

## LINKING ANTIEPILEPTIC DRUG-INDUCED NEUROTRANSMITTER DYSREGULATION AND THE THERAPEUTIC POTENTIAL OF PHYTOPHENOLS

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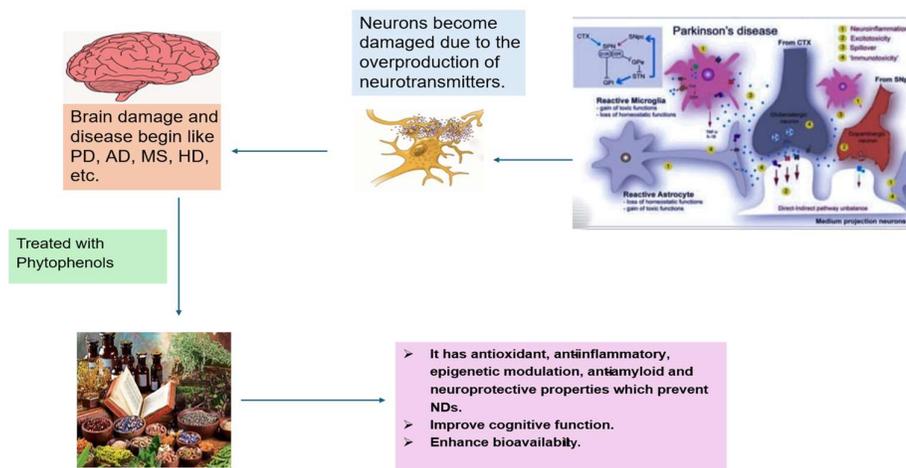
### Abstract

Neurodegenerative disorders (NDs) are a group of conditions affecting the central nervous system (CNS), characterised by advanced neuronal dysfunction and degeneration, leading to cognitive decline and sensory-motor impairments. These extensive NDs include Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), multiple sclerosis (MS), epilepsy, and others. They occur when disturbances in neurotransmission impair synaptic plasticity and cognitive function. Neurotransmitters (NTs) are biochemical messengers responsible for transmitting signals across synapses via electrical and chemical signals, through variable excitatory and inhibitory mechanisms. All disorders significantly impact the CNS, resulting in clinical and biochemical changes. Antiepileptic drugs (AEDs) are designed to bind to neurotransmitter receptors and modulate brain excitability to prevent or reduce seizures. They have multiple mechanisms of action, for example, obstructing voltage-gated Na<sup>+</sup> and Ca<sup>+</sup> channels, enhancing GABAergic inhibition, and regulating glutamate receptors. However, they can also adversely disturb neurotransmitter activities. Side effects include slowed dopamine and other neurotransmitter secretion, which can contribute to the progression of various neurodegenerative disorders like Parkinson's disease and Alzheimer's disease. Additionally, polyphenols and bioactive compounds offer antioxidant activity, anti-inflammatory effects, inhibition of protein aggregation, mitochondrial protection, modulation of cell signalling pathways, chelation of metal ions, and enhancement of cognitive function, among other benefits. This study highlights the importance of careful monitoring of patients on long-term AED therapy and the associated risk of cognitive decline due to neurotransmitter disruption.

**Keywords:** Neurotransmitters, Neurodegenerative disease, Antiepileptic drugs, Parkinson's disease, Alzheimer's disease, Alpha-Synuclein, B-amyloid plaques, Phytophenols.

**Abbreviations:** NTs-Neurotransmitters, AEDs-Antiepileptic drugs, NDs-Neurodegenerative disorders, AMPA-  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, NMDA- N-methyl-D-aspartate receptors, nAChRs-Nicotinic acetylcholine receptors, mAChRs- Muscarinic acetylcholine receptors.

### Graphical Abstracts:



## Introduction

Neurotransmitters are chemical messengers that transmit signals between nerve cells and other target cells in the nervous system. The discovery and understanding of key neurotransmitters, including norepinephrine, dopamine, serotonin, glutamate, and gamma-aminobutyric acid, revolutionised neuroscience and medicine from the mid-20th century onward. These advances, along with progress in receptor pharmacology and neurochemistry, directly led to the development of effective psychoactive drugs and treatments for psychiatric disorders.

