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Review

Role of Cereals and Pseudo-cereals in the Management of Neurodegenerative Diseases (NDDs) with a Special Reference to Alzheimer's and Parkinson's Disease

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Abstract

Neuro degenerative diseases involve protein aggregation that causes neural cell death or loss of neural communication that affects body balance, movement, talking, breathing, and heart function. Aggregation of proteins, like α-synuclein, are found in Parkinson's disease (*PD*), while *tau*, amyloid-β42 and TDP-43, are aggregated in Alzheimer's disease (*AD*). Besides, amyotrophic lateral sclerosis (*ALS*); dementia with Lewy bodies (*DLB*); dystrophic neuritis (*DN*); corticobasal degeneration (*CBD*); argyrophilic grain disease (*AGD*); astrocyte plaque (*AP*); facial onset sensory and motor neuronopathy (*FOSMN*); Limbic-predominant age-related TDP-43 encephalopathy (*LATE*); neurofibrillary tangles (*NFT*); neuronal intranuclear inclusions (*NII*); neutrophil threads (*NPT*); chronic traumatic encephalopathy (*CTE*); glial cytoplasmic inclusions (*GCI*); Guadeloupean Parkinsonism (*GP*); idiopathic REM sleep behavior disorder (*iRBD*); Nodding Syndrome (*NS*); oligodendrocytes glial cells coiled bodies (*OCB*); muscle cells (*MC*); multiple system atrophy (*MSA*); multisystem proteinopathy (*MSP*); neuronal cytoplasmic inclusions (*NCI*); are several neurodegenerative diseases name according to their involved protein factor(s). In this review we will focus only on AD and PD, and how they can

be managed by cereals and pseudo-cereals, as they contain several anti-neurodegenerative factors.

Keywords
Alzheimer's disease; Parkinson's disease; motor neuron diseases; radicals/reactive oxygen species; neurodegenerative diseases; molecular mechanism

1. Introduction

The causes of AD/PD are generally considered as age-related neural damage, but also could be genetic. Besides, some other causative factors like, alcoholism, pesticides, brain injuries are sometimes noticed in the background of those diseases. The AD/PD, however, has no cure, except for some palliative treatments, which may help to improve the symptoms, relieve pain, and increase mobility. Symptomatically AD is known as irreversible forgetfulness [1], and PD is known as shaking palsy [2]. However, in AD the coagulated *amyloid β* and *tau* protein cause the damage of the neural circuit. Similarly, *α-Synuclein,* a presynaptic neuronal protein agglutination, is one of the causative factors of PD [3].

Brain, as we know, controls several aspects of the body's function, these neurodegenerative diseases consequently limit the ability to perform both basic function, like speech, movement, stability, and balance, as well as many complicated tasks (e.g., bladder and bowel functions, and cognitive abilities). There are lots of reviews, which showed specifically some specific macro-, as well as, micro- nutrients and diet patterns that indeed offer indeed a beneficial function. In this connection, we will discuss here about some cereals and/or pseudo-cereals, which are important to be considered for controlling the AD/PD symptoms.

1.1 AD, Some Details of the Disease

In 1906, Dr. Alzheimer discovered many abnormal clumps and tangled bundles of fibers (now known as *Aβ* plaques, and hyper-phosphorylated *tau* tangled protein, respectively) from a deceased brain of a woman who was suffering from memory loss, language problems, and many unpredictable behaviors [1]. Neurons are known to transmit messages from different parts of the brain to muscles and other organs in the body.

Due to the formation of *Aβ* agglutinated deposit, and their ineffective clearance, forms the pore-like structures in the neurons and cause the synaptic damage, alterations in glutamate receptors, mitochondrial dysfunction, and alterations in signaling pathways [1]. Molecular analysis identifies a number of signaling proteins, like *fyn* kinase, glycogen synthase kinase-3β (GSK3β) and cyclin-dependent kinase-5 (CDK5), which are involved in the neurodegenerative progression of AD [4].

The free-radical theory of aging, though has inspired to use many antioxidants such as alpha-tocopherol, ascorbate and coenzyme-Q to treat the AD, but, in fact, the results are with limited success. In AD, the abnormal aggregations of *Aβ* and *tau* proteins are similar to the *prion disease*, suggesting the formation and spread of corruptive protein templates [5]. Although, the antioxidant cannot reverse the autophagy but can serve in removing the damaged or dysfunctional proteins and organelles to preserve the neuronal function as well as their survival [5].

