Cellular Physiology and Biochemistry

Cell Physiol Biochem 2021;55(S2):49-70
DOI: 10.33594/000000350
Published online: 27 March 2021
Accepted: 3 March 2021

Review

Proteome Linked Biochemical Targets: Can Repair Defective Cellular Physiological Mechanisms?

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Key Words
Proteostasis • Neurodegeneration • Neurons • Therapeutic Targets

Abstract
Major cause of proteopathies is the accumulation of unwanted mutant and aberrant proteins. We know that imperfect ageing is one of chief risk factor for most neurodegenerative diseases. Neurodegenerative diseases are characterized by mutant misfolded protein aggregates developing neural stress and debilitating several neuronal processes. Reducing the levels of these abnormal proteins using various natural compounds can be a promising possible therapeutic strategy. But the advancement of natural compound-based therapies in neurodegeneration and imperfect ageing treatment has been impeded by different challenges and unknown molecular patho-mechansim. The complexity in the causative factors generating protein aggregates in neurons and their respective path towards cell death is high, making it a difficult to treat disorder. Several plant based compounds have proven to promote different neuronal homeostasis mechanisms. However, there is a pressing necessity to screen, find and develop cost-effective natural compound-based new therapeutic interventions which can be useful for clinical purposes in treating neurodegenerative ailments. It is critical to discuss and elaborate the applications of few important natural compounds and their connections with following mechanisms: protein disposal machineries, apoptosis, neuroinflammation, neuronal development, synaptogenesis and neural homeostasis. This article summarizes the current knowledge and discusses the unanswered questions linked with the natural compounds and their promising therapeutic avenues primarily focusing on neurodegenerative diseases and defective neurobiological mechanisms.

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Introduction

The brain makes use of highly specialized and organized network of spiking neurons which acts as the basic unit of the nervous system [1]. Neuronal populations are primary electrically active cells in the body with their involvement in various neurological processes. Neurodegeneration can be viewed simply as slow progression of sick neurons towards agony [2]. The degeneration of neurons also leads to the loss of information and incapacitates cognitive, motor and behavioral functions [3]. The cellular or molecular disturbances that lead to pathogenesis of disease are generally progressive and usually initiate in mid-adult life as a result of faulty aging and deteriorates with age, manifesting motor and cognitive defects [4]. However, it is also equally important to consider these degenerative mechanisms to be arising due to neuron's incapacity to abolish such toxic factors. One such example is in case of protein aggregation/an oxidative insult, neuron's ability to relieve from these repercussions is diminished ultimately leading to onset of apoptotic pathways [5-8]. Hence, uplifting such stressed neurons in their ability to defend themselves against such holistic damages would be a vital inclusion in designing a therapeutic approach. Plant systems are also understood to be exposed to a wide-ranging stressors, and therefore, we can draw inspiration from them [9].

Besides the evolved photosynthesis, plants possess diverse mechanisms that have evolved in response to different stress and investigation of these mechanisms or molecules (Bioactive compounds) has been proven to find varied therapeutic applications [10, 11]. Thus development of a combinatorial therapy of such bioactive compounds or extracts would prove to be of high value owing to their novelty and green source. Having a natural plant-based outlook onto such paradigm of defects could be a reasonable treatment option. We have then also tried to put an integrated schematic illustration of the various mechanisms that are known to cause degeneration in neurons and blend them with our existing knowledge of plant potentials. Finally, we have discussed the overall mechanistic loopholes and possible targets that could be explored with the help of plant-derived natural compounds.

How Stresses Mediated Errors Provide Early Warnings of Cellular Physiological Disturbance?

Degeneration of neurons in the body is a severe issue with multifaceted level of defects. A proper therapeutic strategy is still challenging because of the heterogeneity in the cause of disease progression. There are several mechanisms at cellular and molecular levels identified as the cause of neurodegeneration; few of them are explained in Fig. 1. Understanding the precise mechanisms of disease progression that are acting at the level of the neuron seems to be a better strategy in the exploration of cure to the disorder.

Excitotoxicity Hunts Neuronal Health and Survival

Different cellular mechanisms like unfolded protein response (UPR), autophagy, the ubiquitin-proteasome system (UPS), DNA repair mechanisms, mitochondrial stress response all of which are involved in maintaining general cellular homeostasis [12]. However, changes in their activation may be bestowed to diseased conditions. The over-activation of one such homeostatic secondary signal molecule, calcium ions are known to be one of the causative factors of Neurodegeneration [13]. The calcium signaling mechanism is known to be very diverse, performing different types of spatial and temporal functions in cells [14]. Most of the excitatory synapses in nervous system use glutamate as the neurotransmitter and modulate two different kinds of receptors present on the postsynaptic neuron namely, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) [15]. Binding of ligand (Glutamate) to AMPA receptor, a tetrameric protein containing binding site for glutamate in all its subunits, provides specificity to permeabilization towards calcium ions over sodium/potassium ions by exchanging one of the subunit GluR1