The study of these chemical messengers remains a fundamental part of modern neurobiology (Sheffler et al., 2023). They are essential for brain function, enabling communication that is vital for behaviour, thoughts, and more. Nearly 100 neurotransmitters are recognised, each with diverse functions and often localised to specific brain regions (Manca et al., 2025). Neurotransmitters can be inhibitory, like GABA and serotonin, which have multiple effects depending on the receptor type and brain area. Conversely, excitatory neurotransmitters such as glutamate promote nerve cell activation. Balanced neurotransmitter activity is crucial for normal brain function (Chen and Zhang, 2023). Parkinson's disease mainly results from the loss of dopamine-producing neurons in a brain region called the Substantia Nigra.

Alzheimer's disease affects memory, behaviour, thinking, and daily functioning. These conditions involve the progressive destruction and death of brain cells due to neurotransmitter imbalances (Maria Isabel Miranda, 2007). The primary cause of neurotransmitter disruption often involves antiepileptic drugs, which patients frequently use. Antiepileptic drugs (AEDs), also known as anticonvulsants, encompass a diverse group of medications. AEDs influence neurotransmitters such as GABA (gamma-aminobutyric acid), an inhibitory neurotransmitter in the CNS that plays a key role in regulating neuronal activity in epilepsy. They reduce glutamate-mediated excitatory transmission by blocking  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors. Perampanel, an AMPA receptor antagonist, is used to treat epilepsy but may cause dizziness, irritability, and psychiatric side effects [Paul et al., 2023; Cheli et al., 2021].

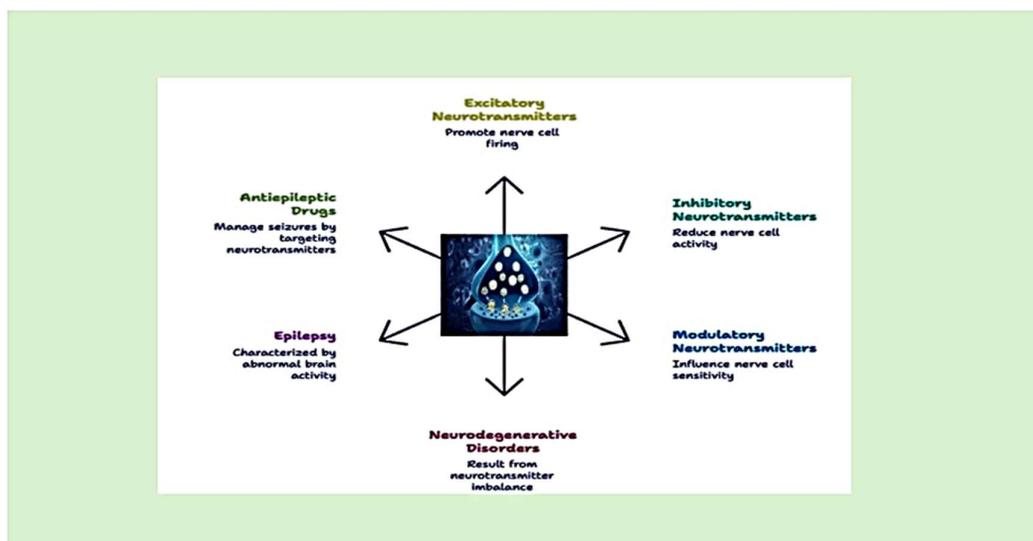
Studies confirm that antiepileptic drugs can impair cognitive abilities. The wide variety of antiepileptic medications requires careful consideration to balance effective seizure control with minimising cognitive side effects, as some drugs have more noticeable impacts than others (Jomova et al., 2024).

Epilepsy is a chronic neurological disorder characterised by abnormal electrical activity in the brain, leading to recurrent and variable disruptions in brain function (Fisher et al., 2005). It is one of the most common brain disorders worldwide, affecting a significant portion of the population, with annual incidence rates ranging from 52 to 900 cases per 100,000 individuals (Feigin et al., 2019).

The development of epilepsy involves complex processes such as neuronal dysfunction, neurotransmitter imbalance, and genetic susceptibility, further influenced by inflammatory and oxidative stress responses (Brodie et al., 2011). Over 25 antiepileptic drugs are available, targeting mechanisms like ion channel modulation, GABA enhancement, and glutamate receptor inhibition. Cognitive dysfunction often accompanies epilepsy, with factors such as the underlying cause, treatment effectiveness, and seizure control affecting the extent and progression of impairment (Halmstaedter et al., 2001).

