive inhibitors. The same effect was observed when galactose-induced ageing was induced in mice in the presence of UA, during manganese treatment accompanied by PUN to induce PD-like symptoms, and with pomegranate juice to counter aluminum toxicity [65][72][73][74].

Long-term use of cholinesterase inhibitors is associated with a series of adverse effects [75], necessitating the search for other therapeutic approaches that affect the cholinergic signal. Potential therapeutic candidates that meet this requirement are the phenolic acids, with EA being a representative of this group. EA as a single substance, however, does not show significant cholinesterase activity in vitro [76]. On the other hand, EA-rich extracts and derivatives, such as walnut (*Juglans regia*) extract, show pronounced in vivo cholinolytic effects [77][78].

The currently available in vitro and in vivo data suggest that EA alone most likely does not possess cholinolytic activity. On the other hand, EA and the ETs found in natural extracts after administration are converted into their biologically active metabolites, urolithins, which exert anticholinesterase activity, as demonstrated by Norouzbahari and co-authors [79].

The levels of the amino acid glutamate (Glu) in sleep deprivation increased and correlated with ROS production and loss of neuronal viability. Treatment of primary hippocampal neurons with EA made them more resilient to Glu exposure and

improved their viability in an Nrf2-dependent process [80]. Pretreatment of hippocampal neurons with PUN also seems to inhibit Glu-induced excitotoxicity [65] and restore the Glu/GABA balance in the striatum following manganese exposure [81].

In depression, the levels of monoamines are lowered. EA improved depressive behavior in mice, and this appeared to be dependent on noradrenergic and serotonergic systems, in both stressed and unstressed mice [52][82][83]. Supplementation with pomegranate juice for a year influenced tryptophan and downstream serotonin metabolism [84]. The improvement in depressive behavior in ovariectomized rats was mediated both by the estrogen receptor ERβ, which is responsible for the mood-regulating role of estrogens, and via the serotonergic system [14]. Serotonergic neurons express ERβ receptors, which regulate the rate-limiting step of the conversion of tryptophan to serotonin (tryptophan hydroxylase, TPH). Given that the animals were treated with a complex pomegranate extract, the authors provided a list of pomegranate compounds besides the ETs, which may have synergistic antidepressant activity. Pomegranate-derived compounds may therefore be beneficial for women, who are especially vulnerable to depression during estrogen fluctuations such as in perimenopause [85]. Interestingly, UA was able to interact with another steroid molecule, 1,25-dihydroxyvitamin D3 and enhanced the transcriptional regulation of TPH2 in rat serotonergic raphe cell line. This translated to higher levels of serotonin being secreted in the presence of UA in the cell culture media [85].

Proinflammatory cytokines can activate indoleamine-2,3-dioxygenase (IDO), which affects tryptophan catabolism, therefore inhibiting its conversion to serotonin downstream, with a consequent reduction in serotonin levels. The levels of IDO were reduced when mice under chronic stress exhibiting anxiety and depressive behavior were given high doses of pomegranate extract. The hypothalamus histology returned to normal and serotonin in this brain region increased [86]. These effects may be due to an upstream inhibition of an inflammatory response and the associated reduction of proinflammatory cytokines by pomegranate polyphenols. Thus, limiting neuroinflammation is one possible pathway by which ETs regulate neurotransmitter levels.

5HT receptors and α1- and α2-adrenergic receptors appeared to be involved in the antidepressant effects of EA [87]. Noradrenaline exocytosis in cortical synaptosomes could be stimulated in old mice treated with EA for 2 weeks. Noradrenaline and adrenaline levels were lowered after pomegranate extract treatment in mice under chronic mild stress and corresponded to Monoamine oxidases (MAO)-B activity responding to the pomegranate polyphenols [88]. The levels of both dopamine and serotonin were restored with pomegranate juice in aluminum toxicity [74][89]. 5HT returned to normal values, as did DA and noradrenaline in the striatum of rodent brains of a PD model, when they were fed PUN prior to exposure to manganese [81]. The effects of ETs on multiple receptors suggest that the ETs do not act on a monoamine neurotransmitter-specific level but rather prevent upstream stress signals that may cause neurotransmitter imbalance.

The anxiolytic effect of EA in mice appeared to be mediated by the inhibition of the serotonergic system for depression, but also relied on GABA-ergic neurotransmission [87][90]. Gamma-aminobutyric acid (GABA) can be influenced by different flavonoids and contribute to their benzodiazepine-like anxiolytic effects [90]. This appeared to be driven by binding to the benzodiazepine site of GABA A receptors. BDNF can also modulate neuronal excitability levels by inhibiting GABAergic mediation and its increased levels after EA administration can indirectly affect the GABA balance [91].

The above results reveal the complexity of ETs as neuroprotective agents and make them potential candidates for preventive and therapeutic agent, which would have the ability to influence the multifactorial pathogenesis of NDD by a multi-targeted mechanism.

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