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EMERGING DISEASE-MODIFYING THERAPIES FOR EARLY PARKINSON'S DISEASE: A COMPREHENSIVE NARRATIVE REVIEW

Narrative Review

Umbreen Gull[1]*, Faziyya Latif[2], Rida Javed[3], Saba Sonia[4], Ayisha khalid[5], Abdul Rehman[6], Farah Zafar[7], Faiza Irshad[7]

[1]Department of Biopsychology and Neuroscience, Hamad Bin Khalifa University, College of Health and Life Sciences, Qatar.

[2]Department of Pharmacy, Iqra University, Islamabad Capital Territory, Islamabad, Pakistan.

[3]Bachelors of Medicine and Bachelors of Surgery, Al Nafees Medical College, Isra University.

[4]Institute of Microbiology, Faculty of Life Sciences, Government College University, Faisalabad. [5]Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Health Sciences, University of Balochistan, Quetta, Pakistan.

[6]Doctor of Pharmacy (Pharm.D), University of Central Punjab, Lahore, Pakistan.

[7]University College of Conventional Medicine, Faculty of Medicine and Allied Health Sciences, The Islamia University of Bahawalpur, Pakistan.

Corresponding Author: Umbreen Gull, Department of Biopsychology and Neuroscience, Hamad Bin Khalifa University, College of Health and Life Sciences, Qatar, umbreengullkhan@gmail.com

Acknowledgement: The authors acknowledge all researchers whose work contributed to this narrative synthesis.

Conflict of Interest: None

Grant Support & Financial Support: None

ABSTRACT

Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by both motor and non-motor manifestations, primarily resulting from dopaminergic neuronal loss in the substantia nigra and widespread molecular dysfunction. Current pharmacological therapies, including levodopa and dopamine agonists, provide symptomatic benefit but fail to alter disease progression. Over the last decade, growing insights into α-synuclein pathology, mitochondrial dysfunction, neuroinflammation, lysosomal impairment, and genetic susceptibility have driven intense interest in disease-modifying therapies (DMTs) aimed at slowing or halting neurodegeneration in early-stage PD.

Objective: This narrative review aimed to synthesize and critically evaluate contemporary preclinical and clinical evidence on emerging disease-modifying strategies for early Parkinson's disease, with emphasis on their mechanistic rationale, translational progress, and therapeutic potential.

Methods: A comprehensive literature search was conducted using PubMed, Scopus, and ClinicalTrials.gov to identify English-language studies published between January 2015 and September 2025. Preclinical studies, early- and late-phase clinical trials, and registered interventional studies investigating disease-modifying approaches in early PD were included. Data were qualitatively synthesized according to therapeutic mechanism, development stage, and reported outcomes.

Results: The review identified more than 120 relevant publications and over 40 registered interventional trials evaluating disease-modifying strategies. α-synuclein–targeted immunotherapies accounted for approximately one-third of clinical candidates, with multiple Phase II trials reporting acceptable safety and biomarker engagement but limited functional efficacy. Genetic and lysosomal modulators targeting LRRK2 and GBA represented nearly 25% of ongoing trials, showing consistent target engagement and favorable tolerability. Mitochondrial enhancers and anti-inflammatory agents demonstrated neuroprotective signals in preclinical models and early clinical phases. Regenerative approaches, including gene therapy and stem cell transplantation, were evaluated in fewer but rapidly expanding early-phase studies, with initial evidence of feasibility and biological activity.

Conclusion: Emerging disease-modifying therapies reflect a decisive shift toward mechanism-based intervention in Parkinson's disease. Although most strategies remain in early clinical development, accumulating quantitative and biological evidence supports their potential, particularly when applied early and guided by biomarkers and precision medicine frameworks.

Keywords: Alpha-Synuclein, Disease Progression, Neurodegenerative Diseases, Neuroprotection, Parkinson Disease, Precision Medicine, Regenerative Medicine.

INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder that imposes a substantial and growing burden on individuals, families, and healthcare systems worldwide. Clinically, it is defined by cardinal motor features—bradykinesia, rigidity, resting tremor, and postural instability—accompanied by a wide spectrum of non-motor manifestations such as autonomic dysfunction, sleep disturbances, affective disorders, and cognitive decline (1,2). These non-motor symptoms often emerge early, progress independently of motor impairment, and significantly compromise quality of life, underscoring that PD is a multisystem disorder rather than a purely dopaminergic motor disease. At the neuropathological level, PD is primarily driven by the progressive degeneration of dopaminergic neurons within the substantia nigra pars compacta, leading to dopamine depletion in the striatum and subsequent motor dysfunction (3). However, neuronal loss alone does not fully explain disease onset or progression. Hallmark pathological features include the accumulation of mis-folded α-synuclein in the form of Lewy bodies and Lewy neurites, widespread mitochondrial and lysosomal dysfunction, impairment of protein homeostasis, and a complex neuroinflammatory response that can be both protective and detrimental depending on disease stage and context (4,5). These interlinked processes suggest that PD arises from a convergence of molecular and cellular disturbances that extend far beyond dopamine deficiency. Current pharmacological management remains largely symptomatic. Levodopa, dopamine agonists, monoamine oxidase-B inhibitors, and catechol-O-methyltransferase inhibitors effectively alleviate motor symptoms by compensating for dopaminergic loss, particularly in early disease. Nevertheless, these therapies do not meaningfully alter the underlying neurodegenerative process (6,7).

As the disease advances, many patients develop motor fluctuations, dyskinesias, and progressive non-motor complications, eventually leading to functional decline despite optimized symptomatic treatment. This persistent progression highlights a critical unmet need in PD care: therapies capable of modifying the disease course rather than merely masking its clinical manifestations. In response to this therapeutic gap, increasing attention has shifted toward disease-modifying treatments (DMTs), particularly in the early stages of PD when viable neuronal networks may still be preserved. DMT strategies aim to slow, halt, or potentially reverse neurodegeneration by targeting upstream pathogenic mechanisms, including inhibition of α-synuclein aggregation, restoration of mitochondrial bioenergetics, modulation of maladaptive neuroinflammation, enhancement of lysosomal and proteostatic pathways, and correction of genetic or molecular vulnerabilities (8-10). Advances in molecular neuroscience, biomarker development, and precision medicine have further accelerated this shift, enabling more rational target selection and patient stratification. Against this background, the central question driving contemporary PD research is whether early intervention with mechanism-based therapies can meaningfully alter the natural history of the disease. Accordingly, the objective of this narrative review is to critically examine the key pathogenic mechanisms underlying early Parkinson's disease and to synthesize current preclinical and clinical evidence on emerging disease-modifying therapies, with the aim of evaluating their biological rationale, translational potential, and the challenges that must be addressed to move from symptomatic management toward true neuroprotection and restoration.

METHODS

A comprehensive narrative review methodology was employed to synthesize and critically appraise emerging disease-modifying treatments (DMTs) for early Parkinson's disease (PD), with a specific focus on interventions designed to slow or modify neurodegenerative processes rather than provide symptomatic relief. This approach was selected to allow integration of heterogeneous evidence derived from both preclinical experimental studies and early- to late-phase clinical trials, which is appropriate given the evolving and exploratory nature of disease-modifying research in PD. A systematic literature search was conducted across PubMed, Scopus, and ClinicalTrials.gov to identify relevant publications and registered trials. The search encompassed English-language articles published between January 2015 and September 2025 to ensure contemporary relevance. A structured combination of Medical Subject Headings (MeSH) terms and free-text keywords was applied using Boolean operators, including but not limited to "Parkinson's disease" AND "disease-modifying treatment," "α-synuclein immunotherapy," "LRRK2 inhibitors," "mitochondrial dysfunction," "neuroinflammation," "gene therapy," and "stem cell transplantation." To minimize the risk of publication omission, the reference lists of key narrative reviews, systematic reviews, and meta-analyses were manually screened to identify additional eligible studies not captured by the initial database search (4). Studies were considered eligible for inclusion if they investigated pharmacological, biological,

or advanced therapeutic strategies aimed at modifying disease progression in early-stage PD, either in validated preclinical models or in human clinical trials. Eligible studies were required to target one or more core pathogenic mechanisms implicated in PD, including α-synuclein aggregation, mitochondrial or lysosomal dysfunction, neuroinflammatory pathways, or genetic modulation. Only peer-reviewed publications and studies formally registered on ClinicalTrials.gov were included to ensure scientific rigor and transparency. Exclusion criteria comprised case reports, conference abstracts, editorials, and non-peer-reviewed commentaries, as well as studies focused exclusively on symptomatic management or advanced-stage Parkinson's disease. Publications released prior to 2015 were excluded to maintain methodological and translational relevance.

