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Emerging Advances in Neuropharmacology: Novel Therapeutic Targets for Neurodegenerative Disorders

[1]Sumairah Qadir, [1]Nisha*

[1] *Department of Pharmacology, School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Punjab, India.*

Keywords

Neuropharmacology, Neurodegenerative disorders, Alzheimer's disease, Parkinson's disease, Neuroinflammation, Protein misfolding, Disease-modifying therapies.

Abstract

Neurodegenerative diseases are a heterogeneous group of chronic and progressive disorders, which are characterized by selective neuronal destruction, synaptic malfunction and progressive cognitive and locomotor dysfunction. The major ones are Alzheimer disease, Parkinson disease, Huntington disease, and amyotrophic lateral sclerosis which are a formidable and growing global health and socio-economic burden mainly due to demographic aging. Even despite the advances in the symptomatic treatment, predominantly through the cholinergic, dopaminergic, glutamatergic, and GABAergic system, the current treatment regimens are not able to stop the underlying neurodegenerative events or reverse them. There is mounting evidence that convergent pathogenic mechanisms, such as protein misfolding and aggregation, oxidative stress, mitochondrial dysfunction, impaired autophagy-lysosomal pathways, synaptic dysfunction, and chronic neuroinflammation, are convergent mechanisms. These convergent molecular and cellular cascades provide a strong rationale behind the identification of new neuropharmacological targets, which include: kinases, phosphatases, epigenetic regulators, neurotrophic signalling pathways and neuroimmune mediators. Advances in the biomarker discovery, genomics and systems biology have further enabled the use of precision based therapeutic stratification and early-intervention approaches. Genetic, nanotechnology, and RNA-based therapeutics as well as biologics are reconfiguring translational models in neurodegeneration. A mechanism-based, multi-target, precision neuropharmacological approach, as a group, has significant potential in achieving long-term neuroprotection, improved clinical and disease modification in neurodegenerative diseases.

***Corresponding Author:**
Ms. Nisha (sharmanishii8@gmail.com)

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1. Introduction

1.1 Neurodegenerative Disorders: Scope and Clinical Impact

The neurodegenerative disorders are a heterogeneous continuum of chronic, progressive pathological entities, which are seen to be the result of gradual and selective neuronal loss in the central and peripheral nervous systems. Significant and growing health burden on the world population is manifested by major entities, including Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, and multiple sclerosis [1]. The problem of these disorders is increasing steadily, which is, in large part, due to the changes of the demographic structure towards the aging population, and is linked to an increase in morbidity, mortality, and long-term disability on a global scale [2]. Neurodegeneration is clinically expressed in form of progressive cognitive deterioration, motor dysfunction, sensory disturbances and behavioural aberrations with the end result of loss of functional independence and worsening of the overall quality of life [3].

In addition to their clinically manifested conditions, neurodegenerative disorders cause a significant socioeconomic cost to the patients, their caregivers,

and health care systems. The long-term care needs, reduced productivity and increased spending on health care have a significant effect [4]. Although the clinical phenotype of many neurodegenerative diseases is highly heterogeneous, they all overlap on common pathogenic pathways, such as protein misfolding and aggregation, mitochondrial impairment, oxidative stress, synaptic impairment and chronic Neuroinflammation [5]. The heterogeneous, multifactorial etiologies of these disorders make it difficult to identify them early and elicit the creation of effective interventions, which further highlights the need to better understand the mechanisms of the disease and to develop more effective disease-modifying therapeutic interventions [6].

1.2 Current Therapeutic Landscape and Unmet Needs

The present paradigms of treatment in neurodegenerative diseases are mostly focused on the amelioration of the symptoms and not on the cure of the diseases. Pharmacological treatments such as cholinesterase inhibitors and NMDA receptor antagonists of Alzheimer disease or dopaminergic treatments of Parkinson disease are approved and provide temporary relief of cognitive or motor impairments but do not prevent the progressive loss of neurons [7]. Such therapies have relatively low clinical efficacies, which reduce with continued use and are regularly limited by side effects that reduce patient compliance. Although considerable research efforts have been made, the translation of promising preclinical candidates into effective clinical interventions has not been fulfilled with many agents not showing improvement in their advanced-phase trials [8]. Thus, there is a strong unsatisfied need of therapeutics that would act on early and central pathogenic mechanisms, demonstrated sustained effectiveness, and enhanced clinical outcome in the long run. The need to deal with heterogeneity of diseases using biomarker-directed and precision medicine approaches is also essential to add to disease therapeutic response, as well as to improve patient care [9].

1.3 Rationale for Novel Neuropharmacological Targets

The ineffective nature of current treatment of neurodegenerative disorders underscores the imperative need to identify and confirm new neuropharmacological targets which resonate with fundamental disease pathology [10]. It has been demonstrated that neurodegeneration has a multicomponent etiology near protein misfolding, autophagy dysregulation, mitochondrial impairment, synaptic loss, and sustained neuroinflammation through recent advances in molecular biology and systems neuroscience. Such intervention in these pathways has the potential to alter the course of the disease and not just to diminish the symptoms [11]. The involvement of non-neuronal cell types, such as microglia and astrocytes is also becoming increasingly engaged, thus, showing other potential therapeutic points of interest that are not limited to the conventional neuron-focused paradigms [12]. Besides, the combination of genomics, proteomics, and biomarker discovery has made the identification of targets and stratification of patients more precise. Taken together, these developments justify a paradigm shift of going towards mechanism-based, multi-target, precision neuropharmacological approaches that will result in sustained neuroprotection and improvements in clinical outcomes [13].

2. Fundamentals of Neuropharmacology in Neurodegeneration

Neuropharmacology in the area of neurodegeneration aims to explain how the pharmacological agonists may interact with neurons and non-neurons to change the progression of disease and clinical presentation [14]. This research brings together a perception of neurotransmitter networks, receptor-based signalling pathways, intracellular mechanisms, and neuroimmune processes that when combined together, affect neuronal survival and disease [15]. In neurodegenerative pathologies the therapeutic interventions will be aimed to restore the synaptic homeostasis, mitigate the neurotoxic processes, and protect the vulnerable neural circuitry[16]. The understanding of the efficacy and safety of neurotherapeutic agents cannot be achieved without a comprehensive understanding of the permeability of the blood-brain barrier, target specificity, and pharmacodynamic correlates of pharmacokinetics [17].