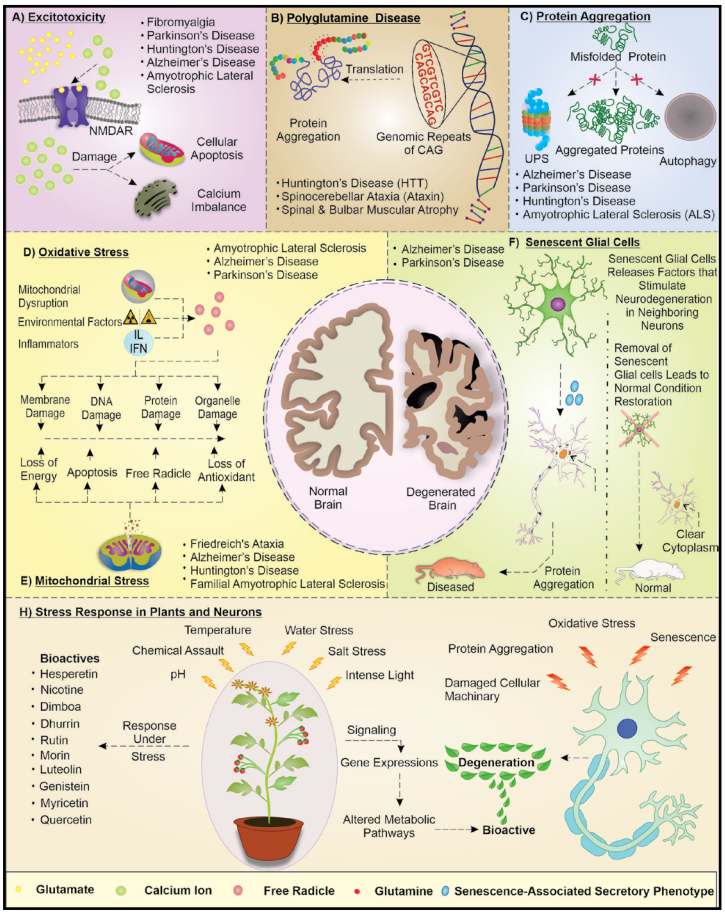

Fig. 1. The figure depicts the general disturbance in cellular and molecular mechanism of neuronal cells that lead to class of neurodegenerative disorders (NDD). (A) Increased calcium concentration inside the cell leads to serious damage to cellular machinery like Endoplasmic reticulum (ER) which would in turn increase the cellular calcium concentration and Mitochondria that would lead to disruption and consequently lead to apoptosis. (B) Occurrence of large stretch of CAG repeats in the genome (>40) lead to polyglutamine track in the protein which leads to destabilization of structure and result in misfolded protein that tend to form aggregated structures. (C) Overload for degradation of these molecular junk these is buildup of the misfolded proteins resulting into development of aggregates in the cytoplasm that forms the pathophysiology of various NDDs. (D) Free radicals lead to an array of malfunction in the cell leading to membrane damage, DNA damage, protein damage and organelle damage all of which lead to degeneration of neuron. (E) Mitochondrial stress could also lead to NDD by directly leading to apoptosis or depletion of energy for physiological activity of the neurons (F) This section shows the modulation of normal neuronal cell to a degenerative neuron by the neighboring senescent glial cells signaling that leads to manifestation of the diseased condition. (H) Plants are known to withhold various different stressful conditions by the production of various bioactive due to alterations in their normal biochemical pathways.

to GluR2 [16]. Over-activation of NMDA receptor leads to Excitotoxicity, wherein excessive inflow of calcium ions in neurons disturbs the calcium balance and causes neuronal damage. Imbalanced calcium ions damages mitochondrial functioning and initiates intrinsic pathway of apoptosis. Besides this, excessive calcium ions may also en-route the cell to apoptotic pathways by directly interacting with the caspases, and cellular damages are amplified by damages to endoplasmic reticulum (Fig. 1A) releasing the cellular calcium reserve back into the cytoplasm [17].

Aberrant Polyglutamine Proteins Stress

Proteins are essentially a polymer of amino acids that share vibrant thermodynamic and electrical properties bestowed by their side chain. Genome is known to contain repeated units of "CAG" tri-nucleotide, which codes for amino acid Glutamine (Q). In polyglutamine disease there are long stretch of glutamine amino acid in the structure of protein (Fig. 1B) and this forms an underlying cause for the beginning of pathogenesis of polyglutamine diseases [18]. Huntington's disease is known to be caused due to polyglutamine tract, which is an inherited autosomal dominant disorder [19]. Polyglutamine tract is naturally present in the gene with shorter length (35-50 repeats) however, their length increases largely (40-100),

rendering the polypeptide susceptible to aggregation [20]. If we look onto the biophysical dynamics of such proteins there is potential change in the secondary structure of proteins with polyglutamine tract like for example, the extended track leads to a change of α-helix to β-folds which gets cross-linked to form aggregates by the process of polar zippers [21].

Elimination of Non-Native Protein: Essential for Cellular Protection

There are highly conserved and ubiquitously present mechanisms inside the cell that govern and implement the process of clearing out these aggregates from the cell (Fig. 1C), UPS and Autophagy [22]. Pathological conditions that arise due to aggregation of protein molecules are recognized as proteopathies [23]. The mechanism of protein misfolding is not very well understood, and therefore, protein aggregation and their role in neurodegeneration is still a mystery. However, various implication are present and despite intensive work, pin-pointing to exact cause is still not possible [24]. Ubiquitin proteasome system is involved in selectively degrading the polypeptide and consists of Ubiquitin (76 amino acid protein) and ubiquitinating enzymes E1, E2 and E3 for ubiquitin activation, conjugation and further ligation to the target protein which is then directed to proteasome machinery for degradation [25]. Autophagy is another mechanism that cells utilize to clear aggregated protein molecules from cytoplasm mostly in bulk form. Selective elimination of cargo is also carried out by using chaperone which selectively binds to the misfolded proteins and help in their ubiquitination by chaperone associated ubiquitin ligases. Further these ubiquitinated proteins follow their path towards lysosomal degradation, such type of degradation is termed as Chaperone Assisted Selective Autophagy (CASA) [26]. Another type of autophagy is identified wherein direct entry of the misfolded protein into the lysosomes occurs via chaperone without the need of vesicle formation which is recognized as Chaperone Mediated Autophagy (CMA) [27].

Oxidative Stress Damages Almost Non-Recoverable

Most of the neuronal damages either originate or culminate into oxidative stress [28]. An imbalance between the functioning of cellular antioxidant systems and free radical generation is what can be understood as Oxidative stress (Fig. 1D). Pathogenic assault in the brain is actively combated by immune system, which is led by glial cells that involve cytokines based activation of leukocytes carrying out ROS/RNS mediated pathogen killing [29]. During an event of excessive pathogenic insult over activation of immune system results in damaging of neurons through oxidative stress. Besides these, mitochondria is known to generate energy for the cell, and it houses the electron transport chain (ETC) that ultimately results into energy formation and therefore subjecting the cell to constant risk of oxidative damage due to the presence of redox carriers [30]. Major Neurodegenerative disorders fostered by the oxidative mechanisms include Amyotrophic lateral sclerosis [31], Alzheimer's disease [32], and Parkinson's disease [33].

Stressed Mitochondria Population

As discussed above, mitochondrial dysfunction is directly a cause for a free radical-mediated pathway for degeneracy (Fig. 1E). Mitochondria houses the antioxidant system of neuron that continually runs to maintain the homeostatic balance ensuring proper functioning [34]. Mitochondria helps neurons with providing energy currency and antioxidative enzymes like superoxide dismutase (SOD), glutathione-S-transferase (GST), glutathione peroxidase and catalase [35]. The presence of various electron carriers and subsequent flow of proton across the membrane possess a considerable risk for formation of free radical species along with oxidative phosphorylation generating superoxide ions, peroxides and highly reactive hydroxyl ion [36]. Besides these, mitochondria are also known as one of the principal regulators of the apoptotic mechanism, and their damage or dysfunction could directly lead to degeneracy [37].

Imperfect Neuronal Aging or Early Neurodegeneration?

Imperfect aging usually contracts accumulation of mutant misfolded proteins along with burdened and inefficient cellular homeostatic mechanisms ultimately leading to death [38]. Neuronal glial and astrocyte cells that are undergoing senescence are seen to cause degeneration in neighboring neurons; however, their exact role in this etiology is yet to be understood (Fig. 1F). Recent studies implicate certain factors released by glial or astrocyte cells that lead to degeneration in neighboring neurons by the formation of protein aggregates [39]. There is a trend of late-onset of many nervous degenerative disorders, which implicates increased tolerance to many of these stressful conditions. There are signs of existence of such pleiotropy in terms of many stresses combated by neurons. However, the exact role by which the senescence leads to death of a cell is not very well understood. Imperfect senescence is seen to be the source of the etiology leading to Alzheimer's and Parkinson's disease [40, 41].