Senescent cells and their mechanisms of action are still under-studied, but potentially important in the field of neuro-inflammation and subsequent neuro-degeneration. Characterization of cellular process(es) and molecules involved in the senescence of the brain-cells, could focus on some novel therapeutic targets for the prevention of chronic age-related ADs [6]. Here below, we summarize the key players of AD (Figure 1). Further, L-glutamate (or L-aspartate) can mediate acute excite-toxicity in the brain, resulting long-term neurodegenerative processes like AD [7, 8].

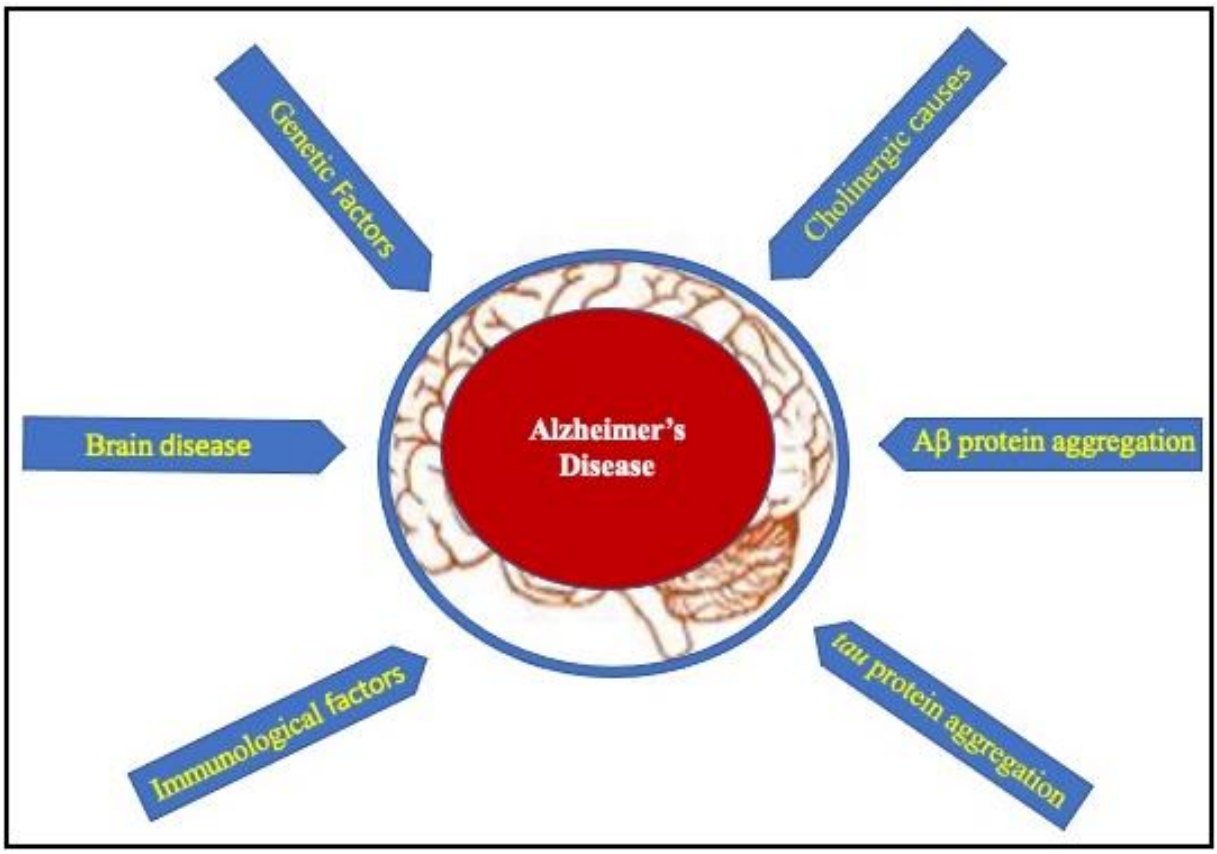

Figure 1 Key Players of AD.

