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REVIEW ARTICLE

Targeting α-Synuclein: Current Strategies and Emerging Therapies for Synucleinopathies

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Abstract: Alpha-synuclein (α-syn) is a crucial protein involved in the pathogenesis of Parkinson's Disease (PD) and other synucleinopathies. It is important with respect to neuron health, regulation of α-syn protein synthesis, and its degradation. Numerous cellular pathways implicated in the process of autophagy, chaperone, and proteolysis play a vital role in the maintenance of α-syn protein homeostasis. Autophagy dysfunction defeats α-syn protein accumulation and neuroinflammation, as present in dementia with Lewy bodies and sporadic PD. Oxidative stress is another key factor that intensifies α-syn protein misfolding and aggregation, thereby leading to neurodegeneration. Involvement in the treatment of α-syn related disorders includes passive and active immunization, inhibitors of protein aggregation, gene silencing technology, modulators of synaptic function, and target drug delivery systems. Other α-syn related therapy approaches include the development of a novel herbal formulation focusing on the gut-brain axis and interventions designed to enhance protein quality control. As clinical trials move forward, minimizing challenges related to the target involved, biomarkers, and patient stratification is crucial to decoding these therapies into effective management. These insights not only advance our understanding of α-syn biology but also highlight the urgency of early and multi-targeted therapeutic interventions.

Keywords: Alzheimer's disease, amyotrophic lateral sclerosis, neurodegeneration, Parkinson's disease, synucleinopathies, α-synuclein.

1. INTRODUCTION

Neurodegeneration, the progressive damage to neurons, their structure, or their function, is a serious health concern and a major contributing factor to the pathophysiology of many brain disorders [1, 2]. Most neurons are produced by neural stem cells in youth, and as people age, their production declines dramatically [3]. Synaptic dysfunction, difficulties with neuronal networks, and the build-up of altered protein variations in the brain are all associated with neurodegeneration [4]. Neurodegenerative Diseases (NDs) refer to a group of disorders marked by progressive neuronal degeneration. [5]. Recent studies suggest that a single neurodegenerative disease may actually involve multiple distinct disease processes. Alzheimer's disease, Parkinson's disease, prion disease, motor neuron disease, Huntington's disease, spinal muscular atrophy, and spinocerebellar ataxia are among the most common NDs [6, 7]. Although age is still the main contributory factor for all NDs, new research suggests that environmental factors and genetic predisposition can both equally raise the risk of ND. Furthermore, even if a person has certain genes linked to ND, the local atmosphere has a significant influence on the rate and degree of neurodegeneration [8-10]. We need to improve early detection, treatment, and prevention of PD and related synucleinopathies, as almost 2.5 million people in the US and more than 8.5 million worldwide have some form of synucleinopathy [11, 12].

Neurodegenerative diseases impact various aspects of human functioning due to the brain's role in controlling numerous bodily functions [13]. Both basic abilities (like speech, mobility, balance, and stability) and sophisticated abilities (like cognitive processes and bladder and bowel control) are hampered by these disorders [14]. Most neurodegenerative diseases are progressive and irreversible; however, certain therapies aim to alleviate symptoms, reduce pain when present, and improve balance and mobility. An outline of a number of prevalent neurodegenerative illnesses will be given in the sections that follow [15, 16].

2. CLINICAL FEATURES OF SYNUCLEINOPATHIES

The progressive neurological disorder known as PD is typified by tremor, rigidity, and bradykinesia with festinant

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gait, and problems with balance and coordination. Growing older is the primary risk factor for the condition, which is caused by both genetic and environmental factors [17]. Other influences, such as high caffeine consumption, tobacco use, and contact with environmental toxins, are believed to affect PD risk, though the exact mechanisms remain uncertain [18]. The pathophysiology of PD is mostly characterized by structural changes in the brain, such as shrinkage of the frontal cortex and enlargement of the ventricles. However, the most prominent structural alteration is the loss of pigmented dopaminergic neurons in the locus coeruleus and substantia nigra pars compacta, resulting from the degeneration of dopaminergic neurons containing neuromelanin. Several neuronal losses disturbed the nigrostriatal pathway, decreasing striatal dopamine levels and resulting in motor symptoms of PD, while further neuronal loss contributes to the non-motor symptoms of the disease [19, 20]. The development of PD is initiated by several primary pathways, including the misfolding and buildup of α-syn, mitochondrial dysfunction, impaired protein clearance systems, and neuroinflammation [21]. At the microscopic level, PD is characterized by the presence of Lewy bodies within neuronal cells, along with dystrophic neuritis [22]. Similar to AD, protein misfolding occurs in PD, with the tau protein being commonly affected, leading to the formation of neurofibrillary tangles. In some PD patients, widespread plaques of neurofibrillary tangles and amyloid-beta are also observed [15,23].

Dementia with Lewy bodies (DLB) is the second most common form of degenerative dementia after Alzheimer's disease and is characterized by the widespread accumulation of α-syn containing Lewy bodies in cortical and subcortical regions [24]. Clinically, DLB presents with a combination of progressive cerebral decay, repeated visual hallucinations, fluctuations in attention and awareness, and Parkinsonian motor symptoms. Rapid eye movement (REM) sleep behavior disorder and manifest sensitivity to neuroleptic drugs are also characteristic features [25, 26]. The correspondence of cognitive and motor symptoms often makes the difference between Alzheimer's disease (AD) and Parkinson's disease dementia (PDD) challenging, but the presence of essential features, such as early hallucinations and cognitive fluctuations are mainly symptomatic of DLB [27].

Multiple system atrophy (MSA) is a promptly progressive neurodegenerative disorder characterized by common glial cytoplasmic inclusions composed of aggregated α-syn [28]. Clinically, MSA is divided into two major phenotypes: Parkinsonian (MSA-P), which manifests with rigidity, bradykinesia, and poor response to levodopa, and cerebellar (MSA-C), which is dominated by gait ataxia, limb incoordination, and dysarthria [29]. Autonomic dysfunction with orthostatic hypotension, urinary incontinence, and erectile dysfunction is a main feature and often appears early in the disease progression. Pathologically, MSA is separate from PD and DLB because α-syn aggregates primarily in oligodendroglial cells rather than neurons, contributing to extensive neurodegeneration in striatonigral and olivopontocerebellar systems. The combination of Parkinsonism, cerebellar ataxia, and autonomic failure differentiates MSA from other synucleinopathies [30, 31].