How Plants Based Natural Compounds Can Drive Cellular Protection?

Plants have evolved to have their growth and development to be regulated by hormones and environment conditions [42]. Neurons are in contact with various stress conditions as discussed above; plants are also subjected to stressful environments. Through the due course of evolution, they have burgeoned with wide range of response mechanisms to different stress conditions and can produce diverse range of molecules [43]. Fig. 1G tries to implicate the basic idea what we are trying to build here with this review. Plants under stress like pH [44], temperature [45], water [46], salt [47], light [48], chemical [49] undergoes different signaling mechanisms that lead to differential expression of genes leading to alteration in the existing metabolic pathways. The bioactive isolated from plant sources are known to have applications in wide-field and to being from natural source, promises secure and sustainable supply into the market and is believed to hold a market value of over billions of dollar per annum [50].

Promising Framework of Natural Compounds Can Repair the Defective Neuronal Mechanisms

In the entire energy cycle plants are critical in harnessing and fixing energy received from the sun which helps all the life forms to survive on earth [51]. Table 1 represents some of the bioactive compounds along with their disease target and nature of the activity in treating neurodegeneration. There is excessive oxidative damage in case of neural tissue along with other modes of molecular mediated assaults to normal neuronal functioning, which has found to be treated by using various plant-based compounds and extracts [52]. In the upcoming sections, we will discuss how certain known bioactive compounds from plant sources can find cellular and molecular targets and aid in improving diseased conditions.

Therapeutic Potential of Intracellular Protein Degradation

Cells that are in a high-stress environment like that of neurons, which are under high oxidative stress, culminate into protein aggregation based cellular death [53]. In order to circumvent such complication cell implies the chaperones, which aid in folding of the protein molecules. Chaperones often when are unable to fold the misfolded proteins target them towards the UPS for their clearance. Fig. 2B describes the overall process and the individual elements involved in the ubiquitin-proteasome system. The ubiquitin molecule, an 8.6 kDa and about 76-amino acid small molecule present ubiquitously in all cells and performs major regulatory role in protein degradation mechanisms both in UPS and autophagy [54]. E3 ubiquitin ligases are presumed to be the most vital element responsible for the transfer of ubiquitin molecule to targeted substrates thus providing specificity to the entire process [55]. Several protein quality control mechanisms are present at the endoplasmic reticulum where the misfolded proteins are cleared with the help of UPR and ERAD. The

overall clearance of the protein aggregates is carried out with the help of the proteasomal machinery or the lysosome. Fig. 2A, B discusses the overall process along with different plant derived compounds applications.

Table 1. Plant Compounds retains therapeutic potential for the treatment of neurodegenerative disorders

S. No	Plant Compounds	Source	Neurodegenerative Diseases	Molecular Mechanisms	References
1	Quercetin	*Pavetta rassipes*	Alzheimer's Disease, Huntington's Disease, Parkinson's Disease	Anti-oxidant	[157, 158]
2	Piperine	*Piper nigrum*	Spinocerebellar Ataxia-17	Anti-oxidant	[157, 159]
3	Luteolin	*Salvia triloba*	Alzheimer's Disease	Anti-oxidant	[157, 160]
4	Eugenol	*Acorus calamus*	Alzheimer's Disease, Parkinson's Disease	Anti-oxidant	[157, 161]
5	Rutin	*Vitis vinifera*	Alzheimer's Disease	Anti-oxidant	[162, 163]
6	Anthocyanin	*Rubus*	Huntington's Disease, Alzheimer's Disease, Parkinson's Disease	Antioxidant	[164-166]
7	Guarana	*Coffea*	Huntington's Disease, Alzheimer's Disease	Protein aggregation	[167]
8	Apigenin	*Matricaria recutita*	Alzheimer's Disease, Parkinson's Disease, Cerebral Ischemia	Amyloid inhibitors	[101]
9	Baicalin	*Scutellaria baicalensis*	Parkinson's Disease	Amyloid inhibitors	[101, 168]
10	Epicatechin	*Cocoa*	Alzheimer's Disease	Amyloid inhibitors	[101]
11	Genistein	*Glycine max*	Parkinson's Disease	Amyloid inhibitors	[101, 169]
12	Myricetin	*Camellia sinensis*	Parkinson's Disease	Amyloid inhibitors	[101, 170]
13	Kaempferol	*Solanum lycopersicum*	Neurodegenerative Diseases	Amyloid inhibitors	[101]
14	Morin	*Maclura pomifera*	Alzheimer's Disease	Amyloid inhibitors	[101]
15	Melatonin	*Oryza sativa*	Alzheimer's Disease, Parkinson's Disease, Ischemic Stroke	Amyloid inhibitors	[101, 170]
16	Protochatechoic acid	*Hibiscus sabdariffa*	Alzheimer's Disease	Amyloid inhibitors	[101]
17	Curcumin	*Zingiberaceae*	Alzheimer's Disease	Amyloid inhibitors	[101, 171]
18	Caffeic acid	*Coffea*	Alzheimer's Disease	Amyloid inhibitors	[101]
19	Azadiradione	*Azadirachta indica*	Huntington's Disease	Polyglutamine disease	[172]
20	Uleine	*Aspidosperma parvifolium*	Alzheimer's Disease	Enzymatic pathway	[135]
21	Mangostin	*Garcinia mangostana*	Alzheimer's Disease	β- amyloid aggregation	[173]
22	Kuromanin	*Hibiscus sabdariffa*	Alzheimer's Disease, Amyotrphic Lateral Sclerosis, Parkinson's Disease	Excitotoxicity	[113]
23	Anthocyanins	*Rubus idaeus*	Alzheimer's Disease, Amyotrphic Lateral Sclerosis, Parkinson's Disease	Excitotoxicity	[113]
24	Callistephin	*Punica granatum*	Alzheimer's Disease, Amyotrphic Lateral Sclerosis, Parkinson's Disease	Excitotoxicity	[113]