This review aims to summarise and discuss neurotransmitter mechanisms, secretion, and the effects of AED therapy in neurodegenerative diseases, which are important for identifying effective therapeutic targets. Phytochemicals are currently under extensive research for their potential to slow disease progression and improve cognitive function.

Their well-documented antioxidant, anti-inflammatory, and neuroprotective properties make them promising candidates for treating neurodegenerative conditions. This work emphasises the biological mechanisms through which phytochemicals act and explores their potential as therapeutic agents for managing neurodegenerative diseases.



**Figure 1. Neurotransmitter molecular basis of cognition, behaviour, and neurological disorders.**

### **Neurotransmitters (NTs) structure and system involved in cognition**

Neurotransmitters consist of a small amino acid backbone, an amine group, aromatic ring, ester of choline, short amino acid chain, nucleotides, and simple diatomic molecules. They can be categorised based on their chemical composition, which includes glutamate, norepinephrine, serotonin, acetylcholine, histamine, glycine,  $\gamma$ -aminobutyric acid, adrenaline, and dopamine (Manca et al, 2025). Glutamate functions both as an amino acid in protein synthesis and as a neurotransmitter in the brain (Kazemi and Hoop, 1991). There are two types of receptors: inhibitory ( $\alpha 1$  and  $\alpha 2$ ) and stimulatory ( $\beta 1$  and  $\beta 2$ ), which modulate cognitive processes. The locus coeruleus (LC) is one of the earliest brain regions affected in Alzheimer's and Parkinson's disease, and damage to neurons here leads to reduced norepinephrine production (Silverberg et al, 1978). Serotonin exerts its effects via several receptors, except 5-HT, which is a ligand-gated ion channel. As neurodegenerative diseases develop, serotonergic dysfunction progressively accompanies cognitive decline through both direct neuronal mechanisms and unintended modulation of other systems (Seyedabadi et al, 2014). Acetylcholine binds to two main receptor types: nicotinic acetylcholine receptors (nAChRs) and muscarinic acetylcholine receptors (mAChRs). The basal forebrain cholinergic system, especially the nucleus basalis of Meynert, projects widely to the hippocampus, amygdala, and neocortex, making it central to cognitive processing. Research shows a noticeable reduction in ChAT activity in the brains of individuals with Alzheimer's and Parkinson's diseases (David A Brown, 2006). Histamine is well-known for its role in hypersensitive reactions and gastric acid secretion in the CNS, functioning as a modulatory neurotransmitter. Disruption of central histaminergic neurotransmission is increasingly associated with age-related cognitive decline and neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington's disease (J C Schwartz, 1975).

Glycine acts as a co-agonist with glutamate at NMDA (N-methyl-D-aspartate) receptors in the brain, which are essential for activation, learning, memory, and synaptic plasticity. Deviations in glycine receptor activity are linked to several neurodegenerative and cognitive disorders. Disruption of GABAergic structures is strongly associated with cognitive dysfunction and neurodegenerative diseases, including Alzheimer's, Parkinson's, and age-related memory impairment (Leon and Tadi, 2025). Cognitive decline, especially in ageing and neurodegenerative diseases like Alzheimer's and Parkinson's, is closely linked to dopaminergic dysfunction. In Parkinson's disease, motor symptoms are often accompanied by cognitive impairments, credited to decreased dopamine in frontostriatal circuits (Yingfang Tian, 2024). Adrenaline plays a modulatory role in memory, attention, and stress responses, all of which impact cognitive impairment and neurodegenerative diseases through various mechanisms (Ring et al, 2013).