3. α-SYN OVERVIEW

While α-syn plays a pivotal role in the pathophysiology of dopaminergic neurodegeneration in Parkinson's disease, developing evidence suggests that the wild-type form of this protein may primarily function as a neuroprotective agent, capable of inhibiting apoptosis in response to several pro-apoptotic stimuli [32, 33]. However, this protective function may be compromised by familial PD-linked mutations, variations in expression levels or clearance, or exposure to certain neurotoxins. Additionally, accumulating evidence indicates that a key function of alpha-synuclein in dopaminergic neurons may be the regulation of dopamine content and tone at the synapse [34, 35]. It also discusses how disturbances in such processes, along with the loss of α-syn's neuroprotective functions, may cause the detected neurotoxicity of α-syn in dopaminergic neurons and lead to degenerative conditions associated with PD [36, 37].

Recent evidence also suggests other mechanisms involving α-syn pathologies, cellular dysfunction, and cell death. Iron was also demonstrated to suppress the degradation of α-syn and increase its accumulation in the cell, causing mitochondrial dysfunction and cytotoxicity [38]. Specifically, α-syn, *via* its association with the mitochondrial permeability transition pore (mPTP), was found to function as a principal killer protein in the programmed cell death process of ferroptosis, which is mediated by iron-dependent lipid peroxidation [39]. The role of α-syn in ferroptosis thus illustrates the duality of iron's role in oxidative damage and its direct impact on α-syn's toxicity, as already proposed in the discussion of the Repurposed Drugs section [38, 40]. Additionally, α-syn was also found to interact with the pro-apoptotic protein BAX and, together with it, induce the permeabilization of the mitochondrial surface membrane and enhance apoptosis [41]. Taken together, the interplay of α-syn's functions illustrates the complex role of α-syn in ferroptosis, mitochondrial dysfunction, and apoptosis, thus broadening the understanding of α-syn's function in neurodegeneration in synucleinopathies [42].

3.1. Structure α-syn

Extensive scientific research has been carried out to understand and recognize the relation between the sequences, structures, and functions of the protein α-syn and how these factors influence the abnormal behavior of the protein in PD and associated disorders. α-syn is composed of 140 amino acids and has a molecular weight of 14 kDa and a pKa value of 4.7 [43]. The protein is composed of different structural domains, as represented in Figure (**1**). The N- and C-terminal domains of α-syn display different roles. The N-terminal domain contains an amphipathic and lysine-rich region, which plays a critical role in protein-membrane interaction. In turn, the C-terminal domain is disordered and acidic, which plays a role in the nuclear localization and communication of different molecules and proteins [44]. The major structural domain contains a highly hydrophobic segment from residues 65-90 and is designated as the non-

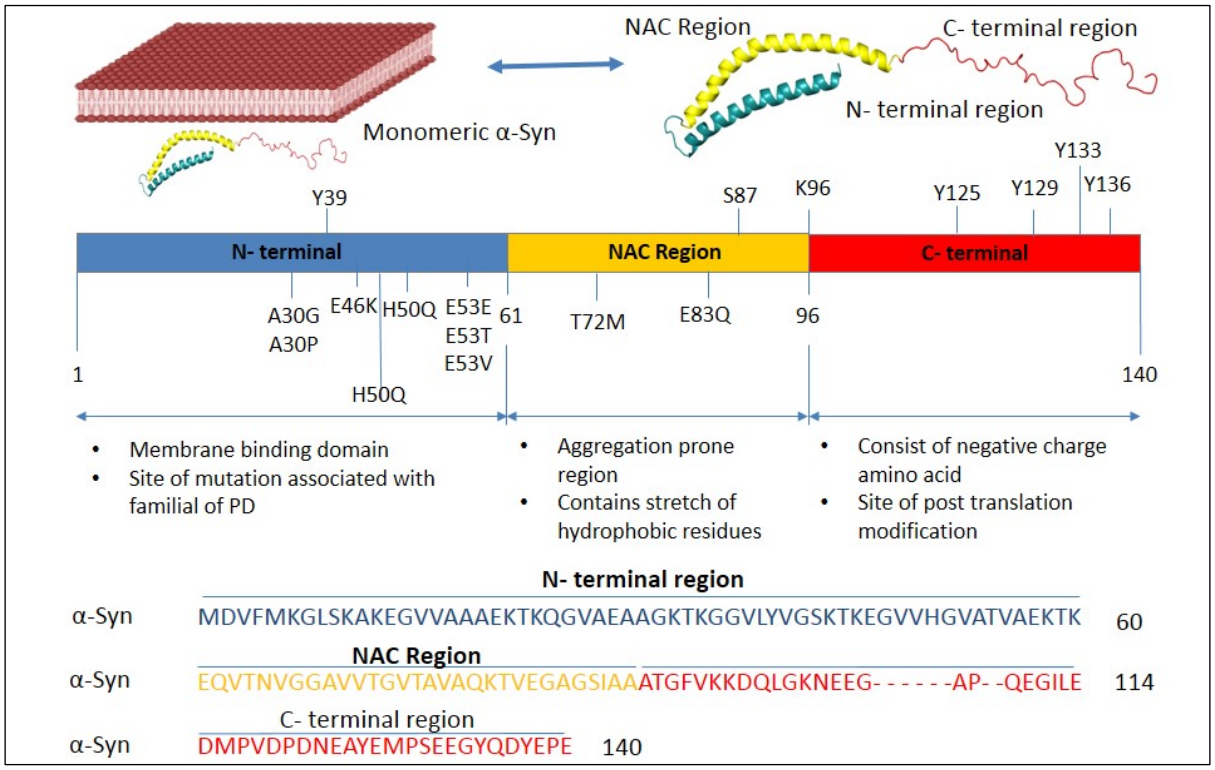

Figure 1. The sequence and structural elements of influence on α-syn. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

amyloid-β component of AD amyloid plaques [45]. This NAC region is essential in the aggregation of the α-syn, as proven by research that demonstrated significant deletions within the protein result in decreased α-syn aggregation [46].

3.2. Mechanisms of Synaptic α-syn

Nerve terminals of neurons contain synaptic vesicles, which are of three types according to the specifics of their functions and locations, including the readily releasable pool, recycling pool, and reserve pool. The readily releasable pool, located close to the cell membrane, represents a small number of synaptic vesicles prepared for prompt release in response to stimulation. The recycling pool, close to the cell membrane, functions during sensory stimulation through the regulation of the balance of synaptic vesicle release and recycling [47]. Although the recycling pool exceeds the readily releasable pool in number, it requires more time for assembly and release. The reserve pool's position and function are questionable since it is very rich in cultured neurons but very low or completely absent in whole brain tissues [48]. Protein α-syn, like its location at the nerve terminal, plays a vital role in the regulation and maintenance of the process of synaptic vesicle recycling and release of neurotransmitters [49]. Numara's *in vitro* and *in vivo* studies investigating the effects of α-syn deficiency or excess have demonstrated that it affects various steps of synaptic vesicle trafficking, *via* techniques such as docking, priming, and fusion of release-ready synaptic vesicles, as well as reassembly of synaptic vesicles following neurotransmitter release [50].