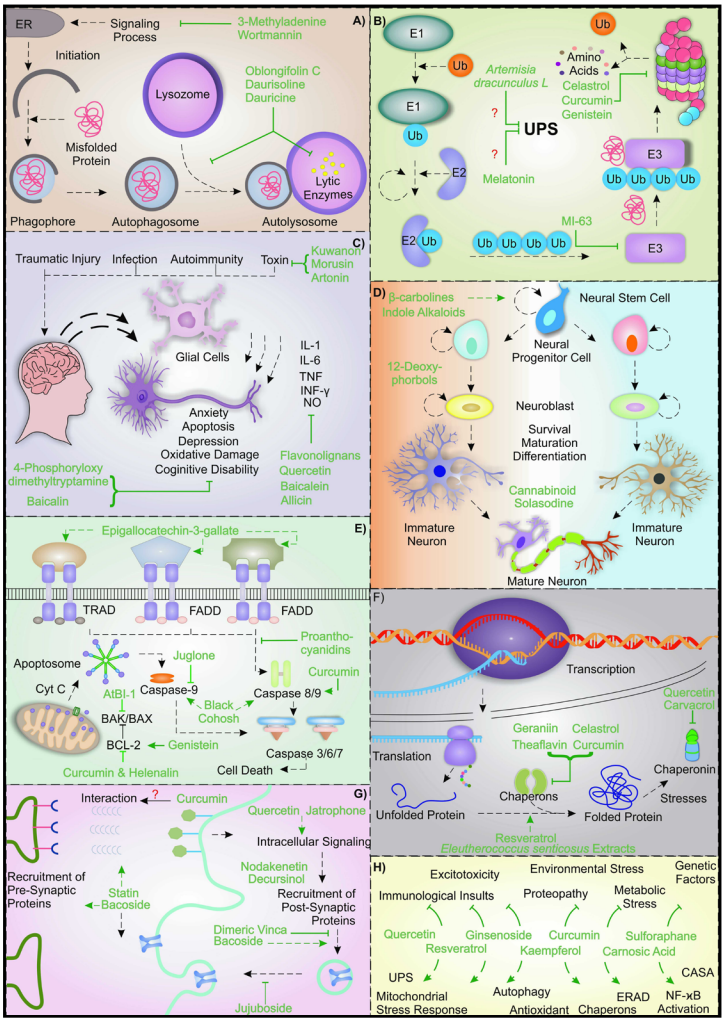

Fig. 2. The figure describes the major neuronal cellular mechanisms that are widely explored as a participant of cellular Pathophysiological condition in Neurodegenerative disorders. The figure is marked (written in green) with major plant-based compounds/extracts that are reported to be involved (Activators/Inhibitors/Modulators) in different cellular processes. A) Autophagy, B) Ubiquitin Proteasome System, C) Apoptosis, D) Synaptogenesis, E) Neuroinflammation, F) Neuro-genesis, G) Protein Synthesis, H) Neuronal Stress response.

Does Neuroinflammation Contribute to Neurodegeneration?

Inflammation is an immunological response generated against an infectious particle's entry into the nervous tissue. Besides the infectious particles, other reasons converging into an inflammation are injuries of brain, toxic metabolites or autoimmunity [56]. Inflammation in the brain is one of the causes of neurodegeneration [57, 58] as we had already discussed earlier and generation of ROS in the process of inflammation in the nervous tissue leads to the cascade of oxidative damage that ultimately leads to neuronal damage (Fig. 2C). Employment of immune cells at the location of inflammation leads to generation of toxic factor that not only targets the pathogen but also affects the neighboring neurons which are affected by creation of oxidative stress, Nitric Oxide (NO) mediated cellular damage, and loss of synapses based mechanisms [59, 60]. Therefore, demands for development of high throughput *in vivo* based approaches to exactly pinpoint the mechanistic nature of neuro-inflammation based neurodegeneration is high [61]. Few plant-based compounds having inflammatory targets possess anti-inflammatory effects blocking the activation of cytokines [62, 63]. Certain plant compounds like Morusin and Kuwanon G are essentially flavones, seen to act as anti-inflammatory and anti-allergic via altering NF-κB mediated pathway in skin cells. These are viewed as promising therapeutic options in chronic inflammatory skin disease thus, their probable neuroprotective activity could be tested based on their brain parenchyma accumulation [64].

Homeostatic Development of Neurons

The process of neurogenesis comprises of five major events such as, the formation of progenitor cells, formation of neuroblast cells their survival, differentiation to immature neurons and further maturation to form Neurons [65]. Furthermore, Gliogenesis is often found to be in association with the process of neurogenesis [66]. Development of neurons in the early embryonic stages begins with formation of neuroectoderm from ectoderm followed by neural tube formation and patterning to form different neuronal cells [67]. All these stages are governed by specific growth and maturation driving signaling molecules those alter specific signaling molecular pathways for example the Notch pathways and Wnt pathways [68, 69]. The progenitor cells are limited in their differentiation capacity and can form neuronal or glial cells [70]. On the other hand, neuroblasts are restricted in their division as well as differentiation potential and are able to originate neuronal cells [71]. Neuroblasts are pluripotent in nature and with the help of differential gene expression can originate diverse types of neural cells. Before the neuroblast can give rise to an immature neuron they undergo migration along with exit to cell cycle [72]. Major differentiation controlling players include noggin and brain-derived neurotrophic factor (BDNF). Noggin is involved in antagonizing the effects of Bone morphogenetic protein (BMP) signaling and promote neural differentiation [73]. Whereas BDNF is involved in modulating the PLC-γ, MAPK/ERK, PI3K pathways [74]. Neurons with their restricted ability to divide/regenerate, it is difficult to contain or secure insults for them. Therefore, search for contenders that would give insights about the several aspects to neurogenesis as well help us to modulate the process of neurogenesis would lead to better understanding of neural systems [75]. Some of promising candidates exists in the plant kingdom [76, 77] and are represented in Fig. 2D, however quest for more is needed.

Apoptotic Abnormalities and Neurodegeneration

Two main pathways that are identified through which apoptosis can be activated inside a cell using caspases (Fig. 2E), one which is governed by extracellular activation of the death receptors containing other gets activated by the mitochondrial contents [78]. There are two significant molecules that exert the effect of apoptosis externally, the Fas Ligand and TNF-α both of which are mainly generated by the immune cells including in the nervous system [79]. They bind to their respective receptors and mediate their apoptotic role by adaptor molecules that contain death domain (FADD/TRADD) which after getting activated stimulates the activation of caspase 8, which then activates the effector caspases [80].

In case of intrinsic pathway the apoptosome complex consisting of APAF-1, cytochrome c, and procaspase-9 is released into the cytosol and then leads to activation of downstream effector caspase [81]. Also the BAK-BAX complex that forms the channel for permebialisation of the mitochondrial membrane are the pro-apoptotic signals that are acting up-stream of Bcl_2 and are the ones that inhibit the Bcl_2 leading to activation of intrinsic pathway of apoptosis [82]. AtBl-1 and Genistein, plant-based compounds that are seen to promote the action of anti-apoptosis through interaction with Bcl_2 [83, 84].