2.1 Neurotransmission and Synaptic Homeostasis

Neurotransmission is a highly controlled biophysical process through which intercellular communication occurs within the brain through controlled release, uptake, and deactivation of chemical/electrical signals at the synaptic junction. It is based on high fidelity excitatory and inhibitory transmitter activity, fine-tuning of the receptor dynamics, and the efficacy of vesicular transport processes all of which are essential towards optimal synaptic performance [18]. In neurodegenerative pathophysiology, alterations in neurotransmitter biosynthesis, vesicular exocytosis, or receptor-mediated signalling result in impaired synaptic plasticity and dysfunctioning of a network of

neurons in general [19]. The changes in glutamatergic, cholinergic, dopaminergic, and GABAergic pathways can often appear, and these alterations are used to manifest the development of initial cognitive and motor impairments before the severe loss of neurons [20].

Synaptic homeostasis refers to the collection of processes that maintain a constant neural activity in the wake of chronic physiological and pathological challenges. Such mechanisms include scaling of activity dependent synapses, receptor trafficking and reactions to intracellular signalling pathways [21]. Neurodegenerative disease is associated with dysfunction of synaptic homeostasis that induces excitotoxicity, abnormal synaptic pruning, and disequilibrium of the circuit. Based on this, the maintenance of synaptic health and the restoration of neurotransmission balance in the brain have become the primary goals of neuropharmacology, meant to slow the progression of the disease and improve functional performance [22].

2.2 Blood–Brain Barrier and CNS Drug Delivery

The blood-brain barrier (BBB) is one of the most exquisitely specialized, selectively permeable boundaries, which maintains homeostasis of the central nervous system (CNS) by strictly controlling the exclusion of solutes between the systemic circulation and the neuro-parenchymal area [23]. The physical wall is established structurally through endothelial cells connected to each other by tight junctions, and astrocytic end- feet and pericytes, and that as a unit, act to limit the entry of potentially harmful substances. This protective architecture, therefore, constitutes a serious impediment to neuropharmacological intervention with many therapeutic agents exhibiting,either low lipid solubility, high molecular weight or serving as substrates of active efflux transporters [24].The therapeutic delivery of therapeutics to the central nervous system requires the successful methods to overcome or take advantage of the properties of the blood brain barrier (BBB) and maintain its structure [25]. There are strategies that encompass chemical modification of pharmacologic agents, exploitation of carrier-mediated transport systems, nanoparticle-based delivery systems, and receptor-mediated transcytosis, which may increase cerebral drug bioavailability[26]. However, the issue of optimization of BBB permeability without losing the safety aspect is a critical aspect in the design of effective therapeutic agents against neurodegenerative pathologies [27].

2.3 Challenges in Target Identification and Validation

The pathology of neurodegenerative diseases is multifactorial and heterogeneous, which hinders the identification of targets. Protein aggregation, neuroinflammation, mitochondrial dysfunction, and synaptic failure are concomitant molecular pathways that occur in parallel and therefore promote the progression of disease [28]. Distinguishing between primary causal drivers and secondary or compensatory changes has been daunting especially when taking into account the dynamic changes in pathology of different disease stages [29]. Furthermore, the restrictions associated with model experimental procedures do not often entirely simulate human pathological neurodegenerative states, thus reducing the translational value of preclinical research [30].

Target validation presents further complications, as the modulation of a single molecular target does not usually induce clinical relevant benefit. Indirect toxicity (off-target effect), pathway and species orthogony can compromise the safety and efficacy of therapy [31]. In addition, the lack of reliable biomarkers to detect target engagement and predict clinical outcomes is also a hindrance to effective translational progression. In that regard, effective validation systems, which involve human-relevant models, longitudinal biomarker profiling, and system analyses are essential to successful neuropharmacological target development [32].

3. Molecular and Cellular Mechanisms of Neurodegeneration

A combination of molecular and cellular processes supporting neurodegeneration perturbs neuronal structure and functions[33]. The most important pathophysiological processes include protein misfolding, aggregation, mitochondrial impairments, oxidative stress, impaired autophagic flux, and calcium homeostasis [34]. These disease-inducing cascades result in dysfunction of synaptic functions, neuroinflammatory cascades and eventual cell death. The communication between neurons, the populations of glial cells, and the signalling through immune mediators further increases the damage of cells and the tissue loss [35]. The rational design of therapeutic interventions that may be used to reduce disease trajectory in neurodegenerative disorders is indispensable without a comprehensive understanding of these interrelated mechanisms [36].

3.1 Protein Misfolding and Aggregation

Protein misfolding and aggregation are important pathological mechanisms of various neurodegenerative diseases such as Alzheimer

disease, Parkinson disease, Huntington disease, and amyotrophic lateral sclerosis [37]. Protein degradation can be maintained by closely regulated mechanisms of molecular chaperones, ubiquitin usually proteasome system and autophagy lysosome in physiological conditions. When these quality control mechanisms are perturbed, the misfolded proteins accumulate and form aberrant conformation and oligomers that form toxic aggregates and insoluble inclusions [38]. These aggregates include amyloid- 2 plaques, tau neurofibrillary tangles, and alpha-synuclein Lewy bodies, and mutant huntingtin inclusions, which impair the normal functioning and synaptic signalling of cells [39].

Recent data are increasingly pointing to soluble oligomeric assemblies having a strong neurotoxic effect through destabilization of membrane integrity, calcium homeostasis, and control of intracellular signalling cascades [40]. Protein aggregates also overwhelm proteolytic pathways, cause oxidative stress, and cause persistent neuroinflammatory reactions through microglial and astrocytic stimulation [41]. Moreover, misfolded proteins are prone to spread in a prion-like manner spreading pathology across the interconnected neural systems. Together, these mechanisms contribute to the progressive neuronal impairment and death, hence supporting the protein misfolding and aggregation to be the key targets of disease-modifying neuropharmacological interventions [42].

3.2 Oxidative Stress and Mitochondrial Dysfunction

The two processes oxidative stress and mitochondrial dysfunction are interdependent processes that play a central role in the pathogenesis of neurodegenerative disorders. Neurons are overly vulnerable to oxidative damage, which can be explained by the high rate of their metabolic activity and limited antioxidant protection [43]. Excessive production of reactive oxygen and nitrogen species induces lipid peroxidation, protein oxidation, and damage of the genome and thus reduces cellular integrity and functional ability of the synapses. The oxidative impairments promote the early neuronal dysfunction and increase cell susceptibility to subsequent degenerative processes [44].

The mitochondrial dysfunction also increases oxidative stress by interfering with ATP production, calcium homeostasis, and apoptotic levels of signalling. Damage in the electron transport chain increases the formation of the free radicals, which propagates a vicious circle of energetic failure and oxidative tissue damage [45]. Additionally, an unchecked aberrant mitochondrial dynamics and mitophagic malformations result in the survival of non-functional organelles. In turn, the synergistic effect of oxidative stress and mitochondrial damage accelerates the process of neuronal degeneration, which explains the urgent need to implement interventions that will preserve mitochondrial integrity and preserve redox homeostasis in neuropharmacological systems [46].