Neurotransmitter release at synapses is a complex process that involves several steps, many of which are modulated by α-syn. Step 1 involves the neurotransmitter uptake into vesicles, which is mediated by specialized membrane transporters. For monoamines, this is mediated by the vesicular monoamine transporter type 2 (VMAT2), whose activity is impaired by α-syn [51]. This has been demonstrated for dopamine uptake in dopaminergic neurons, but may also apply to other monoamines. So far, no direct role of α-syn in vesicular transporters for acetylcholine, glutamate, or GABA has been demonstrated. However, the vesicular GABA transporter (VGAT) has been implicated in α-syn toxicity, although any direct effects in human synapses have not been observed so far [52]. Following uptake, vesicles move to release sites, becoming part of the readily releasable pool, and are primed for fusion with the plasma membrane upon calcium entry. α-Syn knockout or knockdown studies in rodent hippocampi have shown that this leads to a decrease in the number of the reserve/resting vesicle pool, while the readily releasable pool is unchanged. Thus, prolonged, lower-frequency stimulation, which normally depletes the reserve pool, was markedly reduced in α-syn knockout mice compared to wild-type controls [53].

Grounding of the synaptic vesicles for exocytosis involves a priming mechanism, which includes partial formation of the SNARE complex. All these processes are triggered by various protein-protein interactions. Key players in the mechanism have been found to be the protein involved in the SNARE complex, which is called synaptobrevin-2/VAMP2, as well as synapsins, along with different variants of Munc13 and Munc18 proteins, and also Rab GTPases,

Rab-interacting proteins, and RIM-binding proteins [54]. While an exhaustive explanation of the protein priming mechanism is beyond the scope of the current review, it is important to make a special mention of the critical protein players that come into interaction with α-syn. Alterations in these proteins have been reported in the brain tissues of PD patients [55].

The interaction of α-yn and the synaptic membrane is regulated through various mechanisms, *e.g.,* being linked to the membrane and the associated membrane proteins. The connection of α-syn to the phospholipid membrane is not well understood due to technical limitations [56]. α-syn does not contain a transmembrane domain or lipophilic anchor component, causing it to detach from synaptic vesicles during processes of membrane isolation. However, α-syn has a preference for extremely curved membrane structures, such as the synaptic vesicles. The proximity between α-syn and these curved membranes with acidic phospholipid headgroups may trigger the formation of an amphipathic α-helical structure in α-syn's N-terminal region, which then integrates into the lipid bilayer [57]. α-syn might not only be concerned with curved membranes but could also help with membrane curvature. While the specific mechanisms are not fully understood, these observations indicate that α-syn contributes to the membrane bending essential for vesicular exocytosis and recycling [58]. In cellular settings, both native α-syn and its overexpression enhance fusion pore expansion, resulting in more frequent complete vesicle fusion and fewer kiss-and-run actions [57, 58]. Also, normal α-syn, but not the PD-linked variants with mutations in the vesicle-binding N-terminal, hurries neuromodulator release by promoting more complete fusion actions. For example, neuromodulators that release progressively from vesicles, such as monoamines and neuropeptides, are more vulnerable to the influence of fusion pore dilation than amino acid transmitters that diffuse rapidly. Indeed, it has been observed that the release of dopamine is affected by α-syn levels and absence, but not glutamate release [59]. The observation that oligomers and aggregates of α-syn can have different or even opposite effects on membrane morphology and vesicle function further clouds the relationship between α-syn and synaptic vesicles (Figure **2**) [60].

Recent studies have expanded our understanding of α-syn and its importance in postsynaptic functions, in addition to its presynaptic roles. Mutant α-syn cannot restore this property in α-syn knockout mice, whereas normal α-syn has a crucial property in postsynaptic endocannabinoid transmitter release [61]. This study recognized a vesicular release mechanism that is α-syn and postsynaptic SNAREs-dependent, contrary to the common perception that endocannabinoids are synthesized and released on demand [62]. The brain has endocannabinoids, mainly in the cerebellum, hippocampus, neocortex, and basal ganglia [63]. They bind to the presynaptic cannabinoid receptor-I at multiple synapses, including glutamatergic, GABAergic, dopaminergic, and cholinergic synapses, and are not limited to postsynaptic dendrites [61]. The importance of α-syn in regulating synaptic restrictions important for maintaining the balance of excitation, inhibition, and neuromodulation in the brain, is highlighted. These functions are vital for synaptic homeostasis, promoting flexibility while preserving synaptic function. One theory suggests that the adjustment of normal α-syn function, particularly the binding of α-syn monomers to synaptic vesicles for synaptic regulation, may depend on active oligomer creation and breakdown [64]. Since monomers appear to be the primary α-syn class capable of binding curved membranes, reducing presented monomers through multimerization could potentially relief the vesicles. In support of this idea, only monomeric α-syn, not tetrameric, has been shown to bend membranes [65].

3.3. Toxicity of α-syn Oligomers and Fibrils

The multifaceted and varied composition of α-syn oligomers formed in altered circumstances implies that multiple oligomeric types may be responsible for α-syn-mediated damage in neurons and possibly glial cells. The change of α-syn into harmful oligomeric forms could be affected by interactions with lipids or small molecules, as well as post-translational changes like phosphorylation and oxidative stress [66]. In experimental settings, α-syn self-assembly and the creation of soluble, β-sheet-rich aggregates can be initiated by various factors [67]. Recent studies indicate that the procedure of oligomer-to-fibril transformation, rather than fibrils themselves, plays a critical role in α-syn toxicity and Neurodegeneration [68]. Mutations that accelerate fibrillization or oligomerization have been demonstrated to improve α-syn induced toxicity and pathology in animal models. These findings are consistent with observations in the amyloid-β arena, suggesting that the aggregation process itself, rather than just the end products, may be associated with toxicity [46,69-71].

Although current evidence suggests that α-syn oligomerization and/or fibrillogenesis play a crucial role in α-syn toxicity, it is important to recognize that the data indicating lower toxicity for monomeric α-syn is mainly derived from extracellular toxicity assays using recombinant proteins or correlations between increased α-syn oligomer levels on SDS-PAGE gels and the development of neurodegeneration in transgenic animal models and other experimental conditions [46,71]. It is necessary to consider two possibilities not excluded by the available data. First, α-syn oligomerization in exact cellular sections may alter the delivery of functional monomeric α-syn forms or sequester monomers into non-functional oligomeric structures, potentially subsequent in a partial damage of α-syn function [71]. Next, native or misfolded monomeric α-syn may contribute to toxicity and the pathogenesis of PD through aggregation-independent mechanisms, such as abnormal interactions with membranes, proteins, and small molecules, retention in specific cellular compartments, and the disruption of cellular processes [72]. Despite the unchanging oligomeric α-syn forms, which can be easily distinguished from monomers and fibrils, current experimental gears are unable to detect and characterize the different conformers of α-syn monomers, impeding the investigation of the character of α-syn monomers in both health and disease (Figure **3**) [73].