Underlying mechanisms of developing AD/PDs include mostly Oxidative stress (OS) and/or formation of free radicals/reactive oxygen species (ROS) [9]. Genetic linkage, ageing, stress, pesticides, fungicides/insecticides and SUMOylation process are also considered as causative factors for the onset of PD/AD, and also many other NDDs [10]. Several chemicals used in industry or consumer products including metals (e.g., arsenic, lead, manganese), air pollution, and bacteria-made endotoxins are also believed to cause NDDs, like AD/PD. Besides, some dietary factors (e.g., caffeine, tobacco, dietary antioxidants), as well as lifestyle are linked with the appearance of the diseases like AD and PD [11]. In addition, some stress–related proteins and chaperones have high impact on the pathogenesis of AD and PD [11]. All these pathways interact with other pathways like energetic dysregulation, molecular damage, metabolic change(s), abnormalities in ion homeostasis, and adaptation, ultimate cause the onset of the AD/PD symptoms [12].

AD is also known as *Tauopathy* as the *tau* protein gets aggregated and blocks the neural circuit. Whether mitochondrial OS could be an inducer of *tauopathy* (AD), is a matter of consideration. In fact, OS might occur in the early stages of the disease, even before the tau-agglutination [13]. In the early progression of the disease, mitochondria might not be the only source of ROS, there could be

a positive loop between OS generation in any place during the early stages of the disease, which can promote mitochondrial impairment leading to neuronal death. Studies in animal models reveal the importance of antioxidant enzymes in tau pathology. For example, the inhibition of SOD1 and SOD2 leads to increase the tau pathology in mice [13, 14], and in a drosophila model [15]. More research should be conducted to confirm the role of mitochondrial dysfunction and OS in *tauopathies*, which might be the consequence of the age-dependent decrease in antioxidant molecules [16].

1.2 PD/α-Synucleinopathy

Abnormal accumulation of insoluble α-synuclein protein in neurons and glial cells, disturbing normal neural circuit, and resulting in PD, DLB and multiple system atrophy (MSA), altogether called as *α-synucleinopathy* [17-19]. Symptoms of *α-synucleinopathy* include autonomic nervous system dysfunctions along with many others, like constipation, urinary, sexual dysfunction, and reduced heart rate variability, etc. At the molecular level, this is disease is identified as the mutations in the synuclein (SNCA) gene encoding for α-synuclein. Other genes, PARK, LRRK2 and VPS35, have been found to be associated with variants of autosomal dominant PD, while PARK2, PINK1, and PARK7 cause autosomal recessive PD [20, 21].

1.3 Molecular mechanisms of PD

In the familial PD cases, the individual experiences frequent falls 3 years before the onset of the disease, and at molecular level they express triplication of SNCA, and orthostatic hypotension (OH) with evidence of sympathetic cardiac denervation. The sympathetic cardiac denervation is associated with bi-allelic mutations of PARK2 and the LRRK gene mutations, which showed the symptoms such as constipation, neurogenic bladder and erectile dysfunction, in PD [20]. *α-synucleinopathy* affects the central autonomic network system and also the preganglionic sympathetic and parasympathetic neurons [22]. The pure autonomic failure (PAF) involves generalized loss of sympatho-adrenomedullary cells, as reflected by a low level of catecholamines (dopamine, norepinephrine, epinephrine) and their byproducts, metanephrines, in blood, whereas in PD and MSA, an organ-selective sympathetic denervation occurs [23].

Mitochondrial dysfunction is also noticed in PD [1]. Besides, the intimate relationships among microglial activation, nitric oxide formation, and neuro-inflammation are also noticed in relation to PDs [1]. In brief, oxidative stress and formation of free radicals/reactive oxygen species, mitochondrial dysfunctions, impaired bioenergetics and DNA damage, neuroinflammatory processes and disruption of cellular/axonal transport are the prime cause for the onset of the PD [4]. Molecular mechanisms of PD formation are shown in Figure 2.