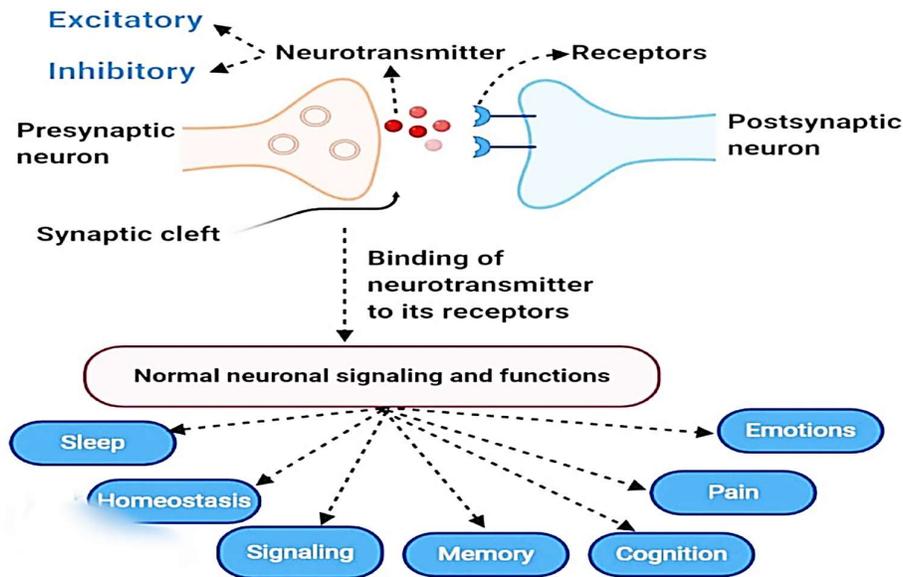


Figure 2. Neurotransmitter signalling regulates key brain functions.

### Mechanism of neurotransmitter linking to cognitive deterioration.

Neurotransmitters enable nerve cells to connect with brain signals and their pathways. Their mechanism of action involves numerous key pathways, such as the cerebral dopaminergic, cholinergic, noradrenergic, GABAergic, and glutamatergic systems (Alarcon et al., 2023). Dopaminergic pathways include neurons that produce and release dopamine, encompassing the nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular tracts. These pathways regulate activities such as movement, with the nigrostriatal pathway involved in Parkinson's disease and the mesocortical pathway in cognition (Luo and Huang, 2016). The path established in the substantia nigra pars compacta, projecting to the dorsal striatum (caudate and putamen), is critical for motor control and is severely affected in Parkinson's disease (Faure et al., 2005). Originating from the ventral tegmental area (VTA) and hippocampus, it influences reward, emotion, and motivation. Dysfunction here links to mood disorders and contributes to non-motor symptoms in neurodegeneration (Alcaro et al., 2007). The VTA is connected to the prefrontal cortex, which controls cognition, memory, and executive functions. Reduced dopamine transmission in this region impairs these functions, declining working memory and more (Quessy et al., 2021). The hypothalamus controls hormone secretion, especially prolactin. Although the tuberoinfundibular pathway is not primarily associated with cognition, its neuroendocrine role, dopaminergic modulation, and effects on key brain regions influence cognitive performance (Qi-Lytle et al., 2023).

The cerebral cholinergic pathways involve neurons that produce and use acetylcholine; imbalances lead to Alzheimer's and Parkinson's disease. These pathways are especially vulnerable in the cerebral cortex, hippocampus, and thalamus, areas vital for higher cognitive functions (Hempel et al., 2018). Neuroinflammation and impaired neurotrophic signalling threaten cholinergic neuron survival, with reductions linked to symptoms such as memory loss, decreased attention, cognitive impairment, and behavioural changes. These neurons mainly originate in the locus coeruleus (LC) of the brainstem (Leslie et al., 1985). Loss of norepinephrine promotes amyloid-beta plaque formation and tau tangles by diminishing neuroprotective and anti-inflammatory signalling. Deterioration of the locus coeruleus leads to non-motor symptoms like depression, anxiety, sleep disturbances, and cognitive decline. The consequent decline in norepinephrine phases contributes to reduced attention, working memory, sleep-wake disturbances, increased neuroinflammation, and altered stress response via the hypothalamic-pituitary-adrenal axis (Berridge et al., 1993).