3.3 Neuroinflammation and Glial Dysregulation

Neuroinflammation is a highly noticeable and persistent phenotype of neurodegenerative diseases, which have their origins in the dysregulated stimulation of glial cells, in particular, microglia and astrocytes. In the physiological state, glial cells play fundamental roles in immune survey, synaptic aid and neuronal homeostasis preservation [47]. However, chronic microglial activation in pathological conditions leads to excessive release of pro-inflammatory cytokines, chemokines, and reactive oxygen species, and therefore synaptic dysfunction and neuronal injury. Astrocytic dysfunction also contributes to the disease progression by reducing metabolic support, neurotransmitter clearance as well as the integrity of the blood-brain barrier [48]. Continued disproportion of glial cells facilitates a poisonous inflammatory atmosphere which enhances neuronal harm and accelerates disease. In addition to causing direct neurotoxicity neuroinflammation impairs synaptic plasticity and promotes aberrant assemblage of proteins [49]. Recent studies indicate that neuroinflammatory processes could produce neuroprotection in the early stages but then lead to maladaptive changes on a long-term basis [50]. Based on this, glial activation attenuation and neuroimmune balance recovery will form a novel therapeutic paradigm to accelerate neurodegeneration and improve clinical outcomes [51].

3.4 Synaptic Dysfunction and Neuronal Loss

Synaptic dysfunction is a primary and focal phenomenon in the pathogenesis of neurodegenerative diseases, and in many cases, precedes the loss of neurons. Changes in the integrity of synapses and dysregulation of neurotransmitter release together with defects in receptor signalling disrupt neural network connectivity and impair synaptic plasticity, which are also involved in the occurrence of cognitive and motor impairments [52]. The pathogenic factors such as misfolded protein oligomers, oxidative stress, and neuroinflammatory mediators directly hinder the process of synaptic transmission and enhance excitotoxicity. Synapses are especially vulnerable to these damaging attacks

given the high dynamism and metabolic activity of the synapse [53].

both apoptotic and necrotic processes. The degeneration of neurons is catalyzed as the neurons lose their synaptic input, which provides them with the necessary trophic support. Death of neurons, in its turn, induces even greater destabilization of neural networks and deterioration of functionality. As the synaptic loss is strongly correlated with the severity of the disease, the maintenance of synaptic integrity and inhibition of neuronal death are key points in the progress of disease-modifying treatments of neurodegenerative diseases [54].

The gradual loss of the synaptic integrity eventually leads to the permanent loss of neurons by activating

Table 1 summarizes the major molecular and cellular mechanisms underlying neurodegenerative disorders. It highlights key pathogenic events, including protein aggregation, oxidative stress, mitochondrial dysfunction, neuroinflammation, impaired proteostasis, and metabolic dysregulation, together with their pathological consequences and associated diseases. These interconnected pathways collectively drive progressive neuronal dysfunction, degeneration, and clinical disease progression [55].

Table 1: Major molecular and cellular mechanisms implicated in neurodegenerative disorders.

Sr. No.	Mechanism	Representative Molecular Events	Pathological Consequences	Associated Disorders	References
1.	Protein misfolding and aggregation	Aβ, tau, α-synuclein, huntingtin aggregation	Synaptic toxicity, neuronal death	AD, PD, HD	[37]
2	Oxidative stress	Excess ROS/RNS production	Lipid, protein, DNA damage	AD, PD, ALS	[56]
3.	Mitochondrial dysfunction	ETC impairment, ATP depletion	Energy failure, apoptosis	PD, AD, ALS	[57]
4.	Neuroinflammation	Chronic microglial/astrocytic activation	Cytokine-mediated neurotoxicity	AD, MS	[58]
5.	Autophagy–lysosomal dysfunction	Impaired protein/organelle clearance	Aggregate accumulation	AD, PD	[59]
6.	Excitotoxicity	Excess glutamate, Ca^{2+} influx	Neuronal injury	ALS, HD	[60]
7.	Axonal transport defects	Microtubule and motor protein disruption	Synaptic degeneration	AD, ALS	[61]
8.	Neurotrophic factor deficiency	Reduced BDNF/NGF signalling	Loss of neuronal survival	AD, PD	[62]
9.	Proteasome dysfunction	Impaired ubiquitin–proteasome system	Toxic protein buildup	PD, AD	[63]
10	RNA metabolism defects	Abnormal RNA splicing/transport	Impaired protein synthesis	ALS, FTD	[64]
11.	Epigenetic alterations	DNA methylation, histone modification	Aberrant gene expression	AD, HD	[65]
12.	Insulin signalling impairment	Brain insulin resistance	Synaptic failure	AD	[66]
13.	Lipid metabolism dysregulation	Cholesterol, sphingolipid imbalance	Membrane instability	AD	[67]
14.	Prion-like propagation	Cell-to-cell protein spread	Disease progression	AD, PD	[68]
15.	Neurovascular unit dysfunction	Impaired cerebral perfusion	Neuronal stress	AD, VaD	[69]

Figure 1 illustrates the interconnected pathogenic mechanisms underlying neurodegenerative disorders. Amyloid and tau aggregation, oxidative stress, mitochondrial dysfunction, neuroinflammation, synaptic impairment, and genomic instability collectively disrupt neuronal homeostasis. These processes interact through multiple feedback loops, ultimately promoting neuronal dysfunction, progressive neurodegeneration, and the clinical manifestations of disorders such as Alzheimer's and Parkinson's diseases [70].