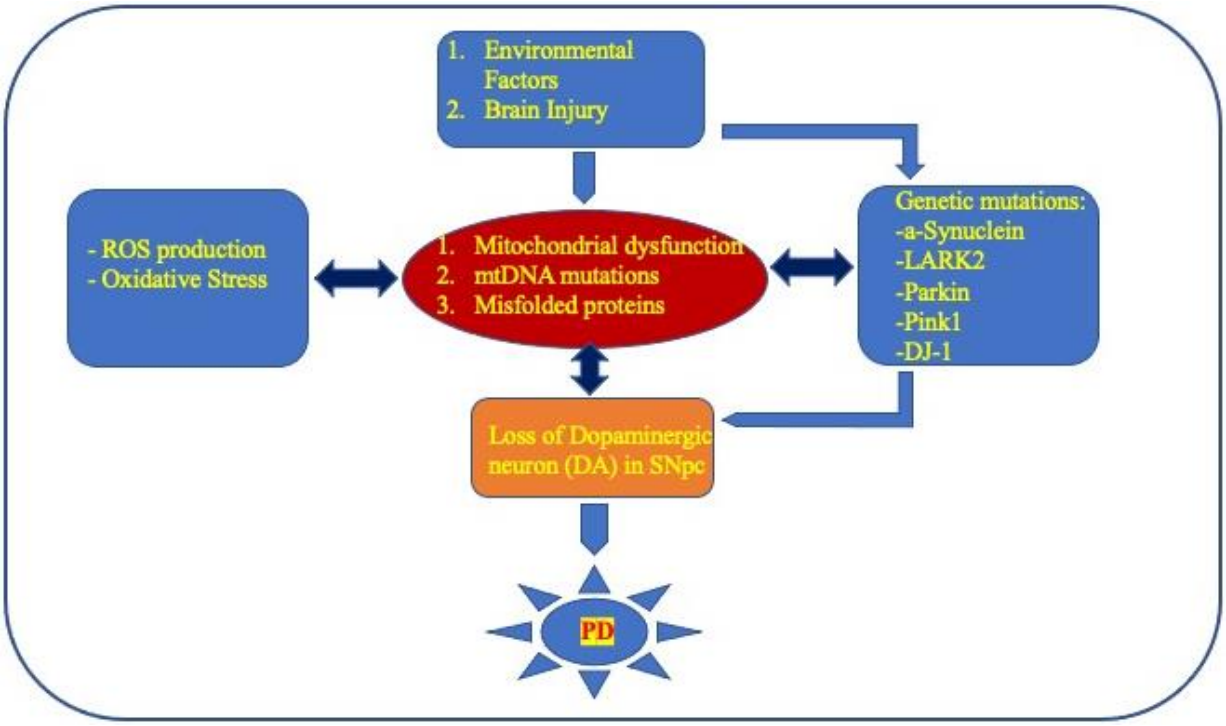

Figure 2 Molecular mechanism of PD formation.

However, having such a fair knowledge of AD/PD we still do not have any cure for those diseases except for some palliative treatments. In that scenario, any other alternative approaches should be welcome. Here we will discuss on cereals and pseudocereals, if they have any merit of cereals and pseudocereals to be considered for that purpose.

1.4 Cereals and Pseudocereals

These granules contain high fiber which aid in gut health, blood sugar control, and cholesterol reduction, crucial for managing diabetes and cardiovascular -disease. They are also excellent sources of iron, magnesium, calcium, B-vitamins, and Vitamin E, important for overall vitality [24].

The Key Grains, Quinoa, are rich with high protein quality, antioxidants. Amaranth contains complete protein, rich in lysine, squalene, and minerals. Buckwheat is high in rutin, polyphenols, and B-vitamins, while Barley are good in blood-sugar management, potential for anti-cancer properties, and contains antioxidants that helps NDD [25].

Pseudocereals have similar structure as cereal grains and most of the seed components are covered by the endosperm (nutrient store) is encased by the aleurone**,** which is then enclosed by the testa (seed coat) and the hull (outer husk). However, despite of having enough similarities, not all pseudocereals are placed in the same family as wheat, maize, and rice [26]. Broomcorn millet *(Panicum miliaceum L.),* canary seed *(Phalaris canariensis L.),* and teff *(Eragrostis teff)* are grouped in the Poaceae family (*grasses*) like wheat, rice, and maize [26]. On the other hand, amaranth (*Amaranthus spp.),* buckwheat (*Fagopyrum esculentum Moench*), chia (*Salvia hispanica L.*), and quinoa (*Chenopodium quinoa Willd*) are placed in the Amaranthaceae, Polygonaceae, Mint, and Chenopodiaceae family, respectively [27].