The cerebral GABAergic system uses GABA as its main neurotransmitter. GABA is synthesised in presynaptic neurons from glutamate by the enzyme glutamic acid decarboxylase (GAD), which exists in two isoforms: GAD65 and GAD67. Once produced, GABA is stored in synaptic vesicles via the vesicular

GABA transporter (VGAT) and released into the synaptic cleft in response to an action potential (Wu and Sun, 2014). Dysfunction within the GABAergic system is involved in numerous neurodegenerative diseases. Neural hyperexcitability, which accelerates cognitive decline, results from decreased GABA receptor function and impaired synaptic plasticity (Aiharbi et al., 2024). The machinery of neurotransmission dysregulation includes blockade of voltage-gated sodium channels, development of GABAergic inhibition, inhibition of the mTOR pathway, blockade of T-type calcium channels, and voltage-gated calcium channels, along with oxidative stress, metabolic dysfunction, epigenetic modulation, neuroinflammation suppression, and mitochondrial dysfunction (Yelamanchi et al., 2015). Neurotransmitters significantly influence mood, memory, movement, and cognition. Even slight disturbances in their secretion, regulation, or function can promote neurodegeneration and cognitive decline (Ningampalle et al., 2023). Physical impairments in Parkinson's and Alzheimer's diseases include resting tremors, muscle stiffness, postural instability, bradykinesia, incontinence, increased risk of infection, shuffling gait, masked facial expressions, and difficulties with speech and swallowing. These physical issues tend to worsen with disease progression (Zhao et al., 2024).

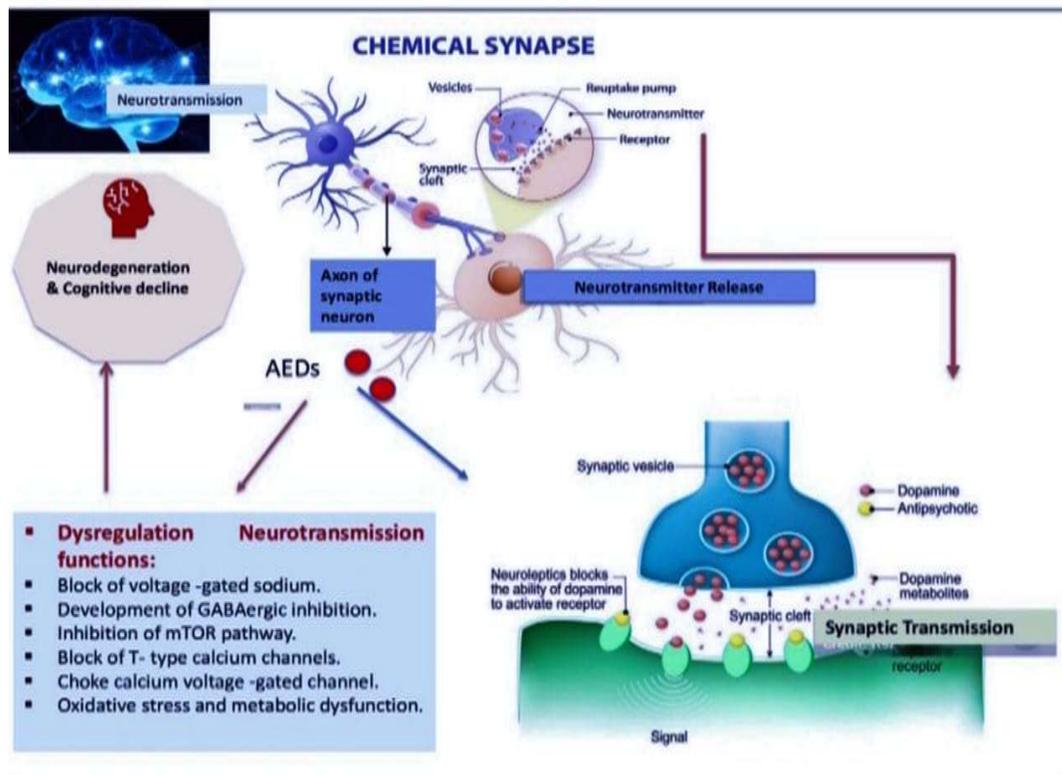


Figure 3. Neurotransmitter disruption is a key contributor to cognitive deterioration.