4. DIAGNOSIS, BIOMARKERS, AND THERAPEUTICS

Current advances in α-syn aggregation assays have significantly extended their potential applications in both

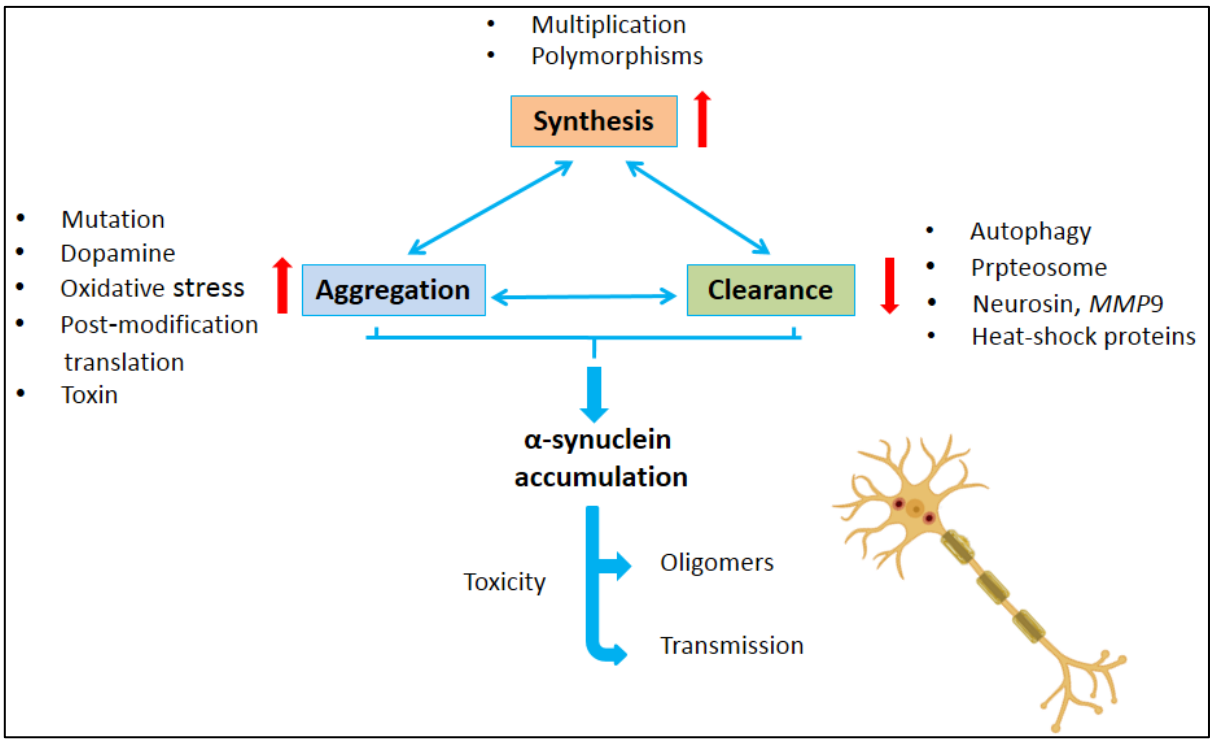

Figure 2. Cellular mechanisms of regulation, accumulation, and transmission of α-syn. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

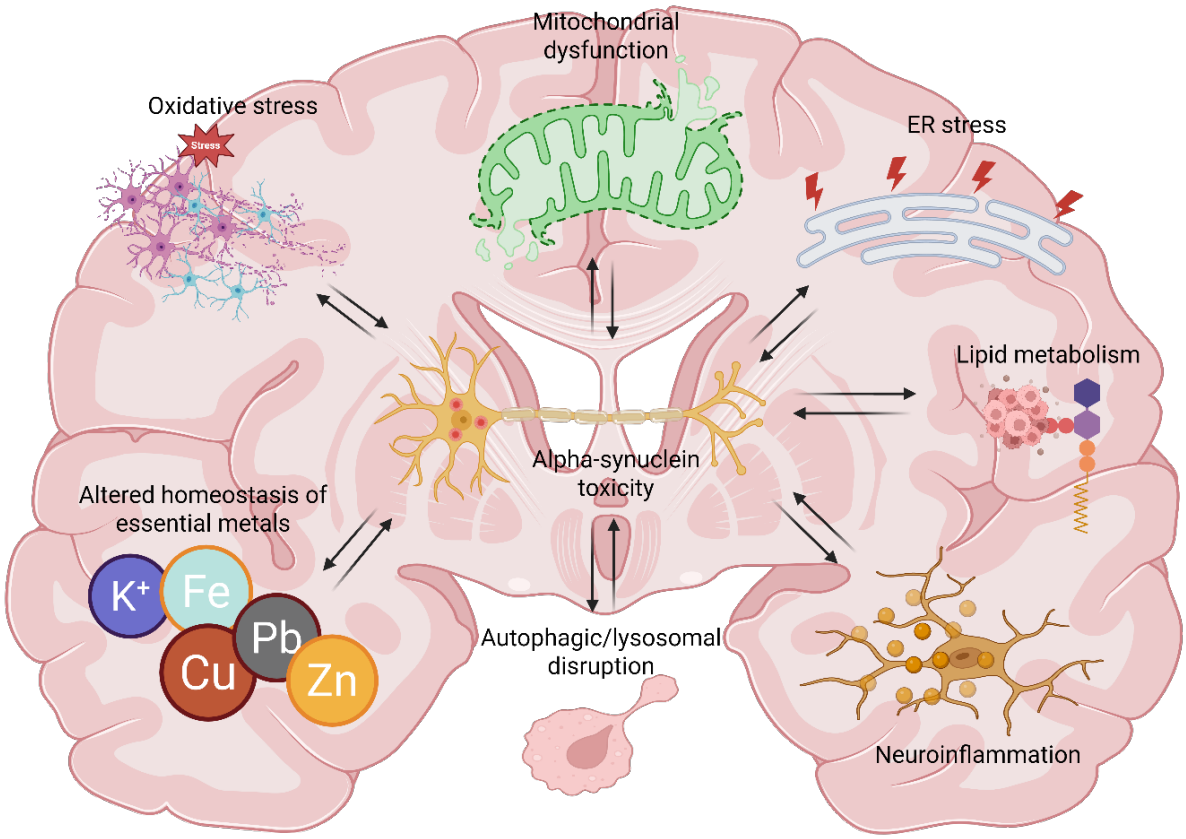

Figure 3. Toxicity of α-syn oligomers and fibrils. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

diagnosis and therapeutic development. Techniques such as real-time quaking-induced conversion (RT-QuIC) and protein misfolding cyclic amplification (PMCA) perceptively detect misfolded α-syn species in cerebrospinal fluid, blood, or peripheral tissues, providing valuable tools for primary and differential diagnosis of PD and other synucleinopathies [74, 75]. In addition to the diagnostic feature, these tests also show the importance of therapeutic assessment through monitoring the level of α-syn seeding activity in response to therapeutic candidates, of course, and the development of relevant therapeutic strategies [76, 77]. It is also conceivable to improve patient stratification, nursing of disease progression, and development of therapies targeting α-syn by integrating these tests into therapeutic approaches [78].