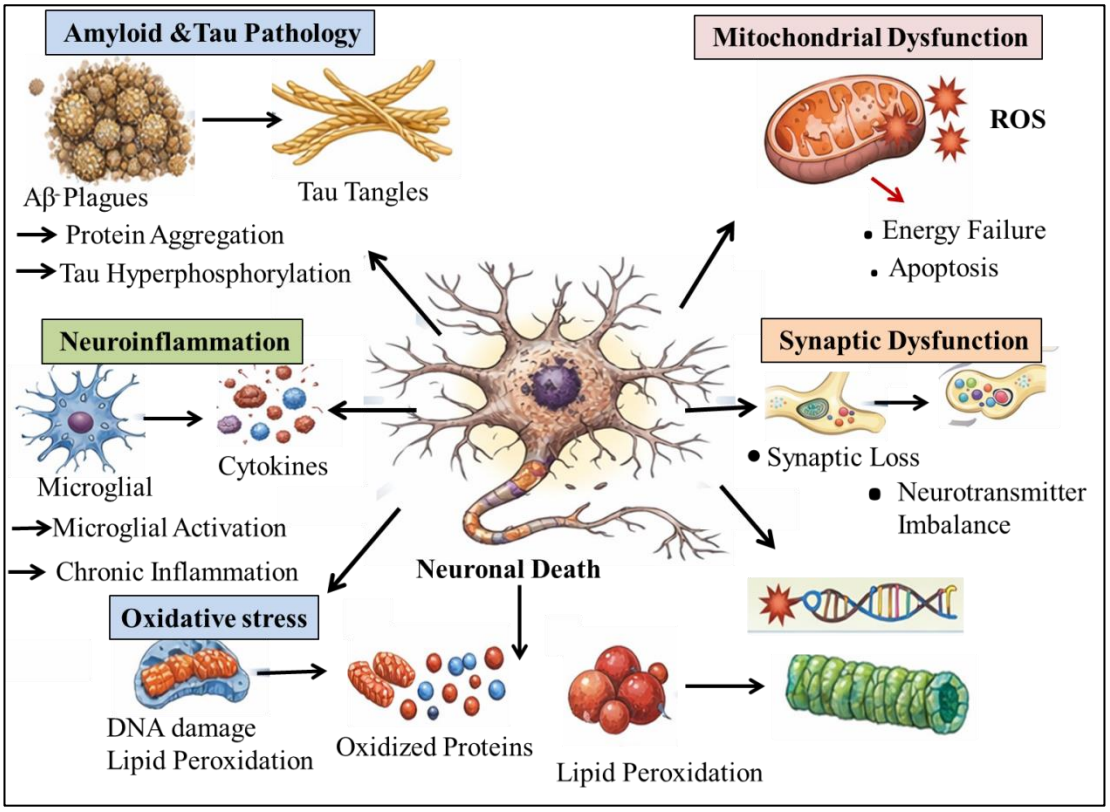

Figure 1: Integrated molecular pathways contributing to neurodegeneration. Schematic representation of the interconnected molecular mechanisms underlying neurodegeneration, highlighting amyloid and tau pathology, mitochondrial dysfunction, oxidative stress, neuroinflammation, and synaptic impairment, which collectively contribute to progressive neuronal dysfunction and eventual neuronal death.

4. Emerging Molecular Targets for Neuropharmacological Intervention

4.1 Kinases, Phosphatases, and Signalling Pathways

Activation and inhibition of diverse intracellular signalling pathways implicated in regulating neuronal survival, synaptic plasticity and cellular homeostasis are controlled by kinases and phosphatases. These enzymes produce control over key cell processes, such as gene transcription, cytoskeleton, and regulation of the neurotransmitter receptor activity through the regulation of protein phosphorylation status. Disturbance of the kinasephosphatase balance is also a typical feature of neurodegenerative diseases and enables the survival of pathological signalling pathways [71].

Pathological phosphorylation of proteins, synaptic dysfunction, and neuronal death have been linked to aberrant activation of such kinases as glycogen synthase kinase -3b, cyclin-dependent kinase -5, mitogen-activated protein kinases, and the mammalian target of rapamycin. On the other hand, reduced phosphatase activity, especially protein phosphatase-2A activity leads to the prolongation of hyperphosphorylation of disease-related proteins including tau hence speeding up neurodegenerative mechanisms [72].

Nevertheless, it is a logical approach to neuropharmacological treatment to target the signal pathways that are regulated by kinases and phosphatases. Specific modulation of these enzymes would be able to recapitulate signalling homeostasis, reduce aberrant protein changes and enhance neuronal resistance. This has prompted the active research of kinase- and phosphatase-based therapeutic interventions as disease-modifying in neurodegenerative diseases [71].

4.2 Epigenetic and Transcriptional Regulators

The regulators of epigenetics and transcription have a central role in the regulation of gene expression programs which are critically important to the neurons and their plasticity and survival. Genetic alterations in DNA methylation, histone post-conveyance, mitochondrial biogenesis, and stress reaction pathways [73]. Together with epigenetic enzymes, e.g., histone deacetylases, DNA methyltransferases, and non-coding RNAs, transcription factors promote the progression of the disease by promoting maladaptive cell phenotypes. These regulators can be targeted to provide a therapeutic approach that allows reversible regulation of the expression of genes without altering the underlying genomic sequence [74]. As a result thereof, the epigenetic-based interventions can be considered as the promising pathways to restoring neuronal homeostasis as well as to the formation of disease-modifying neuropharmacological therapeutic options [75].

4.3 Autophagy-Lysosomal and Proteostasis Targets

The autophagy-lysosomal pathway is a cellular pathway of the paramount which maintains proteostasis through systematic breakdown and re-utilisation of misplaced proteins and defective organelles [76]. Disruption of this process is a characteristic of a continuum of neurodegenerative diseases, and the ultimate outcome is the accumulation of harmful proteinaceous aggregates and cellular distress [77]. Key molecular constituents which are identified in this framework include autophagy-related proteins, lysosomal hydrolases and orchestral controllers of vesicular trafficking and membrane fusion. Proteins also have an extra attenuation of proteasomes, which further enhances proteostatic breakdown, increasing the vulnerability of neurons[78]. Pharmacological correction of autophagy and lysosomal events is suggested to be an interesting approach to increase intracellular clearance, restore proteomic balance, and mitigate neurodegenerative consequences, which contributes to strengthening the potential of disease-modifying neurotherapy systems[79].

4.4 Neurotrophic Factors and Survival Pathways

Neurotrophic factors are also vital controllers of neuronal development, maintenance, and translational alterations, and chromatin remodelling processes have steadily been linked with neurodegenerative illnesses leading to the erratic expression of genes that regulate synaptic

survivability whose actions are mediated through receptor-mediated signalling pathways. Signalling cascades of compounds such as brain-derived neurotrophic factor, nerve growth factors as well as glial cell lineage-derived neurotrophic factor form the basis of synaptic plasticity, axonal integrity, and cellular resistance to stress [80]. The impaired functioning of the nervous system in neurodegenerative pathologies is caused by the reduced availability or altered signalling of these factors.Neurotrophic receptors signal transduction cascades downstream, such as phosphoinositide 3 - kinase/ Akt and mitogen activated protein kinase, have been shown to be required in promoting neuronal resilience and preventing cell death by apoptosis [81]. Interventions aimed to boost neurotrophic signalling, such as direct administration of neurotrophic factors or pharmacological regulation of downstream pathways, are fairly promising in terms of slowing down disease pathogenesis and being able to maintain neural activity [82].