### Clinical implications and therapeutic considerations

Participating polyphenols in dietetic references or supplements may be a key strategy for slowing or preventing neurodegenerative disorders, regulating neurotransmitters properly, encouraging healthier ageing, and improving quality of life. Upcoming research directions include recognising polyphenols, identifying molecular targets, and enhancing their bioavailability, as well as elucidating their role in gut-brain pathways. Polyphenols may offer a new approach to treating neurodegenerative diseases, with potential for future medical advancements. (Rivai and Umar 2023), Numerous complexes exert modulatory effects on the neurotransmitter system to prevent the onset of neurodegeneration, slow disease progression, and improve mental function. One of the key advantages of polyphenols and other bioactive compounds is their ability to target multiple pathogenic processes simultaneously, which is especially valuable in treating multifactorial disorders. Furthermore, many of these compounds influence the gut-brain axis, suggesting a potential link between dietary habits, gut microbiota composition, and

neurodegeneration. However, despite the strong evidence from in vitro and animal studies, translating polyphenols and bioactive compounds into clinical use remains a significant challenge (Batra et al., 2022). Additionally, standardised extraction, purification, and quantification procedures are essential to ensure consistent and reproducible results in clinical applications. There is also growing interest in exploring synergistic effects between different polyphenols and with conventional therapeutics. Moreover, incorporating omics techniques and computational methods can further reveal molecular targets and optimise the pharmacokinetics of these compounds. Their antioxidant, anti-inflammatory, neurogenic, and signalling-modulating properties provide a comprehensive neuroprotective shield. Although the path from research to clinical practice is complex and requires extensive translational work, the current evidence strongly supports integrating natural compounds into protective and therapeutic strategies. Continuous interdisciplinary efforts in phytochemistry, neuroscience, pharmacology, and biotechnology will be crucial to unlocking the full potential of these compounds and ultimately enhancing brain health and cognitive function across populations (Goyal et al., 2022).

S. No.	Neurotransmitter	Physiological role	Clinical implication of dysregulation	Clinical considerations
1.	Acetylcholine	Learning, memory, and neuromuscular transmission	AD, cognitive decline.	Modified cholinergic side effects.
2.	Dopamine	Motor control, reward, motivation	PD.	Long-term use causes dyskinesia and receptor desensitisation.
3.	Serotonin (5-HT)	Mood, sleep, appetite, cognition.	Depression, anxiety, migraine.	Delayed onset of action; sexual dysfunction, serotonin syndrome
4.	Gamma-aminobutyric acid (GABA)	Major inhibitory neurotransmission	Epilepsy, anxiety, and insomnia.	Tolerance, dependence, cognitive impairment
5.	Glutamate	Excitatory neurotransmission, synaptic plasticity	AD, ALS.	Risk of cognitive suppression
6.	Norepinephrine	Attention, stress response, arousal	Depression, ADHD.	Cardiovascular side effects: anxiety
7.	Histamine	Wakefulness, appetite regulation	Sleep disorders, allergic reaction.	Sedation, weight gain
8.	Glycine.	Inhibitory neurotransmission (spinal cord).	Neurodevelopmental disorders.	Limited CNS penetration.

**Table 1.** Neurotransmitter functions, clinical impacts, and therapeutic approaches.

### Diagnostic Tools and Biomarkers for Neurodegenerative Disorders

Neurodegeneration, characterised by innovative neuronal impairment and dysfunction, causes several neurological disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). The incidence of these conditions is rising, mainly due to the increasing number of ageing populations. Investigating NDs in their early stages offers the greatest chance for effective medical intervention (Gómez et al., 2016). Detecting NDs as early as possible can help slow or even halt disease progression, creating a critical window for intervention (Anderson et al., 2017). The term 'biomarker' encompasses a range of molecules, from small to large, including nucleic acids, proteins, and metabolites, which can be identified using advanced technologies similar to genomics and proteomics. MiRNAs show latent potential as biomarkers for detecting NDs (Laterza et al., 2007). Several researchers have also explored phytochemicals that are highly effective in treating neurodegenerative diseases. Phytochemicals modulate key disease-associated biomarkers related to oxidative stress,

neuroinflammation, protein aggregation, and neuronal survival. Neuroactive compounds such as kaempferol, quercetin, resveratrol, and seabuckthorn activate the Nrf2/ARE pathway, boosting antioxidant defences while reducing ROS and lipid peroxidation markers like MDA. Anti-inflammatory phytochemicals suppress NF- $\kappa$ B signalling, thereby decreasing the levels of pro-inflammatory cytokines. Many phytochemicals notably inhibit pathological protein aggregation by reducing amyloid-beta deposition, tau hyperphosphorylation, and alpha-synuclein accumulation. Collectively, these effects enhance neuronal survival by reducing apoptotic markers, evidenced by decreased caspase-3/9 activity and a favourable Bax/Bcl-2 ratio (Araujo et al., 2021).