5. THERAPEUTIC APPROACHES

5.1. Passive Immunotherapy (Monoclonal Antibodies)

Monoclonal antibodies (mAbs) that bind and neutralize toxic α-syn, particularly the extracellular aggregated form, are employed in this method to facilitate their removal and stop their cell-to-cell propagation [79, 80]. Prasinezumab (RO7046015/PRX002), developed by Roche and Prothena, resulted in a reduction of free serum α-syn of over 97% in the phase II PASADENA trial and demonstrated some preservation of motor function, although it failed to achieve the primary endpoint of slowing the progression of early PD. Another promising candidate is Biogen's cinpanemab (BIIB054), which targets the N-terminal domain of α-syn. It showed promising target engagement and safety in early clinical trials; however, it failed to demonstrate efficacy in slowing motor or cognitive decline in the phase 2 SPARK trial, leading to discontinuation of its development [83, 84].

Another agent, Lu AF82422, developed by Lundbeck in collaboration with Genmab, also binds to the C-terminal epitope and has completed phase I studies in healthy volunteers and PD patients [85, 86]. This antibody is currently in phase II trials for the treatment of MSA, which is expected to be completed by 2025 [87]. Other antibodies in early stages of development are ABBV0805, developed from the company's bioArctic discovery program and licensed to AbbVie, which has been shown, in preclinical studies, to selectively bind α-syn aggregates without interfering with its physiological monomeric forms, which may prevent unfavorable effects [88, 89]. However, although a phase I trial for humans had begun, it was reportedly halted by AbbVie development, and updates remain limited [90].

UCB7853 is a new α-Syn antibody, which targets the reduction of α-Syn protein aggregation in the basal ganglia. There is no data suggesting its effectiveness in any preclinical or *in vitro* studies. Nonetheless, it is entering phase 1 human trials [91]. Further expanding the portfolio of α-Syn targeting mAbs, MEDI1341, also known as TAK-341, is a highly active mAb developed by AstraZeneca and Takeda. In a completed phase 1 trial, it exhibited promising results, revealing good pharmacokinetics and safety. MEDI1341 also targets the C-terminus of α-Syn. Furthermore, it is now being evaluated for its efficacy in phase II trials for the treatment of MSA [92, 93]. In addition to these mAbs, a series of alpha syn-specific antibodies being developed by AC Immune, including those from its Supra Antigen portfolio, are found to be in the preclinical stage and to feature a promising entry into human trials in the coming years [94, 95].

These investigations into using mAbs as a form of passive immunotherapy for PD also reflect a targeted approach to targeting the propagation of pathological α-Syn protein, a process thought to play a major role in disease development in PD as well as other α-Syn diseases [96]. Although the outcomes have been inconsistent, indicating the difficulty in determining the timing, targets (N or C terminal), and brain penetration of the therapies, the evolution of antibody therapies also shows promise as a whole. Notably, the therapies already approved and under investigation show satisfactory preclinical and clinical drug safety and drug tolerability, a critical aspect when considering the long-term management of chronic neurodegenerative diseases [97]. Moving forward, different approaches combining mAbs and small molecular inhibitors of protein aggregation or gene therapies will likely enhance the efficacy of the therapies, especially in genetically at-risk populations (*e.g.,* SNCA duplication). Furthermore, passive immunotherapies currently show the most advanced disease-modifying therapies in the α-syn therapeutics pipeline with the completion of phase II and III trials (Table **1**) [98].

5.2. Active Immunotherapy (Vaccination)

Active immunotherapy, or vaccination, represents a promising approach to treat synucleinopathies by inducing the body's immune system to generate antibodies against pathological forms of α-syn [99]. Vaccines, exemplified by AFFiRiS AG's AFFITOPE® vaccines, induce a persistent immune response, which is not the case with passive immunotherapy. The peptide vaccines, PD01A and PD03A, also focus on pathological α-syn epitopes without cross-reactivity [100, 101]. Phase I clinical trials in early PD patients showed a significant amount of α-syn-specific antibody production and a good safety profile. Currently, PD03A, also known as ACI-7104.056, is in phase II trials, which are expected to be completed by 2028 [102]. Vaxxinity's synthetic peptide vaccine, UB-312, has moved into phase II trials in 2023 after showing significant antibody production in serum and cerebrospinal fluid in phase I trials [103, 104].

5.3. Small Molecules Targeting α-syn Aggregation

Small-molecule drugs directing α-syn aggregation are being developed for the treatment of synucleinopathies such as PD and MSA [105]. These drugs are generally designed to block the misfolding, oligomerization, or disassembly of α-syn aggregates to preserve neurons and arrest disease progression [106]. Of the molecules reviewed, Anle138b (also known as MODAG-001 or TEV-56286) is a hopeful lead that selectively targets the oligomer conformation of α-syn and blocks its aggregation and neurotoxicity. From preclinical studies, Anle138b has shown that it crosses the BBB, can prevent α-syn pathology, and alleviate symptoms of the disease. In addition, results from Phase I clinical trials on Anle138b confirm its safety in patients with PD and

Table 1. Key α-Syn targeted therapies.