Figure 2 depicts the complex interplay of molecular mechanisms underlying neurodegeneration. The accumulation of misfolded and aggregated proteins disrupts cellular homeostasis, while mitochondrial dysfunction impairs energy production and increases the generation of reactive oxygen species. Excessive oxidative stress further damages cellular components, including proteins, lipids, and DNA, thereby aggravating neuronal dysfunction. Concurrently, persistent neuroinflammation and dysregulated inflammatory signaling promote microglial and astrocytic activation, contributing to a sustained neurotoxic environment. Synaptic dysfunction and impaired neuronal communication further compromise cognitive and neurological functions. These pathological mechanisms are closely interconnected and can reinforce one another, creating a self-perpetuating cycle of neuronal injury. Collectively, these molecular disturbances accelerate neuronal degeneration, disrupt neuronal homeostasis, and contribute to the initiation and progression of diverse neurodegenerative disorders [83].

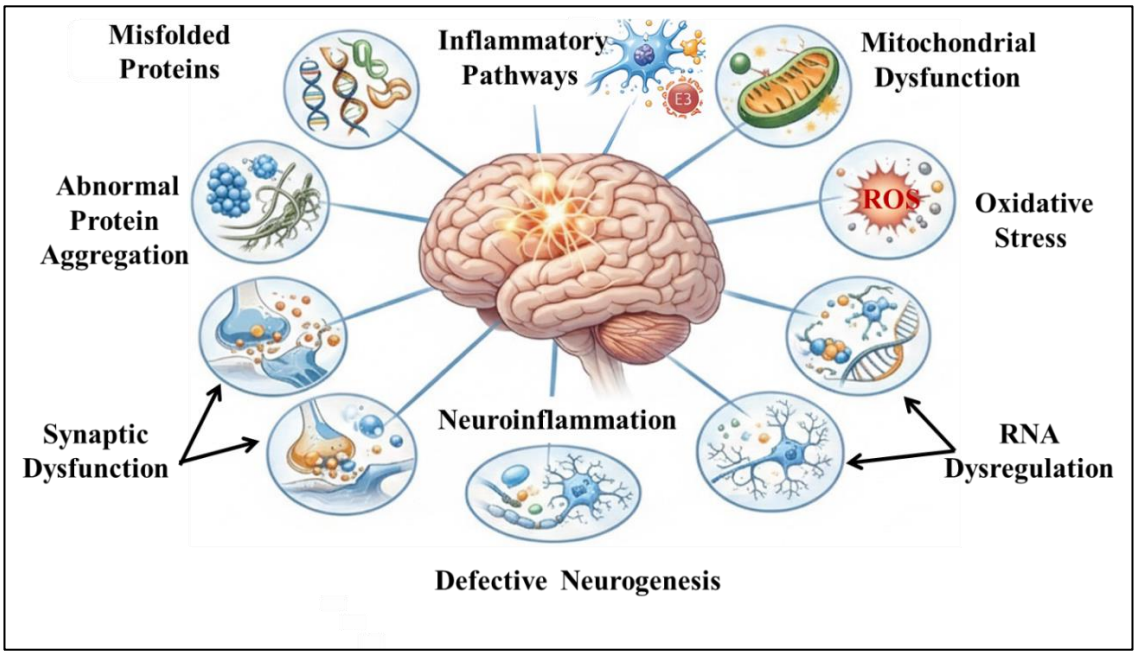

Figure 2: Novel and emerging molecular targets for neurodegenerative disorders**.** Schematic illustration depicting the central role of neuroinflammation in neurodegenerative disorders, highlighting the interplay between misfolded proteins, inflammatory signalling pathways, mitochondrial dysfunction, reactive oxygen species (ROS) generation, and neuronal damage, which collectively contribute to progressive neurodegeneration and impaired brain function.

5. Neurotransmitter- and Receptor-Based Therapeutic Targets

These neurotransmitter- and receptor-based targets focus on the recovery of the disrupted neurodegenerative disorder synaptic signalling. Cholinergic, dopaminergic, glutamatergic and GABAergic receptor modulation have been proven to improve cognitive and motor functioning. Although they mostly treat the symptoms, these objectives are the key elements of the multifaceted neuropharmacologic interventions [84].

5.1 Glutamatergic and GABAergic Systems

The glutamatergic system is the main excitatory pathway of neurotransmission in the central nervous system, and it is necessary in learning, memory, and synaptic plasticity. During neurodegenerative states, disruption of glutamate signalling leads to over-stimulation of the receptors, dysregulation of calcium and excitotoxic death of neurons. Both ionotropic and metabotropic glutamate receptor dysfunctions have been well-supported by synaptic dysfunction and gradual neuronal loss [85].

GABAergic system is the major inhibitory control system that is needed to maintain exciter-inhibitor homeostasis in neural networks. Weakened GABAergic transmission or receptor dysfunction is likely to increase network hyperexcitability and predisposes to excitotoxic damage [86]. The clinical target of glutamatergic and GABAergic therapy aims at finding the balance of synapses, neuronal integrity, and improved functioning in neurodegenerative disease [87].

5.2 Cholinergic and Dopaminergic Modulation

Cholinergic system is a key part of higher cognitive processes, which entail learning, memory, and attentional processes. Salient neuropathological exemplars in a continuum of neurodegenerative conditions, such as the Alzheimer disease, are degenerative alterations in the basal forebrain cholinergic neurons, combined with reduced acetylcholine transmission [88]. Cholinergic receptor-targeting or acetylcholinesterase-inhibiting therapeutic interventions aim to increase the synaptic levels of acetylcholine and, consequently, reduce the cognitive impairment but they do not have a disease-modifying effect [89].

Dopaminergic modulation is one of the critical components of the therapeutic treatment of movement related neurodegenerative disorders, and especially Parkinson disease. Degeneration of the nigrostriatal dopaminergic neurons is linked to severe motor impairment and dysfunction of basal ganglia circuitry [90]. Both strategies to restore dopamine levels or to normalize dopamine receptor function has been proved to reduce motor impairments, and partially restore neural network integrity, thus supporting their continued applicability in the field of neuropharmacological therapies [91].

5.3 Serotonergic and Noradrenergic Targets

Serotonergic system coordinates affective states, cognition, sleep architecture, and neuroplasticity and

its malfunction is progressively reported in neurodegenerative pathologies. The neuropsychiatric phenotypes such as depressive syndromes, anxiety disorders and cognitive impairments are caused by aberrant signalling of serotonergic receptors and impaired serotonergic innervation. The pharmacologic stimulation of serotonergic receptors and transporters is a potential cure of non-motor clinical manifestation and, as a result, an increase in the quality of life of affected individuals [92].It has been demonstrated that the noradrenergic system which is mostly derived in locus coeruleus is central in the regulation of attention, arousal, and neuroinflammatory events. Noradrenergic neuron degeneration aggravates cognitive impairments and predisposes an individual to neuroinflammation [93]. Therefore, noradrenergic receptor- and transport-based interventions can have therapeutic utility in stabilizing neuronal circuitry and curbing the effects of inflammation as well as enhancing neuroprotective mechanisms in relation to neurodegenerative disorders [94].