In general, all pseudocereals have higher protein and lipid contents and lower carbohydrate content than maize, wheat, and rice. Unlike cereal grains, pseudocereals are rich in bioactive

compounds, including dietary fiber, unsaturated fatty acids, lignans, antioxidants, flavonoids, polyphenols, phytosterols, minerals, vitamins, high quality proteins with a balanced aminoacids composition, and essential micronutrients [28-30]. Therefore, the high nutrient-rich pseudocereals are found to be associated with health benefits, such as hypolipidemic, anti-inflammatory, anti-hypertensive, anti-cancer, and hepato-protective properties. They also offer benefits against obesity and diabetes [31, 32]. Thus, it is hypothesized that the nutrient imbalance created due to carbohydrate-rich cereals (maize/wheat/rice) may be corrected by replacing them with pseudo-cereals in the diets.

Significant emphasis has been placed on the cultivation, research, and new product developments using amaranth, buckwheat, and quinoa [33-35]. Therefore, this review first highlights the unique aspects of the chemical composition of amaranth, buckwheat, and quinoa in comparison to that of maize, wheat, and rice are highlighted. Second, the impacts on the compositions of amaranth, buckwheat, and quinoa due to common processing treatments are discussed. Finally, food products that can be formulated using these pseudocereals are covered to inform consumers about potential ways of including pseudocereals in their daily diets while maintaining high nutritive value and sensorial acceptance.

2. Effect of Whole Grains on Neurodegenerative Diseases

- Whole grains are rich in polyphenols, which inhibits the oxidative and inflammatory effects on neural cells. They also can modulate the host-immune response, as observed in many experimental studies [36-38].
- Moreover, polyphenols can modulate Bcl-2 and PERK functions, and release anti-oxidant enzymes including catalase and superoxide dismutase, and inhibit mitochondrial dysfunction [39-41].
- Polyphenols can block the action of acetylcholinesterase and butyrylcholinesterase, thus inducing metal chelation, autophagy regulation and prion elimination, which help in improving cognitive functions [42, 43]. Preclinical data from mice experiments suggest that resveratrol might prevent neuronal loss [44].
- SRT501, an oral formulation of resveratrol, can activate SIRT1, an NAD+-dependent deacetylase, and thus can stimulate mitochondrial function. These results were noticed in some preclinical studies with mice model of multiple sclerosis [45].
- Resveratrol also showed a neuroprotective effect in 6-hydroxydopamine (6-OHDA)-induced PD-rat model. The results are accompanied by the reduction in DNA condensation and vacuolization of dopaminergic neurons in the *substantia nigra* [46]. In addition, a lower expression of COX-2 and TNF-α has also been found [47].
- Therefore, whole grains and their constituents, especially polyphenols, may exert a beneficial, neuroprotective effect, thus representing a feasible therapeutic opportunity in this setting [48, 49].
- Cereals and pseudocereals (like quinoa, amaranth, buckwheat) offer neuroprotective compounds (phenolics, antioxidants, fiber, quality protein) that combat oxidative stress and inflammation [50, 51]. Also, they are the key drivers of neurodegenerative diseases (NDDs) like AD/PD, by improving gut-brain axis, reducing glycation, and providing sustained energy,

potentially slowing progression [52], though they're not a cure but part of a beneficial diet for brain health, especially whole grains and pseudocereals rich in bioactive compounds.

Below, we have depicted the molecular target(s) of the cereal and pseudo-cereal bioactive(s) towards the neuroprotective effects (Table 1).

Table 1 Molecular Targets of Bioactive(s) and their effects on neuro-protection.

Bioactive	Molecular target(s)	Effect(s)	Exptl. Evidence	Ref.
Flavonoids	● Target enzymes involved in oxidative stress, inflammation, and neurotransmitter systems ● Can modulate signaling pathways such as the MAPK and PI3K/Akt pathways	Protect from neuronal death and abnormal function	● Flavonoid-rich diets can improve cognitive function and reduce neurodegeneration in animal models	[53]
Phenolic Acids	● Primarily target oxidative stress pathways, reducing reactive oxygen species (ROS), and thus enhancing antioxidant defenses	Helps to protect neurons from oxidative damage	● Phenolic acids can reduce oxidative stress and enhance neuroprotection of neuronal cells	[54]
Saponins	● Modulates NF-kB pathway, which is involved in inflammatory responses	Protects from apoptosis	● Saponins have shown promise in preclinical studies for their neuroprotective properties, in neurodegenerative disease model	[55]

Further, the above bioactives, as they are known for their antioxidant properties, they also have the ability to inhibit glycation [56], which is the process where sugars bind to proteins or lipids, potentially leading to various health issues, including diabetes and aging-related diseases.