Synaptogenesis Regulation and Vulnerabilities of Neural Homeostasis

Synaptogenesis can be viewed as the process of formation of neurotransmitter release sites as well their reception counters at the respective pre-synaptic and post-synaptic termini [85]. It has been seen that although the formation of new synapses occurs throughout the life of an organism however, they are found to be more active during the early phase of nervous development. Cell adhesion molecules (CAMs), adaptor proteins, cytoskeleton components, Epidermal Growth Factor like repeats (Neurexin, Neuroligin) are certain molecules that are arranged on the pre-synaptic neuron and their respective partner on the postsynaptic cell that mediates the formation of synapse [86]. These CAMs help to establish cell-cell recognition and guide the path for synapse formation between neurons [87]. Synaptogenesis has also met few of its components as targets of plant-based compounds. The process is described along with certain known compounds in the Fig. 2G. Many plant derived components are known to rescue and have neuroprotective roles which essentially helps in maintaining neuronal homeostasis [88, 89]. Plant compounds have found many applications in diverse cellular functions and systems (Fig. 2H). In the upcoming sections we will discuss few of such bioactive compounds having applications in removing neural anomalies.

Therapeutic Potential Mapping Natural Compounds: Neuroprotection & Improved Ageing

In some cases aggregated proteins are seen to form regular structures that tend to clutch together to form small slender fibrils of large insoluble unfolded protein aggregates called amyloid fibrils. These fibrils are widely studied and categories as one of the significant causative function of neurodegeneration [90]. One such example causing Alzheimer's disease is the formation of amyloidβ peptide through sequential processing of membrane-associated Amyloid precursor protein (APP) [91]. These structures are large making it difficult to target by the intracellular degradation machinery making the condition worse. In order to circumvent such proteotoxic problems, several plant derived natural compounds have demonstrated promising outcomes. Flavonoids are color imparting compounds present in several plants and possess a basic 15 carbon structure. Based on the chemical structure flavonoids can be further classified, of which flavones, flavonols, and anthocyanin share several antioxidant properties [92]. Besides polyphenols, terpinoids have also found several application in protein aggregation disorders some of which are discussed in upcoming sections.

Flavonoids

Flavonoids forms the largest class of polyphenols and are well known for their antioxidant functions in nutraceutical industries. Structurally, flavonoids consists of basic structure of 15 carbons composed of two phenyl and one heterocyclic rings. The keto substitute of flavonoids are flavonols which are mostly formed in the aerial tissues. Flavones on the other hand consists of 2-phenyl-1-benzopyran-4-one substitution in their backbone and, are found in rich amounts in yellow or orange fruits and vegetables. Anthocynanins are water soluble pigments responsible for different colors based on pH consisting of charged oxygen atom in heterocyclic ring structure of flavonoids [93]. These flavonoids along with other classes are understood to possess antioxidant potentials creating their therapeutic

value. Antioxidants are one such class of phytochemicals known to possess neuroprotective roles. Plants experience oxidative assaults due to the photo-oxidative cycles, and they combat it by the use of anti-oxidative molecules that are generated from the alteration of their normal metabolic pathways [94]. Quercetin, Luteolin, and Eugenol are some of the bioactive molecules that are known to find application as quenchers of the free radicals inside the neuronal systems. Quercetin is a flavonoids that is present in citrus fruits and is known for its many benefits such as anti-inflammatory, antioxidant, and anti-proliferative. However, the effects of Quercetin are restricted to be beneficial in a concentration-based manner [95]. It has been seen that even Nano-formulation of Quercetin can relieve the oxidation induced damage to neurons by quenching the reactive species as well the caspase functions that otherwise would lead to degeneration [96]. Another molecule belonging to the same group, flavonoids that are found in abundant amounts in broccoli is Luteolin. Luteolin, a flavone is crystalline and yellow used as dye for ages. It can be obtained from many of the vegetables and fruits and have different therapeutic roles mentioned in Chinese traditional medicine. Its therapeutic roles in nervous system comprise of anti-oxidant, immunomodulatory functions that provide neuroprotective effects against degeneration [97, 98]. Besides the antioxidant function luteolin is also known to ameliorate amyloid β based toxicity in neurons [99].

Apigenin is again a flavone that can be obtained richly from parsley, tea, cereals are known to ameliorate the β amyloid toxicity in Alzheimer's [100]. Myricetin and Genistein that are flavonoids and isoflavones present in tea, berries, fruits, lupine, fava beans, and soya beans respectively also have known to act as anti-amyloid compounds [101-103]. As summarized in Fig. 3B the action of these polyphenols is seen to act either by up-regulating the survival pathways of neurons, or as they essentially are flavonoids they act as anti-oxidants. Besides this they could directly interact with the amyloidβ structure and prevent their association from different cellular functions rendering them inactive [104, 105]. For example apigenin is known to decrease the synthesis of β amyloid aggregates by downregulating the functional

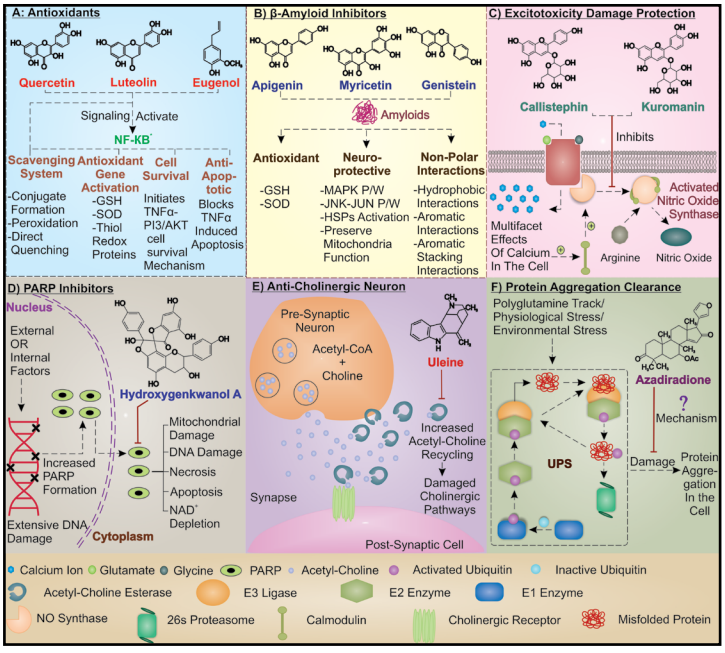

Fig. 3. Molecular mechanisms of plant compounds against neurodegeneration. (A) Antioxidant function of plant compounds Quercetin, Luteolin and Eugenol is depicted in the figure by signaling mechanism that activates the central molecule in the redox reaction of cell that is NF-KB. (B) Plant compounds like Apigenin, Myricetin and Genistein are known to ameliorate Amyloids in the cell by activating antioxidant functions of cell, rendering Neuroprotective function to the cell by activating various survival mechanism mitochondrial function preservation and Heat Shock Proteins (HSPs) activation. (C) Callistephin and Kuromanin are known to inhibit Nitric oxide synthase and thereby reducing the damage caused by excessive production of nitric oxide in the neuron that lead to neurodegeneration (D) Hydroxygenkwanol A, a plant derived compound is known to inhibit Poly ADP Ribose Polymerase (PARP) and clear the cytological effects of neurodegeneration. (E) Uleine is a phytochemical that is known to inhibit acetyl-choline esterase and resolve the symptoms of neurodegeneration in cholinergic neurons. (F) Azadiradione is known to ameliorate the molecular defects linked with ubiquitin proteasome system (UPS) via an unknown mechanism to clear the protein aggregation in the cell.