6. Neuroimmune and Inflammatory Targets

6.1 Microglial and Astrocytic Modulation

Microglial and astrocytic activity is another approach to neurodegenerative diseases, as the glial populations that microglia and astrocytes display play a fundamental role in neuroinflammation and neuronal homeostasis [95]. Activated microglia promotes disease progression through secretion of pro-inflammatory cytokines, reactive oxygen species and neurotoxic mediators, and astrocytes through the regulation of synaptic support, metabolic control and blood-brain barrier integrity [96]. The pharmacological approaches aimed at dampening the excitation of chronic glia, or promoting the adoption of anti-inflammatory phenotypes, have the potential to reduce neuronal damage, as well as to restore homeostatic cues [97]. This is because exploiting glia specific receptors, inflammatory processes and intracellular signalling pathways suggest the presence of disease modifying interventions which are more specific and less neurotoxic to the cells thus conforming to a mechanism based therapeutic paradigm [98].

6.2 Cytokines, Chemokines, and Complement Pathways

The cytokines and chemokines as well as the complement pathways are the key mediators of neuroimmune crosstalk with essential roles in the etiology of neurodegenerative conditions. Chronic inflammation is perpetuated by aberrant cytokine signalling and is consequently followed by the induction of synaptic damage and relative neuronal degeneration [99]. The chemokines are also important in controlling the recruitment of immune cells and glial activation in the central nervous system. Recurrent overexpression of chemokines enhances the migration of microglia and perpetuates inflammatory events affecting neurodegenerative pathways and disabling neuronal regeneration processes [100].

In physiological conditions the complement system plays a role in the pruning of synapses and immune surveillance but its binding in an aberrant manner increases the rate of synapse loss and neuronal damage. Targeted intervention of these mechanisms provides a therapeutic approach to the reduction of neuroinflammation and retention of key immune functions [101].

6.3 Immunomodulatory Pharmacological Strategies

Immunomodulatory pharmacological approaches are meant to help regain immune homeostasis in neurodegenerative disorders by selective, specific intervention of inflammatory signalling pathways. These interventions include cytokine inhibitors, microglial-phenotype modulators and complement-cascade regulators in order to reduce chronic neuroinflammation [102]. Immunomodulatory agents can slow down the development of the disease and prevent neuronal damage by balancing the over activation of the immune system but not suppressing the necessary immune reactions that help in the protection of the body [103]. Such mechanisms-based interventions are disease-modifying potential and contribute to improved targeted therapies with improved efficacy and safety profiles in the sphere of neuropharmacological studies [104].

7. Novel Drug Modalities and Advanced Neuropharmacological Strategies

The experimental drug modalities and developed neuropharmacological approaches are transforming the treatment paradigm of the neurodegenerative disorders by improving the specificity of targets and the delivery efficiency [105]. Gene therapy, RNA-based therapeutics, nanocarrier systems, and biologics are just some of the techniques that allow the accurate modulation of disease-relevant signalling cascades, thereby enhancing clinical outcome, and at the same time decreasing off-target effects and systemic toxicity [106].

7.1 Small-Molecule and Biologic Therapeutics

Small-molecule therapeutics remain positioned centrally in terms of neuropharmacology, which is due to their exceptional oral absorption, ability to cross the blood brain barrier and their ability to regulate intracellular targets [107]. These agents are

widely used to regulate enzymatic activity, receptor interactions, ion channel dynamics that are linked to neurodegenerative diseases, to produce symptomatic benefits and, in some cases, have disease-modifying effects. Their selectivity and safety profiles have been further optimized by the application of the rational design principles and the high throughput screening technologies [108].

Monoclonal antibodies, peptides, and recombinant proteins have a high target specificity and long biological activity, which means they can serve as biologic therapeutics. Still, barriers to efficient delivery of the central nervous system persist, but new developments in the engineering of antibodies and development of delivery platforms have expanded the ability of these agents to specifically attack extracellular proteins, as well as neuroinflammatory mediators [109].

7.2 Gene- and RNA-Based Neurotherapies

Neurotherapies based on genes and RNAs represent the new approaches in reducing molecular imbalances underlying neurodegenerative diseases. Gene therapy methods use both viral and non-viral vectors as vectors to deliver functional genes or to regulate the expression of pathogenic genes, which will lead to the establishment of long-term therapeutic reactions [110]. The modalities endow the ability to correct genetic maladaptations and to control the expression of pathogenic pathways in their inception.One therapeutic approach, which involves RNA, is the control of target genes by antisense oligonucleotides, small interfering RNAs, messenger RNA platforms, and small interfering RNAs [111]. The recent advances in technologies of delivery and chemical modification methods have improved their stability, brain-targeting properties and safety profiles, strengthening their growing application in precision neuropharmacology [112].

7.3 Nanotechnology and Targeted Drug Delivery

Nanotechnology, alongside precision drug delivery architectures, has risen to a new hegemony in the context of the mitigation of the limitations that plague conventional neurotherapeutics, most notably the lack of permeability of therapeutics across the blood-brain barrier and the systemic toxicity that remains as a persistent consequence [113]. Within the given paradigm, Nano carriers, such as liposomes, polymeric nanoparticles, dendrimers, and solid lipid nanoparticles, provide control of drug delivery in actively being developed to slow the advancement of the disease. A more modern understanding of non-motor symptomatology and neuroinflammatory time, increase pharmacokinetic stability, and improve cerebral targeting. These carriers can also be functionalized with certain ligands or monoclonal antibodies, further allowing specific translocation across the blood-brain barrier to neuronal or glial cell sub-compartments to improve the level of therapeutic specificity [114]. Also, these Nano platforms allow simultaneous delivery of several pharmacologic agonists, which allow synergistic regulation of pathogenic pathways, which interact. Collectively, the nanotechnology-based delivery platforms provide a strong and potentially radical direction of improving the efficacy and safety of neuropharmacological practice [115].