- Flavonoids can reduce the formation of advanced glycation end products (AGEs) by scavenging free radicals and inhibiting the glycation process itself [57].
- Similar to flavonoids, phenolic acids exhibit antioxidant activity and can interfere with glycation pathways, thereby protecting proteins from glycation damage [58].
- Saponins also contribute to reducing the glycation by enhancing antioxidant defenses and potentially modulating glucose metabolism [59, 60].

3. Cereals and Pseudocereals Show Neuroprotective Roles in Neurodegenerative Disease Models

Oats contain avenanthramides (Avns), a group of polyphenol amides that have been identified as having significant neuroprotective roles in AD and PD models.

- **Alzheimer's Disease (AD):** Preclinical studies have shown that avenanthramide-C (Avn-C) from germinated oats can reverse amyloid-β (*Aβ*)-induced neurotoxicity. In Tg2576 AD mouse models, Avn-C restored impaired long-term potentiation (LTP) in the hippocampus by scavenging the reactive oxygen species (ROS) [61].
- **Parkinson's Disease (PD):** Synthetic bis-avenanthramide-B (Bis-B), an analog of oat avenanthramide, acts as an antioxidant and Nrf2 inducer (nuclear factor erythroid 2-related factor 2), which protects against rotenone-induced oxidative damage in SH-SY5Y cells, a model for PD [62].
- **Cognitive Function Studies:** Clinical trials have found that short-term consumption of green oat extracts can significantly improve cognitive function (accuracy and speed of performance) in humans, likely through better brain metabolism [63].
- **Oat Peptide (RW-9):** A specific novel peptide identified from oat protein has been shown to ameliorate learning and memory impairments in mice by regulating oxidative stress and acetylcholinesterase (AChE) in the brain [64].

4. Pseudo-Cereals Are Recognized for Their Superior Nutritional Profile Compared to Traditional Cereals and Their Ability to Combat Oxidative Stress

- **Stress-Related Memory Loss:** A study using a quinoa-based functional food (QFF) in adolescent rats showed that it mitigates stress-induced hippocampal dendritic atrophy and prevents spatial memory impairment [65].
- **PD Model:** Quinoa extract has been shown to protect against locomotor impairment and memory deficits in *Drosophila* models of PD induced by rotenone [66].
- **Alzheimer's Model:** Fermented quinoa (rich in betaine) has shown the ability to reduce homocysteine levels and reduce neuroinflammation/amyloid plaque accumulation. Rutin has been shown to reduce pro-inflammatory cytokines and improve memory in Alzheimer's disease models [67].
- **Neuroprotective Compounds:** Buckwheat contains high levels of rutin (RUT) and quercetin (QE), which are strong antioxidants that help reduce neuroinflammation and improve the activity of antioxidant enzymes [68].

5. Key Mechanisms of Action of the Cereal and Pseudocereals Bioactives

- Avenanthramides (AVNs), the unique plant alkaloids of secondary metabolites found in oats cereal, and phenolic compounds in pseudo-cereals activate the Nrf2/ARE pathway, which increases the expression of cytoprotective enzymes that protect neurons from oxidative death [69].
- Further, this bioactive modulate the PI3K/AKT/GSK3β signaling pathway, crucial for cell survival and reducing amyloid-β accumulation [62].
- Quinoa and buckwheat compounds directly decrease the concentration of pro-inflammatory cytokines such as TNF-α and IL-1β [70].

6. Bioavailability and Blood Brain Barrier (BBB) Permeability of the Cereals and Pseudo Cereals Bioactive Compounds

Bioactive compounds in cereals and pseudocereals generally exhibit low bioavailability and limited blood-brain barrier (BBB) permeability due to their complex chemical structures and extensive metabolism in the gut. Despite these barriers, certain low-molecular-weight metabolites can cross into the central nervous system to exert neuroprotective effects.