Type	Drug	Target site	Mechanism of action	Stage	Statuses	Outcome	NCT Number	References
Passive Immunotherapy	Prasinezumab (PRX002/ RG7935)	C-terminus	Aggre α-Syn at AA 118-126	Phase 1 Phase IIB	Active, not recruiting Recruiting	Well-tolerable and safe; brain penetration and decreased α-syn levels in free serum -	NCT03100149 NCT04777331	[81, 82]
	Cinpanemab (BIIB054)	N-terminus	Aggre, fibrillar α-Syn	Phase 1 Phase 2	Completed Closed	Well-tolerable and safe The study did not meet its primary outcome	NCT02459886 NCT03318523	[83, 84]
	Lu AF82422	C-terminus	Aggre α-Syn at AA 112-117	Phase 2	Recruiting	Consistent slowing in clinical progression albiet not statistically significant	NCT05104476	[86]
	ABBV0805/ BAN0805	C-terminus	Aggre α-Syn oligo/ proto-fibrils at AA 121–127	Phase 1	Withdrawn	Well-tolerable and safe Discontinued due to the unknown company withdrawn	NCT04127695	[90]
	UCB7853	C-terminus	Aggre α-Syn	Phase I	Active, not recruiting	Ongoing	NCT04651153	[91]
	MEDI1341	C-terminus	Monomeric and aggregated α-Syn at the AA 103–129 region	Phase I Phase III	Active, not recruiting	Result pending -	NCT04449484 NCT05526391	[92, 93]
Active Immunotherapy	PD01A AFF	C-terminus	Peptide-based vaccine	Phase I	Completed	Good tolerability and safety of subcutaneous administration	NCT01568099	[102]
	PD03A AFF	C-terminus	Mimics αSyn peptide vaccination acts as B cell epitope	Phase I Phase IB	Completed Completed	Safe and tolerable Result pending	NCT02267434 NCT02618941	[103]
	UB-312	C-terminus	Targets oligomeric and fibrillar αSyn	Phase IA and B	Completed	Safe, well-tolerated, and induced antiα-Syn antibodies in serum and	NCT04075318	[104]
Small-Molecule Inhibitors	Anle138b	α-syn aggregates	Oligomer aggregation inhibitor	Preclinical	-	Promising in animal models; advancing to clinical	-	[107]

(Table 1) Contd….

Type	Drug	Target site	Mechanism of action	Stage	Statuses	Outcome	NCT Number	References
-	UCB0599	α-Syn protein	Misfolding inhibitor	Phase II	Completed	Completed 18-mo PD trial; results pending	NCT04658186	[108]
	ATH434	Labile iron / α-syn regions	Metal redistribution + aggregation inhibition	Phase II	Completed	Positive efficacy in MSA; biomarker indicated target engagement	NCT05109091	[109]
	ANVS-401 (Buntanetap)	Amyloid-β precursor protein (APP)	Synthesis of multiple toxic proteins by reducing mRNA translation.	Phase III	Completed	Promising cognitive and motor improvements	NCT06709014	[110]
ASOs & RNA Therapies	ION464 (BIIB101)	SNCA mRNA	ASO reducing α-syn synthesis	Phase I/II	Completed	Safe/tolerated; extension ongoing	NCT04165486	[112]
Synaptic Modulation Drugs	Memantine	NMDA receptors	Uncompetitive NMDA antagonist	Approved	Completed	Modest symptomatic benefit in Alzheimer's	NCT03858270	[118]
	Perampanel	AMPA receptors	Non-competitive AMPA antagonist	Approved	Completed	Efficacious in epilepsy; ongoing observational studies	NCT01393743	[119]
Adjunctive Delivery Tools	Focused ultrasound	Varies (*e.g.,* subthalamic nucleus)	Physical ablation/modulation	Investigational	-	Results depend on the indication; specify context for details	-	[122]

MSA, and it is being translated into mid-stage efficacy studies [107]. In addition, another potential therapeutic candidate, UCB0599 or NPT200-11, has also been developed collaboratively between Neuropore and UCB Pharma. UCB0599 works by binding to α-synuclein monomers, thereby preventing them from becoming toxic oligomers on lipid membranes. The Phase I study has confirmed its CNS penetration and tolerability. Currently, it is undergoing a phase II trial (ORCHESTRA-PD) for early-stage PD [108]. ATH434 (previously named PBT434), developed by Alterity Therapeutics, acts by antagonizing α-syn binding with metal ions. This interaction is essential in catalyzing α-syn. ATH434 completed phase I trials and is currently undergoing phase II trials in MSA [109]. A new potential therapeutic small compound is Buntanetap, also known as Posiphen. It evades α-syn-mediated cell damage by downregulating translation through mRNA. Early clinical trials, including those for AD and PD, have promising potential, with a phase III trial currently underway in PD [110].

5.4. Gene-Silencing Strategies

These gene silencing strategies target α-syn and represent a promising method to minimize α-syn levels by directly interfering with the gene responsible for its synthesis, SNCA. This therapy aims to reduce the intracellular levels of α-syn, subsequently limiting the extent of α-syn aggregates formed and neurotoxicity [111]. Among the most advanced gene silencing therapies is ION464, which is an ASO produced by a collaboration between Ionis Pharmaceuticals and Biogen. This ASO targets SNCA mRNA degradation, leading to a subsequent reduction in the levels of α-syn. It is presently being tested in a phase I clinical trial (NCT04145451) for patients with MSA [112]. Preclinical studies of ION464 demonstrated significant knockdown of α-syn levels in brain tissue with favorable tolerability. Another approach involves RNA interference (RNAi) using small interfering RNAs (siRNAs) or short hairpin RNAs (shRNAs) to silence SNCA expression [113]. While these have shown promise in rodent and primate models, often delivered *via* viral vectors such as AAVs, none have yet reached late-stage clinical trials due to delivery and safety challenges [114]. Additionally**,** microRNA (miRNA) mimics targeting SNCA regulatory pathways are under investigation. More recently, CRISPR/Cas9-based gene expurgation has been proposed as a potential long-term silencing solution, though it remains in the preclinical proof-of-concept stage [115]. Overall, gene-silencing strategies provide a highly

targeted and potentially disease-modifying approach to treating synucleinopathies, especially in patients with genetic SNCA duplication or triplication [115, 116].

5.5. Synaptic Modulation & Repurposed Drugs

Synaptic dysfunction and pathological α-syn spread across neuronal networks are significant to the progression of synucleinopathies such as PD. Therapeutic strategies aimed at modulating synaptic activity and repurposing existing drugs hold considerable promise in slowing or halting disease progression [117]. Among repurposed agents, memantine, an NMDA receptor antagonist mostly used in AD, is being evaluated in phase III clinical trials for PD. Memantine's capacity to inhibit excitotoxicity and indirectly modulate the synaptic transmission of toxic α-syn has the potential to safeguard vulnerable neurons [117, 118]. Similarly, perampanel, an antagonist of the AMPA receptor recently approved for the treatment of epilepsy, has been shown to reverse the accumulation of phosphorylated α-syn and improve motor function in preclinical animal studies. In addition to glutamatergic receptor modulators, other small-molecule therapeutics are also of interest for further development. For instance, Ca++ channel blockers, like isradipine, have been examined with respect to the exercise of neuroprotective capabilities; however, results are less consistent with respect to clinical benefit [119]. Even iron chelators, such as deferiprone, work by inhibiting iron-induced oxidative stress that leads to α-syn pathology. In addition, antibiotics like rifampicin are of interest with respect to α-syn aggregation capabilities. Recently, the gut-brain axis has started to gain attention for the treatment of α-synopathy with therapeutic options involving the microbiome and probiotics [120]. Cyclosporine, an immunosuppressive drug, is a lead compound showing neuroprotective efficacy in synucleinopathies by inhibiting mPTP *via* binding to cyclophilin D. Thus, mitochondrial depolarization, calcium overload, and apoptosis are blocked, protecting against α-syn-induced mitochondrial dysfunction and oxidative stress. Although its potential is marred by the immunosuppressive effects that cannot be tolerated in the long term, its efficacy serves to highlight the therapeutic potential lying with the mitochondrial permeability transition pore pathway for treating α-syn induced neurodegeneration [121]. Furthermore, new drug delivery platforms such as focused ultrasound with microbubble-mediated techniques are being used to achieve a temporary opening of the BBB, thus facilitating drug administration directly to neurodegenerative disorders. Although these repurposed drugs used for neuroprotection with synaptic modulators still require further clinical validation, their pre-existing safe profiles and multifarious mechanisms offer promise for their use in a combined therapeutic cocktail to combat α-syn-induced neurodegeneration [122].