8. Disease-Specific Targeting Approaches

8.1 Alzheimer's Disease

Alzheimer is a progressive neurodegenerative disease with significant impairment of cognitive ability, synaptic degradation, and massive neuronal dysfunction [116]. Its neuropathology is characterized by extracellular deposition of amyloid -2 plaques, intracellular neurofibrillary tangles of hyperphosphorylated tau and chronic neuroinflammatory responses. The current treatment interventions mainly provide symptomatic treatment by regulating cholinergic deficiencies and blocking glutamatergic excitotoxicity [117]. However, the latest disease-modifying treatments are aimed at reducing amyloid and tau-pathology, controlling microglial activation, and strengthening synaptic functions. The future of disease management is being enabled by the recent advancements in biomarker-based diagnostics and precision pharmacology that provide the opportunity to intervene earlier and develop specific therapies that can slow down the disease progression [118].

8.2 Parkinson's Disease

Parkinson disease is a neurodegenerative movement disorder that is associated with the selective death of dopaminergic neurons in the substantia nigra and intracellular accumulation of alpha 2-synuclein [119]. Existing pharmacotherapeutic paradigms are still largely based on the paradigm of dopamine replacement, with levodopa and dopamine agonists being the main modalities that are used in curbing motor manifestation. New treatment opportunities are directed toward neuroprotection, mitochondrial abnormality, oxidative stress, and pathologic aggregation of α-synuclein [120]. The investigation methods that include immunotherapies, gene-based interventions, and the precision delivery systems are pathways is increasingly defining the development of a more comprehensive and integrative treatment model [121].

8.3 Huntington's Disease

Huntington disease is a neurodegenerative condition that is caused by the expansion of CAG repeats in the huntingtin gene, which causes progressive motor, cognitive, and psychiatric impairments and is an inherited and neurodegenerative condition. Existing treatment methods are mostly symptomatic, and they aim at relieving the chorea and associated behavioural manifestations [122]. Disease-modifying interventions are becoming biased towards the inhibition of mutant huntingtin expression with antisense oligonucleotides, RNA interference and genome-editing technologies. Treating mitochondrial dysfunction, excitotoxicity and neuroinflammation is a promising area of treatment. Evidence of the most current developments in molecular genetics and precision neuropharmacology has significantly expanded the range of targeted intervention in this disorder [123].

8.4 Amyotrophic Lateral Sclerosis and Related Disorders

Amyotrophic lateral sclerosis (ALS) is characterized by selective hypergamy of upper- and lower-motor neurons, to the end that leads to progressive muscular weakness and respiratory failure. Existing licensed pharmacotherapies have only a small benefit in survival, making a significant contribution via prevention of excitotoxicity and oxidative stress. Recent research focuses on immunomodulation, RNA-based therapies and gene-directed therapies as a measure to address sporadic and familial etiologies. The concepts of novel drug delivery systems and biomarker-based clinical strategies can improve the accuracy of therapy, and in the long term, the main goal is to slow the disease and increase the quality of life of people with ALS and similar motor neuron diseases [124].

Table 2 summarizes disease-specific molecular targets and emerging therapeutic strategies for major neurodegenerative disorders. It highlights key pathogenic targets, including amyloid-β, tau, α-synuclein, LRRK2, GBA, mutant huntingtin, and C9orf72, alongside corresponding therapeutic approaches and clinical development stages, emphasizing the transition toward precision medicine and targeted disease-modifying therapies [125].

Table 2: Disease-specific novel targets and emerging therapeutic strategies in neurodegenerative disorders.

S. No.	Disorder	Novel Target	Target Type / Pathology	Therapeutic Strategy / Status	References
1.	Alzheimer's Disease	Amyloid-β	Protein aggregation / Plaque formation	Monoclonal antibodies / Phase III	[126]
2.	Alzheimer's Disease	Tau	Protein phosphorylation / Neurofibrillary tangles	Immunotherapy / Small molecules / Phase II	[127]
3.	Alzheimer's Disease	BACE1	Enzyme / Aβ production	Small molecule inhibitors / Phase II/III	[128]
4.	Alzheimer's Disease	APOE4	Genetic variant / Lipid metabolism & amyloid clearance	Gene therapy / Small molecule / Phase I	[129]
5.	Parkinson's Disease	α-Synuclein	Protein aggregation / Lewy body formation	Immunotherapy / Phase I/II	[130]
6.	Parkinson's Disease	LRRK2	Kinase / Mutation-driven neurodegeneration	Small molecule inhibitors / Phase II	[131]
7.	Parkinson's Disease	GBA	Enzyme / Lysosomal dysfunction	Small molecule chaperone / Phase II	[132]
8.	Huntington's Disease	Mutant huntingtin	Protein / Toxic gain-of-function	ASO / RNAi / Phase III	[133]
9.	Huntington's Disease	RNA toxicity	RNA / Transcriptional dysregulation	ASO / RNAi / Phase II	[134]

10.	Huntington's Disease	Epigenetic dysregulation	DNA / Histone / Transcriptional misregulation	Small molecules / Phase I	[135]
11.	ALS	C9orf72	Genetic repeat / RNA foci & dipeptide toxicity	ASO / Gene silencing / Phase I/II	[136]
12.	ALS	Glutamate excitotoxicity	Neurotransmitter / Motor neuron death	Receptor antagonists / Phase II	[137]
13.	FTD	Tau	Protein / Frontotemporal tangles	Immunotherapy / Phase I/II	[138]
14.	FTD	C9orf72	Genetic repeat / RNA foci & dipeptide toxicity	ASO / Gene silencing / Phase I	[139]
15.	Alzheimer's Disease	Synaptic dysfunction	Synapse / Cognitive decline	Small molecules / Peptides / Phase I/II	[129]

9. Translational and Clinical Perspectives

Neuropharmacology Translational and clinical approaches promote the need to connect mechanistic knowledge to therapeutic practice through the preclinical validation of rigour and clinically relevant outcomes [140]. The preclinical models, which include transgenic rodents, toxin induced paradigms, patient induced pluripotent stem cells and three dimensional organoid constructs, are essential in target validation, mechanistic dissection and pharmacodynamic studies [141]. With these systems, interrogation of disease-specific pathways, such as protein aggregation, mitochondrial dysfunction, neuroinflammation, and synaptic pathology, can be done, and dose optimization and safety profiling is also achieved. However, the nature of the constraints people may face in cross-functional predictions requires the implementation of multi-omics approaches and models of humans to enhance construct validity [142].

Biomarkers play a central role in clinical development, which provides early diagnostic ability, patient stratification, and therapeutic monitoring. Individually and in combination, fluid biomarkers (e.g., cerebrospinal fluid tau, amyloid-2, neurofilament light chain), neuroimaging (MRI, PET), and digitally derived variables obtained as a result of cognitive and motor testing have become objective disease progression and therapeutic response indicators. It is crucial that the proper clinical endpoints (i.e., cognitive scales and functional tests) and composite progression indices should be used to prove the disease-modifying effects. In spite of these achievements, there are still issues facing clinical translation, which comprise, but are not limited to, patient-population heterogeneity, blood-brain barrier limitation, insufficient target engagement, late-stage intervention, and high attrition rates during clinical trials [143].