- **Cereals (e.g., Wheat, Rice, Corn):** Rich in phenolic acids like ferulic acid, which are often bound to cell wall polymers, requiring release during digestion or fermentation to become bioaccessible [71].
- **Pseudocereals (e.g., Quinoa, Buckwheat, Amaranth):** Contain high levels of flavonoids (like **rutin**), lignans, and phytosterols. Their bioavailability is influenced by food processing techniques like germination, which can increase the levels of bioavailable phenolics and GABA by up to 800% [72].
- **General Barriers:** Most phytochemicals undergo extensive transformation by gut microbiota, resulting in metabolites that may have different biological activities than the parent compounds [73].

6.1 Blood-Brain Barrier (BBB) Permeability

The BBB is highly selective, excluding approximately 98% of small molecules from entering the brain.

- **Permeable Compounds:** Small, lipophilic molecules and specific low-molecular-weight (LMW) metabolites (such as methylated or sulfated phenolic acids) have been shown to cross the BBB [74].
- **Transport Mechanisms:** Some compounds cross via passive diffusion, while others may use specific transporters, suggesting a degree of stereoselectivity [75].
- **Neuroprotective Action:** Even at low concentrations (pM to low nM), these compounds can mitigate oxidative stress and neuroinflammation within the brain parenchyma [76].
- **Indirect Effects:** Some bioactives may provide neuroprotection without crossing the BBB by modulating peripheral targets or the gut-brain axis [77, 78].

6.2 Summary

In the summary table (Table 2), different Cereals, their major bioactive compounds, and neuro-protective functions are listed.

Table 2 Different Cereals, major bioactive compounds, and their neuroprotective functions.

Cereals and Pseudo-cereals	Mechanism of action	Effects	Ref.
Many cereals and pseudo-cereals	Antioxidant properties	Reduces neuro-degeneration	[79]
Whole grains like oats and quinoa	Anti-inflammatory	Lowering the risk of neuro-inflammatory diseases	[80]
High fiber content in cereals	Promotes gut health	Improved brain function and reduced neuro-degenerative risks	[79]
Essential nutrients	B vitamins and magnesium mineral	Support cognitive health	[81]
Certain Grains	High in Polyphenols	Neuro-protection and cognitive function	[82]
Whole grains	Have low glycemic index, and maintain stable blood sugar levels	Crucial for brain health	[80]
Phytochemicals	May modulate neurotrophic factors	Promote neuronal growth and survival	[83]
Fermentable Carbohydrates: (Probiotics)	Supports beneficial gut bacteria	Influence brain health	[84]

7. Limitations of Cereal and Pseudo-Cereal Bioactives

- Excessive intake can lead to deficiencies in essential nutrients not found in these grains and may cause nutrient imbalance.
- High fiber content may cause bloating, gas, or digestive discomfort if consumed in excess.
- Some cereals contain anti-nutrients like phytic acid, which can inhibit mineral absorption.
- Overconsumption can contribute to excessive calorie intake, leading to weight gain.
- High amounts of refined cereals can cause rapid increases in blood sugar levels.
- Some individuals may experience allergic reactions or intolerances to specific grains [85].

8. Conclusions

Cells naturally grow old and eventually die, therefore proper nourishment and regulation of cellular proteins are crucial to maintaining a healthy brain, especially when ageing starts. In neurodegenerative diseases, aggregation of clumped fragments of mis-folded proteins, followed by spreading to neighboring cells, is still poorly understood. The Rutgers researchers found that roundworms when stressed, their nerve cells can extrude neurotoxic proteins in large packets,

called *exophers.* This *exophers* production was found during fasting and also in neurodegenerative diseases like AD and PD.

Since a healthy brain is critical to overall health and longevity, it is important for to understand the brain health and the effect of neurological disorders on the brain. Many neurological disorders that disrupt the normal brain functions include, *traumatic brain injury*, *brain tumors, meningitis, and communication and sensory disorders.* During all those conditions overproduction of reactive oxygen species (ROS) exert neurodegeneration effect on the neural cells and promote cell death. Considering the importance of managing protein aggregates during aging and in neurodegenerative diseases, a detailed understanding of how those aggregates are formed and transferred. New research in the area of brain mechanisms may open a new avenue for the disease prevention and treatment. Until then we can use the benefits that may be available from cereals and pseudocereals as they contain Antioxidants & Phenolics compounds which can fight free radical damage (oxidative stress) and save the brain cells from getting damaged. Another context of cereals and pseudocereals is Fiber which supports a healthy gut microbiome, influencing the gut-brain axis, a pathway for inflammation. Similarly, B Vitamins which are essential for cognitive function and brain energy are found in whole grains.