enzymes that are responsible for their formation and processing; besides its role in signalling apigenin is found to be as anti-oxidative in function and reduce neuronal toxicity caused by the β amyloid induced oxidative stress [106]. Myricetin is known to reduce amyloidogenesis by directly interacting and inhibiting the beta-secretase, enzyme responsible for amyloidβ faulty processing, or by activating and up-regulating the alpha-secretase, enzyme responsible for amyloidβ standard processing [107]. Apart from this it is involved in depolymerisation and oxidation of the monomeric units of amyloid and interferes with the build-up of the amyloid structures and prevents the hydrophobic peptides from interacting with each other in order to get aggregated [108]. β amyloid can activate apoptosis leading various cellular damages and Genistein has been reported to reduce such cellular anomalies [109]. Genistein is involved as one of the significant neuroprotective molecules by up-regulating the cell survival pathways of neuron like JNK pathway, PK C pathway [110, 111].

The mechanism of action of neuronal damage exhibited due over activation of NMDA receptors is widely contributed by the action of calcium ions in the neuron that enters through the NMDA receptors [112]. In addition to this the toxic insults could arise as a result of reactive species generation or by direct generation of reactive nitrogen species upon reaction with superoxide to form peroxynitrite. Such effect of nitric oxide gets amplified with the diffusion of the gaseous molecules to the neighboring neuronal sites leading to further damage. Callistephin and Kuromanin, which are extracted from fruits like pomegranate, strawberries and other berries are belonging to anthocyanin groups, known to quench the adverse effects of excitotoxicity. Callistephin is a 3-O-glucoside of pelargonidin, a pigment responsible for orange color in plants and kuromanin (Chrysanthemin) is a 3-O-glucoside of cyanidin which is a color pigment responsible for red color. The action of both the compounds is seen to inactivate the nitric oxide synthase enzyme to reduce the synthesis of nitric oxide (Fig. 3C) and hence quench the damage resulting from the glutamate-induced excitotoxicity [113].

The genetic lesions do participate in the pathogenesis of degeneration in neurons. Fig. 3D tries to give a schematic representation to describe the effects of excessive DNA damage resulting into initiation of excessive DNA damage repair pathways in neuron. DNA damage attracts the initiation of poly (ADP-ribose) polymerase 1 (PARP 1) which is the primary enzyme that is responsible for activation of various repair pathways [114, 115]. PARP-1 binds with the impaired DNA and undergoes conformation change and performs polymerization to form poly ADP-ribose polymer by using NAD^+ as substrate [116]. Extensive oxidative insults results into the identification of open DNA ends by PARP-1 which then undergoes auto modification and leads to activation of a cascade of polymerization reaction forming poly ADP-ribose polymer attracting the DNA repair elements at the site of DNA damage [117]. Moreover PARP-1 is also involved in triggering necrosis due to depletion of limiting co-factors [118]. Plant kingdom houses compounds that can neutralize the overproduced PARP-1 and one such example is Hydroxygenkwanol A which again is a flavonoid found in Daphne belonging to thymelaeaceae family. It has been used in traditional medicinal system of Jordan for treating inflammatory disorders [119].

Phenylpropanoids

Phenylpropanoids are derivatives of the shikimate pathway and are found in almost all the plants. They are responsible for protection against infestants and ultra violet radiations. Eugenol that is found most abundantly in clove, cinnamon, bay leaf is a phenol molecule acting as anti-oxidant in nervous pathologies. It has found profound application in manifesting its neuroprotective [120] effects by inhibiting the NMDA receptors mediated Excitotoxicity and as well superoxide radical modulation [121]. Scavenging system is majorly involved in directly interacting with the reactive species and performs their function by the formation of conjugates; inhibit peroxidation reactions or directly neutralizing the reactive species [122]. Intracellular signaling is mostly the role played by these bioactive, and they have been seen to converge their mode of action to single point in activating NF-κB molecule which tends to activate different cellular system in the neuroprotection. NF-κB can be considered

as one of the essential modulator of cellular homeostatic pathways, whose modulation can either lead to cellular survival or cellular death fates [123, 124]. Activation of anti-oxidant genes and TNFα-PI3/AKT signaling improves survival functions whereas NF-κB is also seen to provide neuroprotective effects by blocking the apoptosis [125]. The overall effects of these antioxidants bioactive comprise of (Fig. 3A) terminal activation of antioxidant genes, modulation of different cell survival signaling pathways, and direct interaction with the reactive species, which help to maintain a healthy homeostatic balance in neurons.

Terpinoids

Isoprenoids or terpenoids are large class of multicyclic compounds composed of 5 carbon isoprene units. Terpenoids are found in most of the medicinal plants and some microbes forming the largest class of natural bioactive compounds. Their further classification is based on the number of isoprene units that constitute them [126]. Terpenoids are also known to help ameliorate the degenerative effects in neurons. As we can see from the causative factors described above, it is clear that the level of diverseness is vast if we look at the *in-vivo* condition. Apart from these mechanisms there is another effect that is not described in the earlier sections and is found to be associated with certain types of degenerative disorders, cholinergic dysfunctions (Fig. 3E). Cholinergic neurons are those that use the primary neurotransmitter that is acetylcholine, which is the first neurotransmitter to be identified with exciting history and nature of activity, as chemical messenger at their synapses [127]. These cholinergic pathways are found to be the primary mode of transmission in the parasympathetic system and are involved in development and storage of memory [128, 129] and therefore are associated with dementia mediating neurodegenerative disorders especially with Alzheimers disease. There is mounting proof of the participation of Neural Growth Factor (NGF) mediated pathway in pathogenesis of the cholinergic dysfunctions [130]. So the next approach is to target the process of formation of acetylcholine in the neuron itself which is carried out by the critical enzyme choline acetyltransferase that uses acetyl-CoA subunits to be added onto choline residues [131]. It is then further released into the synaptic cleft upon neural stimulation with the help of calcium-mediated vesical fusion [132].

The release of the acetylcholine into synaptic cleft is followed by immediate binding to their receptors onto the postsynaptic neuron. It is then released from the receptor of acetylcholine and then acted upon by an interesting molecule that degrades the acetylcholine, Acetylcholinesterase [133]. Our discussion is, however, limited to plant-based approach in treating the condition wherein we have Uleine that is obtained from *Himatanthus lancifolius* (Agoniada) which essentially is an Indol Alkaloid acting as an inhibitor of the enzyme acetylcholinesterase [134]. Uleine is relatively new compound that has been identified to find application in treating degenerative problems. Furthermore anti-cholinesterase function it is also reported to be possessing anti-amyloidogenic effects by inhibiting β secretase that is responsible for generation of altered length fragments in Alzheimer's Disease [135]. It can, therefore, an active agent in targeting cholinergic dysfunctions associated with development of degenerative diseases like Alzheimer's Disease. Uleine besides this is recognized for its anti-inflammatory functions [136], gastroprotective [137] and anti-malarial [138] activities as well.