5.6. Novel & Adjunctive Approaches

Besides the traditional immunotherapy and small molecules, a variety of new and additional therapeutic strategies are being studied for the treatment of α-syn-related diseases, including PD, dementia with Lewy bodies, and MSA [73, 123]. Nanotechnology-based drug delivery systems are also being investigated for the treatment of α-syn-related diseases. In nanotechnology-based drug delivery systems, nanocarriers such as liposomes, polymeric nanoparticles, and exosome-mimetic vesicles have been studied for the treatment of α-syn-related diseases due to their ability to efficiently traverse the blood-brain barrier [124]. Similarly, peptide inhibitors that mimic regions of the α-syn protein that are crucial for fibril formation have been synthesized to compete with α-syn aggregation. When effective, these peptides have the potential to be linked with motifs that will allow them to cross the cell membrane [124]. Another approach that is innovative in the field is the control of protein expression, especially improving the ability of molecular chaperone proteins, proteasomes, and the autophagy lysosomal pathway, which are in charge of clearing misfolded α-syn protein aggregates. Small molecules, such as rapamycin and its analogs, induce autophagy, effectively clearing α-syn aggregates in animal models, although the translation of this approach is limited by the immunosuppressive impact. Along these lines, modulators of Heat Shock Protein (HSP) expression have the potential to restore proteostasis, especially by enhancing proper protein folding and promoting clearance of aggregates [125, 126].

The microbiome-gut-brain axis is emerging as an adjunctive therapeutic target; modification of the composition of the gut microbiota has been known to impact neuroinflammatory and α-syn-related pathology. Probiotics and dietary interventions with the purpose of normalizing microbial composition will possibly indirectly impact α-syn pathology and disease course. Such interventions are currently under clinical investigation to confirm efficacy in conjunctive treatment with pharmacotherapy [127, 128]. Furthermore, there have been stem cell-based therapies showing promise for neuronal replacement and neuroprotective strategies. Encouraging pluripotent stem cells and mesenchymal stem cells, which are known to secrete neurotrophic factors and modulate neuroinflammatory pathways, are also under investigation for impact on α-syn pathology; however, this is still unknown [129]. Physical therapies such as transcranial magnetic stimulation (TMS) and deep-brain stimulation (DBS) could also have neuroprotective properties in modulating the complex neuronal circuits involved in the spread of α-syn. Moreover, lifestyle modifications such as exercise and cognitive training could also affect the progression of the disease by improving synaptic resilience and lowering oxidative stress [130]. Taken together, these therapeutic approaches widen the therapeutic armamentarium in dealing with the complexities associated with α-synuclein pathology and neurodegeneration.

5.7. Herbal Remedies in α-Synucleinopathies

Epigallocatechin-3-gallate (EGCG), a prominent polyphenol obtained from Camellia sinensis, is widely recognized for its ability to prevent α-syn fibrillation and remodel preformed fibrils into nontoxic forms through direct interactions with the protein's hydrophobic domains [131]. Curcumin, which is obtained from Curcuma longa, prevents not only the oligomerization of α-syn but also enhances the autophagic flux and reduces neuroinflammation *via* the

inhibition of NF-κB signaling [132, 133]. Baicalein, isolated from Scutellaria baicalensis, binds to α-syn monomers to reduce misfolding and toxic oligomer formation, and at the same time, it is a potent antioxidant and anti-inflammatory agent [134]. Dihydromyricetin from Ampelopsis grossedentata enhances chaperone-mediated autophagy by upregulating LAMP-2A and LC3, facilitating intracellular clearance of α-syn [135]. Geniposide is an iridoid glycoside from Gardenia jasminoides with GLP1 receptor agonist activity that reduces α-syn toxicity *via* the PI3K/Akt and Nrf2 signaling pathways [136]. Ginsenoside Rb1, a saponin from Panax ginseng, has anti-aggregatory properties and protects mitochondria, thus protecting dopaminergic neurons from toxicity [136]. Quercetin, a flavonol with onion and apple origins, reduces α-syn aggregation and is neuroprotective *via* its antioxidant and anti-inflammatory activities [137]. Kaempferol, with green tea and broccoli origins, facilitates lysosomal biogenesis and combats neuroinflammation, thereby assisting in the degradation of α-syn [138]. Luteolin, isolated from celery and green peppers, suppresses microglial activation and inhibits inflammatory responses through the MAPK and NF-kB signaling pathways [139]. Berberine, from Berberis, induces autophagy and suppresses α-syn expression, preventing accumulation. Isoliquiritigenin, a flavonoid from licorice root, inhibits α-syn aggregation and has cytoprotective effects [140, 141]. Honokiol, from Magnolia officinalis, protects mitochondrial function and reduces α-syn fibril formation [142]. Hydroxytyrosol, a phenolic compound from olives, destabilizes fibrils and protects neurons from oxidative stress. Piperine, from black pepper, improves the bioavailability of compounds such as curcumin and participates in antioxidative protection [143, 144]. These phytoconstituents, in combination, offer a multi-targeted approach to synucleinopathies, targeting protein aggregation, inflammation, oxidative injury, and cellular clearance, as listed in Table **2**.

Table 2. Phytochemicals in the treatment of synucleinopathies.