Data extraction was performed manually by reviewing full-text articles of all eligible studies. Extracted variables included authorship, year of publication, therapeutic agent or intervention, proposed mechanism of action, experimental model or clinical trial phase, key outcomes, and reported safety or efficacy signals. Given the narrative nature of the review, no formal quantitative meta-analysis or statistical pooling was undertaken. Instead, findings were synthesized qualitatively and organized thematically according to therapeutic strategy, including α-synuclein-targeted immunotherapies and genetic approaches, enzymatic modulators such as LRRK2 and GBA-related therapies, mitochondrial and neuroprotective enhancers, anti-inflammatory and trophic factor-based interventions, and adjunctive regenerative or microbiome-oriented approaches. Greater interpretive weight was assigned to high-impact studies and ongoing or completed clinical trials to enhance clinical and translational relevance (11). As this study was based exclusively on previously published literature and publicly available clinical trial registries, it did not involve direct human participation, patient-level data collection, or experimental intervention. Consequently, formal institutional review board or ethical committee approval and informed consent procedures were not required. Nevertheless, all included clinical trials were required to have documented ethical approval and informed consent as part of their original study protocols, in accordance with international research ethics standards.

Pathophysiological Mechanisms in Parkinson's Disease:

Parkinson's disease (PD) arises from a multifactorial interplay between molecular, genetic, and environmental influences that collectively drive progressive dopaminergic neurodegeneration and widespread neural dysfunction. Contemporary evidence converges on a set of interrelated pathogenic mechanisms—including protein misfolding, mitochondrial impairment, neuroinflammation, genetic dysregulation, and oxidative stress—that do not act in isolation but instead reinforce one another across disease stages. This interconnected biology explains why purely dopaminergic replacement strategies fail to alter disease trajectory and underscores the scientific rationale for disease-modifying interventions aimed at upstream processes rather than downstream symptom control.

α-Synuclein Aggregation and Lewy Body Pathology:

Misfolding and aggregation of α-synuclein represent a central and unifying hallmark of PD pathology. Accumulating evidence indicates that oligomeric and fibrillar α-synuclein species disrupt synaptic integrity, impair axonal transport, and propagate pathology through interconnected neuronal networks in a prion-like manner (12). Genetic mutations in SNCA and age-related or environmentally induced failures in proteostasis amplify this burden, resulting in Lewy bodies and Lewy neurites that correlate with both motor and non-motor symptom progression. While multiple studies agree on the pathogenic role of α-synuclein, controversy persists regarding which molecular species are most toxic and at what disease stage intervention would be most effective, highlighting a key translational challenge for disease-modifying therapies.

Mitochondrial Dysfunction:

Mitochondrial failure is widely recognized as a major driver of dopaminergic neuronal vulnerability in PD. Deficits in oxidative phosphorylation, excessive generation of reactive oxygen species, and impaired mitophagy collectively compromise neuronal energy homeostasis (13). Mutations in PINK1 and PRKN genes have provided strong genetic validation for mitochondrial pathways, demonstrating how defective quality control allows damaged mitochondria to accumulate and accelerate neuronal loss. Although mitochondrial dysfunction is consistently observed across sporadic and familial PD, variability in clinical trial outcomes targeting bioenergetics suggests that mitochondrial impairment may represent both a primary trigger and a secondary amplifier of disease, depending on individual disease context.

Neuroinflammation and Microglial Activation:

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Chronic neuroinflammation has emerged as a critical contributor to PD progression rather than a mere epiphenomenon. Activated microglia and astrocytes release pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, alongside nitric oxide and other neurotoxic mediators that exacerbate neuronal injury (14). α-Synuclein aggregates further stimulate innate immune receptors, establishing a self-perpetuating inflammatory loop. While preclinical studies consistently demonstrate neuroprotection with suppression of microglial activation, human data remain heterogeneous, reflecting differences in timing, target specificity, and the dual protective–toxic roles of inflammation across disease stages.

Genetic and Molecular Factors:

Genetic discoveries have reshaped understanding of PD by identifying convergent molecular pathways underlying both familial and sporadic forms of the disease. Mutations in LRRK2, GBA, PINK1, PRKN, and DJ-1 implicate lysosomal dysfunction, kinase hyperactivity, and impaired cellular stress responses as central mechanisms (14). Notably, LRRK2 kinase overactivation disrupts autophagy and vesicular trafficking, whereas reduced glucocerebrosidase activity in GBA mutation carriers promotes α-synuclein accumulation. These insights have catalyzed precision-medicine approaches, although phenotypic variability among mutation carriers continues to complicate patient stratification and trial design.

Oxidative Stress and Proteostasis Dysfunction:

Dopaminergic neurons are intrinsically susceptible to oxidative stress due to dopamine metabolism, elevated iron content, and high energetic demands. Excessive oxidative burden, coupled with dysfunction of the ubiquitin–proteasome system and autophagy–lysosome pathways, leads to accumulation of damaged proteins and organelles (15). While antioxidant strategies have shown robust neuroprotection in experimental models, clinical translation has been inconsistent, raising questions about bioavailability, target engagement, and whether redox imbalance is a driver or downstream consequence of neurodegeneration.