Celastrol, a Quinone methidetriterpene isolated from *Celastrusorbiculatus Thunb*, is one such bioactive that can modulate protein quality control system by modulating the HSF-1 activation [139, 140]. Also endoplasmic reticulum plays active role in maintaining the protein quality inside a cell. A report by Denzel et al. showed that via modulating the hexosamine pathway, branch of glycolysis, by introducing precursors of the pathway helps with ER based protein quality control and hence maintaining proteostasis [141]. Green compounds, those isolated from plant sources, also find application in modulating the activity of autophagic flux of cell and hence find various anticancer applications, for example, Rg2 a steroid glycoside is known to increase the autophagic status of cell [142]. E3 ligases are themselves present with great diversity which provides specificity to different molecular

destruction [143]. With existence of various chemical modifiers, we describe the natural compound (Fig. 3F) that has recently been found to up-regulate the UPS by activating E3 ligase and further leading to clearing of aggregated proteins from cytoplasm, which is Azadiradione [144]. Azadiradione is a tetracyclic triterpenoid that is isolated from *Azadirachtaindica indica* (Neem) a medicinal tree that is widely known for its vast therapeutic potentials in different medicinal systems like Ayurveda, Homeopathy, and Unani [145]. Azadiradione is seen to up-regulate the chaperone system via HSF-1 pathway as well increasing the activation of E3 ubiquitin Ligase (Ube3a) and ameliorate the pathogenesis of Huntington's disease in mouse models along with improvement in gross symptoms of the disorder.

Conclusions and Key Questions

After having a rudimentary understanding of different mechanistic genesis of the large class of disorders; Neurodegeneration, we have been discussing throughout their high heterogeneity, making it challenging to come up with a brawny treatment. Fig. 4 tries to represent what we have been discussing throughout in a short nutshell and explains the integral mechanisms of various assaults that lead to degeneration. The neuron which gets damaged is compromised in its ability to get renewed [146], houses vast information in the form its molecular status which is dynamic that could be believed to provide the complex mechanistic behavior of our brain. Therefore, like any other cell in the body these molecular insults lead to loss of survival potential of these neurons. However, as they are limited in their division potential they tend to accumulate these insults [147] and still perform their vital functions. As a person ages the gradual build-up of those insults finally lead to the

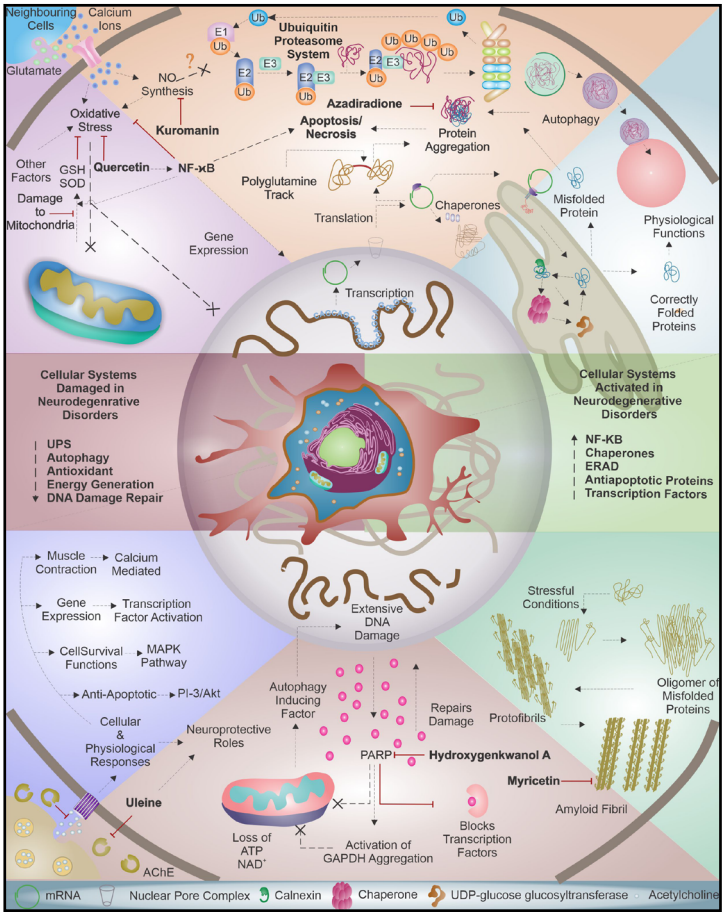

Fig. 4. The figure tries to represent a snapshot of overall cellular and molecular insults resulting in neurodegeneration. Major players involved in various pathways are represented to signify their collective effects in the pathology. Known plant derived compounds are also shown to comprehend the application of natural bioactive compounds in finding a secure treatment option for neurodegeneration.

neuronal death leading to degeneration which gets manifested in the form of a type of neurodegenerative disorder [148]. Nevertheless, our fight is still on, and we have received success with many of the disorders. Along with the various causative mechanisms there are also green hallmarks of plant-derived compounds that are targeting respective mechanisms. The cellular systems which get damaged like protein quality control, Antioxidant systems, ATP loss, genomic damage in the course of neurodegeneration, which tries to explain that such cellular damages are the primary mechanisms leading to neuronal death.

Targeting to safeguard them or compounds that ameliorate the problems with such systems could be helpful in treating the condition. Also, there are specific cellular systems like DNA repair, ERAD, Chaperones, certain Transcription factors that have shown to mask the development of neurodegeneration. Hence, they could be believed as neuronal strategy to mitigate the buildup of damage over time and targeting their up-regulation should help to ameliorate the symptoms. The system is confusing if looked superficially, however, over a closer look certain elements come up as significant player like for example NF-κB that is believed act in antioxidant pathway along with various cell survival pathway [149]. Its activation can restore the balance of neuronal cytoplasm. However, NF-κB is also understood to be involved in cytotoxic mechanism by participating in apoptotic pathways and mitochondrial damage [150, 151]. Hence, its involvement in the dual pathway suggests specific link which can be explored and NF-κB mediated cell survival function may be elevated [152, 153]. Last but the most essential strategy is to use of plant compounds that provide neuroprotective roles by activating cell survival pathways and have anti-apoptotic roles [154, 155]. Collectively, the putative role of NF-κB, enhancing the activation of UPS and other quality control systems, treating genomic abnormalities and finally enhancing the survival related pathways are certain targets that could be explored by using plant derived compounds. This review provide a conclusion linked with the Ubiquitin-Proteasome System which is undoubtedly a major player in maintaining healthy status of neuron [156]. It is therefore imperative to quest for more compounds that are potentially involved in up-regulating its activity. ERAD also helps in maintaining the overall protein quality in the cell in conditions of stress and maintains a healthy proteome. Plant compounds helpful in activating such response possibly help in degenerative progression. The DNA damage is the most apparent cause to disturb any cellular health, and therefore molecules that help in up-regulating the DNA repair mechanisms or modulating the activity of PARP (as discussed earlier) would help with the pathogenesis.