Bioactive compounds in pseudocereals help reduce chronic inflammation and rescues brain from NDDs. Glycation inhibitory compounds are present in pseudocereals (e.g., buckwheat, chia), which can inhibit advanced glycation end products (AGEs) and protects from NDDs. Further, the whole grains release energy slowly, preventing glucose spikes that can harm the brain.

Therefore, it is recommended to substitute refined grains with whole grains and pseudocereals. Incorporate pseudocereals, like quinoa, amaranth, or buckwheat in salads, porridges, or as gluten-free flour; choose minimally processed grains for maximum fiber and nutrients, and consider sprouting/Germinated bioactive compounds to increase their neuroprotective potential (Figure 3). However, while beneficial, cereals and pseudocereals are part of a dietary strategy, not a cure, for neurodegenerative diseases.

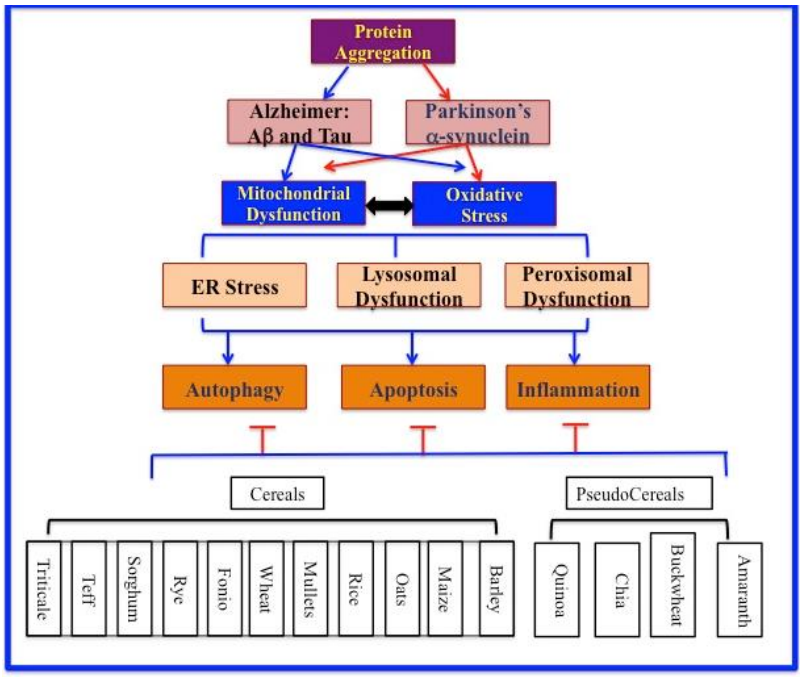

Figure 3 Neuroprotective Function of Cereals and Pseudocereals.

Last but not least, it should be mentioned that the cereals and pseudo-cereals may be included in diet to support the neural system, but not to be considered as medicine for any neurological disorders. Future research on this topic should be done with more clinical trials and with standardized dietary intervention, along with their mechanistic study to explain the out come of the results.

Abbreviations

AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
Aβ	β-amyloid
CDK5	Cyclin-dependent kinase-5
ER	Endoplasmic reticulum
GBA	Glucocerebrosidase-beta
GSK3β	Glycogen synthase kinase-3β
HD	Huntington's disease
MNDs	Motor neuron diseases
SNCA	Synuclein
NDDs	Neurodegenerative diseases
NMJ	Neuromuscular junction
OS	Oxidative stress
PD	Parkinson's disease
ROS	Radicals/reactive oxygen species
SASPs	Senescence-associated secretory phenotypes
TDP-43	Transactive response DNA binding protein 43 kDa
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

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Author Contributions

The concept and main writing of the first Draft are done by AC. SG did the editing and paraphrasing the article, designed the Figs, and did the literature search. Both did approve the final writing of this manuscript.

Competing Interests

Both of the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AI-Assisted Technologies Statement

AI-assisted tools were used in some parts in the writing process, to improve the readability and language of the work. All scientific content, data interpretation, and conclusions were developed independently by the author. The authors have thoroughly reviewed and edited the AI-assisted text to ensure its accuracy and accept full responsibility for the content of the manuscript.

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