S. No.	Diagnostic tools	Biomarkers	Disorders.
1.	MRI, PET, CSF analysis, and neuropsychological.	CSF alfabeta42, phosphor-tau.	Alzheimer's disease (AD).
2.	DAT-SPECT, MRI, olfactory testing.	CSF alpha-synuclein.	Parkinson's disease (PD).
3.	Genetic testing, MRI, and cognitive testing.	Mutant huntingtin protein.	Huntington's disease (HD).
4.	MRI, CSF oligoclonal band.	Oligoclonal IgG bands.	Multiple sclerosis (MS)
5.	EMG, MRI.	CSF\Plasma NfL, TDP-43.	Amyotrophic lateral sclerosis (ALS).

**Table 2. Diagnostic tools, biomarkers, and diseases associated with neurodegenerative disorders.**

### Gap and Future Development Directions for Research

Neurodegeneration is a chronic neurological disorder characterised by recurrent seizures, which are commonly treated with antiepileptic drugs (AEDs). Future research in NDs focuses on understanding how the dopaminergic, cholinergic, and glutamatergic systems interact across different stages of diseases like Parkinson's and Alzheimer's. It also aims to explore future remedies for neuroprotection, enzyme pathway-based drug discovery, stem cell therapy, regenerative medicine, neuroimmune modulation, biomarker discovery (multi-target and early-stage interventions), advancements in neuroimaging, and combination therapies to reduce risks of NDs (Hermans et al, 2025). Future drugs will target specific neurotransmitter receptors or receptor subtypes, reducing side effects and increasing efficacy. Understanding these interactions provides a critical opportunity to develop safer therapies with neuroprotective and cognition-preserving profiles. The future of AED research lies in precisely mapping neurotransmitter disruptions associated with each AED class. Modern technologies such as liquid chromatography-mass spectrometry (LC-MS), magnetic resonance spectroscopy (MRS), and PET imaging can give quantitative insights into neurotransmitter levels in specific brain regions (Song et al, 2025). Nevertheless, future research holds great promise through multi-dimensional strategies that integrate molecular, neurochemical, and behavioural neuroscience. Exploring these interactions offers a vital opportunity to design safer therapeutics with neuroprotective and cognition-sparing effects (Gao et al, 2025).

### Conclusion

Antiepileptics affect by modifying the excitatory and inhibitory constancy in the brain, mainly by communicating with the most important neurotransmitter systems, such as the gamma-aminobutyric acid (GABA) system, glutamate, acetylcholine, dopamine, serotonin, and norepinephrine. Although aiming these systems is essential to regulate hyperexcitability, non-selective and chronic changes of these neurotransmitters can damage synaptic homeostasis and neuroplasticity, both of which are crucial for knowledge and memory. However, excessive GABAergic stimulation might impair enduring potentiation, a cellular correlate of learning and memory, mainly in the hippocampus. Furthermore, chronic GABAergic improvement can result in sedation, attentional deficits, and psychomotor slowing, which cumulatively contribute to mental decline. The intellectual side effects associated with these AEDs often present as

word-finding difficulty, working memory impairment, and condensed verbal fluency. Despite these challenges, it is significant to note that mental outcomes are not uniform transversely all patients or AEDs. Factors such as drug type, dosage, period of treatment, patient age, comorbidities, polypharmacy, genetic predispositions, and even the type of neurodegeneration impact the grade of cognitive impairment. In summary, the connection between antiepileptic drug therapy, neurotransmitter disruption, and cognitive deterioration is a complex yet critically important area of research. Although AEDs remain essential for seizure control, their impact on brain chemistry and cognition must not be overlooked. Nonstop research into the mechanisms of neurotransmitter disruption, coupled with scientific innovations and patient-centred care strategies, will be vital for developing safe, effective, and neuroprotective treatment options for people with neurodegeneration. The future of neurodegeneration management should aim not only at seizure freedom but also at preserving and enhancing cognitive health, recognising that mental well-being is fundamental to overall quality of life.

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