As we can observe from the explained major mechanism that leads to degeneracy, it could debatably be said that oxidative damages resulting from various internal and external insults are the major or we would take this liberty to say it as the ubiquitous causative factor. In different forms oxidative insults can activate various pathways that lead to degeneration. They are something seen with almost all the pathways of neurodegeneration thus it is not only an indicative of being the cause or effect of certain damage in neuron but also to act in amplifying the existing damage. Another critical aspect could be inferred from the principle mechanisms is the involvement of mitochondria which gets terminally damaged leading to activation of cell death pathways. Hence, the maintenance of mitostasis and improving mitochondrial health are one of the principal aspects that should be considered in development of preventive and curative policies to neurodegeneration. Thus, while developing strategies to come up with cure to such class of disorders it is exigent to include the use of antioxidants or compounds that help with treating oxidative insults of neuron. It is critical to look from a perspective to block such iterative insults and use them as preventive policy against neurodegenerative disorder, which is possible with plant, derived compounds.

We have represented a comprehensive conclusive idea in Fig. 5 to present the major challenges and prospects of study in the field of neurodegeneration using plant derived compounds. However, as we have been discussing how exactly these causative factors are manifesting their role in degeneration, we can certainly target their downstream effects. The cellular effects tend to be little less heterogeneous and seen to converge to the activation of apoptotic mechanism. To understand simply we can consider that destroying the aggregated

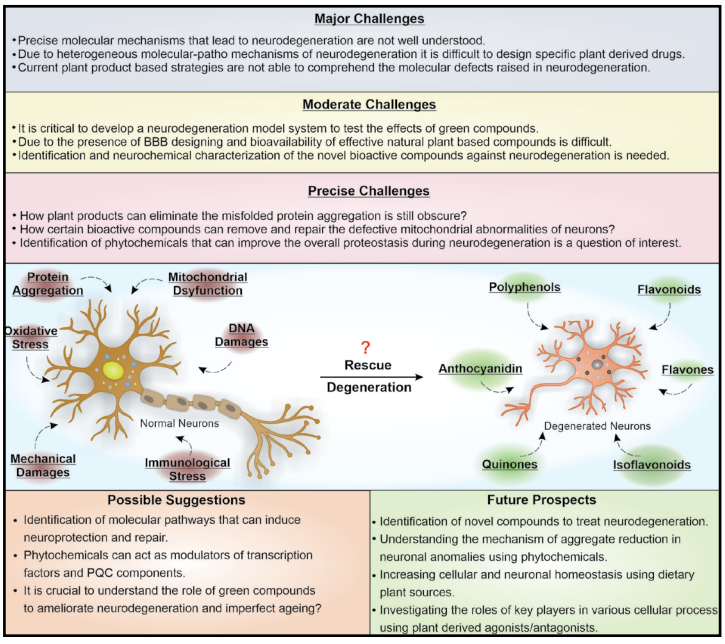

Fig. 5. Collective challenges are represented in the figure along with most probable solutions that could be explored using plant-based compounds signifying their prospects in treating neurodegeneration.

structures is difficult. However, we can help in avoiding them to damage the other neuronal components and somehow strengthen the neuronal defence to its functioning, which is precisely what have these plant derived compounds mastered in doing.

Abbreviations

AD (Alzheimer's Disease); AIF (Apoptosis inducing factor); AChE (Acetylcholinesterase); AKT (Protein kinase B); ALS (Amyotrophic lateral sclerosis); AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic); APCs (Antigen presenting cells); APP (Amyloid precursor protein); AtBl-1 (Arabidopsis Bax Inhibitor-1); BAK (Bcl_2 antagonist killer); BAX (Bcl_2 associated protein); Bcl_2 (B-cell lymphoma 2); BDNF (Brain derived neurotrophic factor); BMP (Bone morphogenetic protein); CAM (Cell adhesion molecule); CASA (Chaperone assisted selective autophagy); CDK (Cyclin dependent kinase); CMA (Chaperone mediated autophagy); Cyt (C, Cytochrome c); ERAD (Endoplasmic Reticulum Associated protein Degradation); ERK (Extracellular signal regulated kinase); ETC (Electron transport chain); FADD (Fas associated death domain); GAPDH (Glyceraldehyde 3-phosphate dehydrogenase); GluR1 (Glutamate receptor 1); GluR2 (Glutamate receptor 2); GSH (Glutathione); GST (Glutathione-S-transferase); HD/HTT (Huntington's disease); HECT (Homologous to E6-associated protein C-terminus); HSF-1 (Heat shock factor 1); HSP (Heat shock protein); IL-1 (Interleukin 1); IL-6 (Interleukin 6); Ile44 (Isoleucine residue-44); INF-γ (Interferon gamma); JNK (c-Jun N-terminal kinase); Lys-48 (Lysine residue-48); MAPK (Microtubule associate protein kinase); NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells); NGF (Neural growth factor); NMDA (N-methyl-D-aspartate); NO (Nitric oxide); PAF-1 (Apoptotic protease activating factor 1); PARP1 (Poly (ADP-ribose) polymerase 1); PI3K (Phosphoinositide 3-kinase); PKC (Protein kinase C); PLC-γ (Phospholipase C gamma); RBR (Ring between ring); Rg2 (Ginsenoside Rg2); RING (Really interesting new gene); RNS (Reactive nitrogen species); ROS (Reactive oxygen species); SOD (Superoxide dismutase); TNFα (Tumor necrosis factor alpha); TRADD (TNF receptor associated death domain); Ub (Ubiquitin); Ube3a (Ubiquitin-protein ligase E3A); U-box (Modified RING motif without the full complement of Zn^{2+} binding ligands); UPR (Unfolded protein response); UPS (Ubiquitin proteasome system).

Acknowledgements

Author Contributions

A.R.D, performed the figures design framework and perform the writing of first draft. A.P and K.M.P, perform critical observations of manuscript, and AW. K and A.K finalize draft in line with concept of manuscript. A.M contributed to the overall design of concept in figures formation, formulate and analyze the contents and perform the final writing of the manuscript. All authors discussed the results and contributed to the final manuscript.

Funding

The work was supported by the Science & Engineering Research Board (SERB), Department of Science & Technology, Government of India grant to (AM) EMR/2016/000716 and from BRNS grant to (AM) 54/14/16/2020-BRNS-Government of India.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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