Figure 3 illustrates the translational pathway involved in the development of therapeutics for neurodegenerative diseases. The process begins with the identification and validation of promising molecular or cellular targets, followed by preclinical studies to evaluate pharmacological efficacy, mechanisms of action, pharmacokinetics, and safety. Successful candidates progress through phased clinical trials to assess tolerability, efficacy, dose optimization, and clinical outcomes in patient populations. Throughout this process, biomarker development and translational research support patient stratification, treatment monitoring, and evaluation of therapeutic responses. Regulatory evaluation subsequently assesses the quality, safety, and efficacy of the candidate before granting marketing authorization. Post-approval surveillance further evaluates long-term safety and real-world effectiveness. Collectively, this integrated pathway facilitates the systematic translation of promising discoveries into safe, effective, and clinically relevant disease-modifying therapies for neurodegenerative disorders [144].

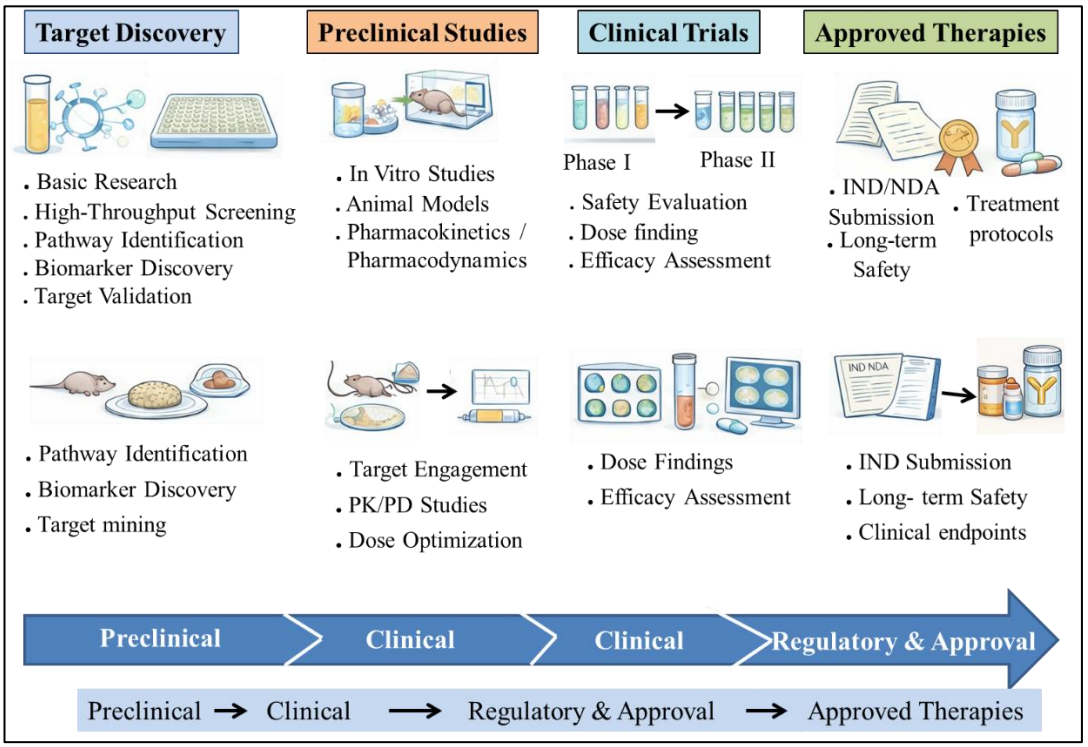

Figure 3: Translational pipeline from target discovery to clinical application. Schematic representation of the drug development pipeline, illustrating the progression from target discovery and preclinical studies to clinical trials, regulatory review, and ultimately approved therapies.

10. Future Directions and Emerging Trends

The future trends of neuropharmacology focus more on accuracy and customization where genomic, transcriptomic, proteomic and biomarker information is combined to customize therapeutic interventions to specific disease patterns and progressions. Precision neuropharmacology aims to categorize patients using molecular signatures and, therefore, providing specific interventions that would increase therapeutic efficacy and reduce adverse effects. Simultaneously, developments in machine learning and artificial intelligence (AI) are reshaping the target discovery and drug design process by accelerating novel molecular target discovery, drug-target interactions, lead compound optimization and re-using the pharmacotherapies available in the clinic through large-scale data analytics and in silico models. Furthermore, due to the multifactorial etiology of neurodegenerative diseases, new concepts predict multi-target and combination therapies, which simultaneously change interconnected pathological processes, including: protein aggregation, neuroinflammation, oxidative stress, and mitochondrial dysfunction. The combination of such integrative, technology-driven methods has the potential to develop disease modifying therapies and the next-generation neurotherapeutics.

Conclusion

Neurodegenerative diseases are chronic diseases that involve loss of neurons, dysfunction of synapses and a multifactorial process that goes beyond the conventional neurotransmitter depletion. The existing treatment options mainly provide symptomatic treatment without slowing down disease advancement, which is why the implementation of disease-modifying interventions is urgently needed. The recent developments in the field of molecular biology have provided major pathogenic pathways, such as protein misfolding, dysfunction of the mitochondria, oxidative stress, neuroinflammation, impaired proteostasis, and synaptic degeneration. These findings have given neuropharmacology a new path of multi-target, mechanism-based therapeutic techniques. Newer targets like kinases, epigenetic regulators, neuroimmune mediators and autophagy pathways offer good prospects of intervention. At the same time, translational potential is being broadened by biologics, RNA-based, and gene-based approaches, and drug delivery systems based on nanotechnology. Precision medicine strategies are also enhanced by the use of biomarkers to stratify. However, such issues as target validation, clinical heterogeneity, and blood-brain barrier permeability are also major issues. A coordinated, individualized and translational model must be applied in the realization of effective neuroprotection and enhancement of long-term clinical outcomes.

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Ethics approval and consent to participate

Not applicable

AI Declaration

The authors declare that they did not use artificial intelligence (AI) tools to generate or draft the scientific content of this manuscript. ChatGPT and Grammarly AI were used solely to improve the language, grammar, readability, and clarity of the manuscript. All AI-assisted suggestions were carefully reviewed, verified, and edited by the authors, who take full responsibility for the accuracy, originality, and integrity of the final content.

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