Phytochemical	Source Plant	*In Vitro* Models	*In Vivo* Models	Mechanism of Action
EGCG (Epigallocatechin-3-gallate)	*Camellia sinensis* (Green tea)	Inhibits α-syn fibril formation, disaggregates fibrils, and ThT assays	MPTP/rotenone PD mice and monkeys	Prevents α-syn fibrillation, antioxidant, anti-inflammatory
Curcumin	*Curcuma longa* (Turmeric)	Inhibits α-syn oligomerization, disaggregates fibrils	MPTP and LPS-induced PD mice	Modulates autophagy, inhibits NF-κB, reduces oxidative stress and inflammation
Resveratrol	Grapes, red wine	Enhances autophagic clearance of α-syn, inhibits oligomer formation	MPTP mouse PD model	Activates SIRT1, AMPK, enhances autophagy, and antioxidant
Baicalein	*Scutellaria baicalensis*	Inhibits α-syn fibrillization, disassembles oligomers	Rotenone-induced PD model	Inhibits toxic oligomers, antioxidant, promotes autophagy
Ginsenoside Rb1	*Panax ginseng*	Inhibits fibrillation, reduces α-syn oligomer toxicity	Not always validated *in vivo*	Neuroprotective, mitochondrial protection, anti-aggregatory
Berberine	*Berberis vulgaris*, *Coptis* spp.	Inhibits α-syn expression, reduces cell toxicity	PD rat model	Promotes autophagy, anti-inflammatory, and regulates α-syn expression
Geniposide	*Gardenia jasminoides*	Enhances autophagy, inhibits α-syn aggregation	6-OHDA-induced PD rat model	GLP-1R agonist, antioxidant, modulates PI3K/Akt/Nrf2
Dihydromyricetin	*Ampelopsis grossedentata*	Inhibits α-syn fibril formation and toxicity in H4 cells	α-syn transgenic mice	Activates chaperone-mediated autophagy (CMA), improves motor function
Isoliquiritigenin	*Glycyrrhiza glabra* (Licorice)	Inhibits α-syn fibrillization and seeded aggregation	Not extensively tested *in vivo*	Anti-aggregatory, antioxidant
Quercetin	Apples, onions, *Moringa oleifera*	Inhibits α-syn fibril formation, reduces oxidative damage	PD mouse model	ROS scavenging, inhibits inflammation, modulates proteostasis
Kaempferol	Tea, broccoli, grapefruit	Reduces α-syn aggregation, enhances lysosomal function	MPTP mouse model	Promotes lysosomal biogenesis, antioxidant, anti-inflammatory

(Table 2) Contd….

Phytochemical	Source Plant	*In Vitro* Models	*In Vivo* Models	Mechanism of Action
Luteolin	Green pepper, celery, chamomile	Reduces α-syn aggregation, suppresses microglial activation	PD rodent models	Inhibits NF-κB, modulates MAPK, antioxidant
Honokiol	*Magnolia officinalis*	Inhibits α-syn fibrillization	PD mouse model	Inhibits fibrillation, improves mitochondrial function
Squalamine / Trodusquemine	Marine sources	Displaces α-syn from membranes	C. elegans & rat models	Blocks membrane binding, reduces toxicity
Celastrol	*Tripterygium wilfordii*	Promotes α-syn clearance	PD mouse model	Induces autophagy, antioxidant, and proteostasis enhancement
Hydroxytyrosol	*Olea europaea* (Olive)	Disrupts α-syn fibrils	Not always validated *in vivo*	Fibril destabilization, antioxidant
Piperine	*Piper nigrum* (Black pepper)	Supports the bioavailability of other compounds	Synergistic *in vivo* studies with curcumin/EGCG	Bioenhancer, mild antioxidant

6. CHALLENGES AND FUTURE PERSPECTIVES

However, significant growth has been made in developing α-syn targeted therapies; numerous significant challenges continue to hinder clinical success. The failure of monoclonal antibody therapies such as Cinpanemab and Prasinezumab to meet their primary endpoints underscores the complexity of α-syn biology. Possible reasons include differences in epitope targeting (N *versus* C-terminus), insufficient timing of intervention, since pathology may previously be too advanced in enrolled patients, and the fundamental limitation that the antibodies currently available are not capable of effectively targeting intracellular α-syn aggregates, where much of the pathology resides. Another major difficulty is the blood-brain barrier (BBB), which restricts therapeutic antibody penetration into the CNS, often resulting in insufficient drug concentrations at sites of pathology. The stage of disease at treatment initiation also appears critical; although present trials focus on patients with recognized symptoms, earlier intervention may be required to change disease trajectories expressively. Similarly important is the absence of sensitive and specific biomarkers for patient stratification and for observing disease progression or therapeutic response. Without these tools, trials risk enrolling heterogeneous populations where drug effects may be covered. Moreover, there remains extensive debate about which α-syn species monomers, oligomers, or fibrils are the most pathogenic and thus the most suitable therapeutic targets. Finally, it is increasingly recognized that combination strategies may be essential, combining immunotherapies with methods that control lysosomal function, mitochondrial health, or neuroinflammation. While promising, such methods typify additional challenges in trial design, regulatory approval processes, and potential safety issues. These issues will be key to understanding how preclinical success is translated into active disease-modifying treatments for PD and related synucleinopathies.

CONCLUSION

α-syn is central to the pathogenesis of PD and related synucleinopathies, and its aggregation is a key driver of neurodegeneration. Although understanding its underlying structural forces and lethal conformations has been important, the challenge at this point is how to translate such knowledge into effective therapies. Many strategies are now in, or about to enter, clinical pipelines, including passive and active immunotherapies, small-molecule aggregation inhibitors, gene-silencing techniques, synaptic modulators, and repurposed drugs, each targeting different aspects of α-syn pathology. Adjunctive and novel approaches include nanotechnology-based delivery systems, modulation of protein quality control, and herbal formulations that further broaden the therapeutic landscape. Going forward, integrated approaches that couple α-syn targeted interventions with neuroprotective and disease-modifying strategies have the greatest potential to alter disease progression and improve outcomes for patients with synucleinopathies.

AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: VCB; data collection: VCB, AKG, AK, SKT, MKS. Analysis and interpretation of results: SK, AKG, MKS, VCB. Draft manuscript: VCB, SK. All authors reviewed and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

α-syn = Alpha-synuclein

AD = Alzheimer's Disease

ALS = Amyotrophic Lateral Sclerosis

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (Receptor)

APP = Amyloid Precursor Protein

ASO = Antisense Oligonucleotide

BBB = Blood–brain Barrier

CB1 = Cannabinoid Receptor Type 1

CNS = Central Nervous System

DLB = Dementia with Lewy Bodies

FDA = Food and Drug Administration

GABA = Gamma-aminobutyric Acid

GWAS = Genome-wide Association Study

mPTP = Mitochondrial Permeability Transition Pore

MSA = Multiple System Atrophy

NDs = Neurodegenerative Diseases

NMDA = N-methyl-D-aspartate (Receptor)

PD = Parkinson's Disease

PDD = Parkinson's Disease Dementia

SNARE = Soluble NSF Attachment Protein Receptor

SNCA = Synuclein alpha Gene

VMAT2 = Vesicular Monoamine Transporter 2

VGAT = Vesicular GABA Transporter

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declared no conflict of interest, financial or otherwise.

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