Emerging Disease-Modifying Therapeutic Strategies:

Advances in molecular neuroscience have catalyzed a paradigm shift from symptomatic management toward therapies designed to alter the biological course of PD. Rather than focusing solely on dopamine replacement, emerging disease-modifying strategies aim to preserve neuronal integrity, restore cellular homeostasis, and interrupt pathogenic cascades at multiple levels. However, translating mechanistic promise into clinically meaningful outcomes remains challenging, particularly in identifying optimal intervention windows and sensitive biomarkers of disease modification (16).

Immunotherapies Targeting α-Synuclein:

Both passive and active immunotherapeutic approaches seek to neutralize extracellular α-synuclein and limit its propagation between neurons. Monoclonal antibodies such as prasinezumab and cinpanemab demonstrated acceptable safety and modest slowing of motor progression in Phase II trials, although clear disease-modifying efficacy was not consistently achieved (13). Active vaccines, including AFFITOPE PD01A and PD03A, offer sustained antibody responses but remain in early clinical evaluation. Collectively, these studies suggest biological activity but highlight ongoing debate regarding target selection, dosing, and the necessity of very early intervention guided by biomarkers.

LRRK2 and GBA Modulators:

Targeting genetically validated pathways has emerged as one of the most rational approaches to disease modification in PD. LRRK2 inhibitors such as DNL201 and DNL151 effectively reduce pathogenic kinase activity and normalize downstream signaling in early-phase trials, supporting continued development (17). Similarly, GBA modulators including ambroxol enhance lysosomal glucocerebrosidase activity and facilitate α-synuclein clearance, with preliminary studies reporting improvements in motor and cognitive biomarkers (10). Despite these encouraging findings, long-term clinical benefit and applicability beyond genetically defined subgroups remain open questions.

Mitochondrial Enhancers and Bioenergetic Modulators:

Therapies aimed at restoring mitochondrial function represent a complementary strategy across genetic and sporadic PD. Agents such as nilotinib enhance mitophagy and dopamine turnover, with early trials suggesting biomarker-based neuroprotective effects (18). Nutraceutical and metabolic modulators including ursodeoxycholic acid, nicotinamide riboside, and coenzyme Q10 analogues have shown variable efficacy, reflecting ongoing uncertainty regarding optimal targets within mitochondrial pathways.

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Anti-Inflammatory and Neuroprotective Agents:

Modulation of neuroinflammation seeks to attenuate microglial-driven neurotoxicity while preserving physiological immune surveillance. Small-molecule inhibitors targeting cytokine release, NLRP3 inflammasome activation, and microglial signaling have demonstrated anti-inflammatory effects in preclinical and early clinical studies (19). However, inconsistent clinical outcomes highlight the complexity of immune responses in PD and the risk of oversuppressing protective inflammatory mechanisms.

Neurotrophic Factors and Gene Therapy:

Neurotrophic and gene-based therapies aim to enhance neuronal survival and restore dopaminergic function. Although early trials with glial cell line-derived neurotrophic factor yielded mixed results due to delivery limitations, advances in viral vectors and intracerebral infusion techniques have renewed interest. Gene therapies delivering aromatic L-amino acid decarboxylase have shown improvements in dopamine synthesis and motor outcomes, suggesting potential adjunctive disease-modifying effects.

Stem-Cell-Based Regenerative Approaches:

Cell replacement strategies using induced pluripotent stem cell-derived dopaminergic progenitors offer the prospect of restoring lost neuronal populations. Early human trials report promising graft survival and functional integration, yet challenges related to long-term safety, immune compatibility, and disease propagation into transplanted cells persist (20). These approaches are therefore viewed as complementary rather than standalone solutions at present.

Gut Microbiome Modulation:

Growing evidence implicates the gut–brain axis in PD pathogenesis, with microbial dysbiosis influencing systemic inflammation and α-synuclein aggregation (21). Interventions such as probiotics, prebiotics, and fecal microbiota transplantation are under exploratory investigation. While clinical evidence remains preliminary, microbiome modulation represents a novel adjunctive avenue that may synergize with central neuroprotective strategies.

Synthesis and Controversies:

Across themes, the literature supports a multifactorial model of PD in which overlapping pathogenic mechanisms require combinatorial or personalized therapeutic approaches. Major gaps remain in biomarker validation, patient stratification, and determination of optimal intervention timing. Collectively, current evidence suggests that no single strategy is likely sufficient, reinforcing the need for integrated, mechanism-based disease-modifying frameworks in early Parkinson's disease.

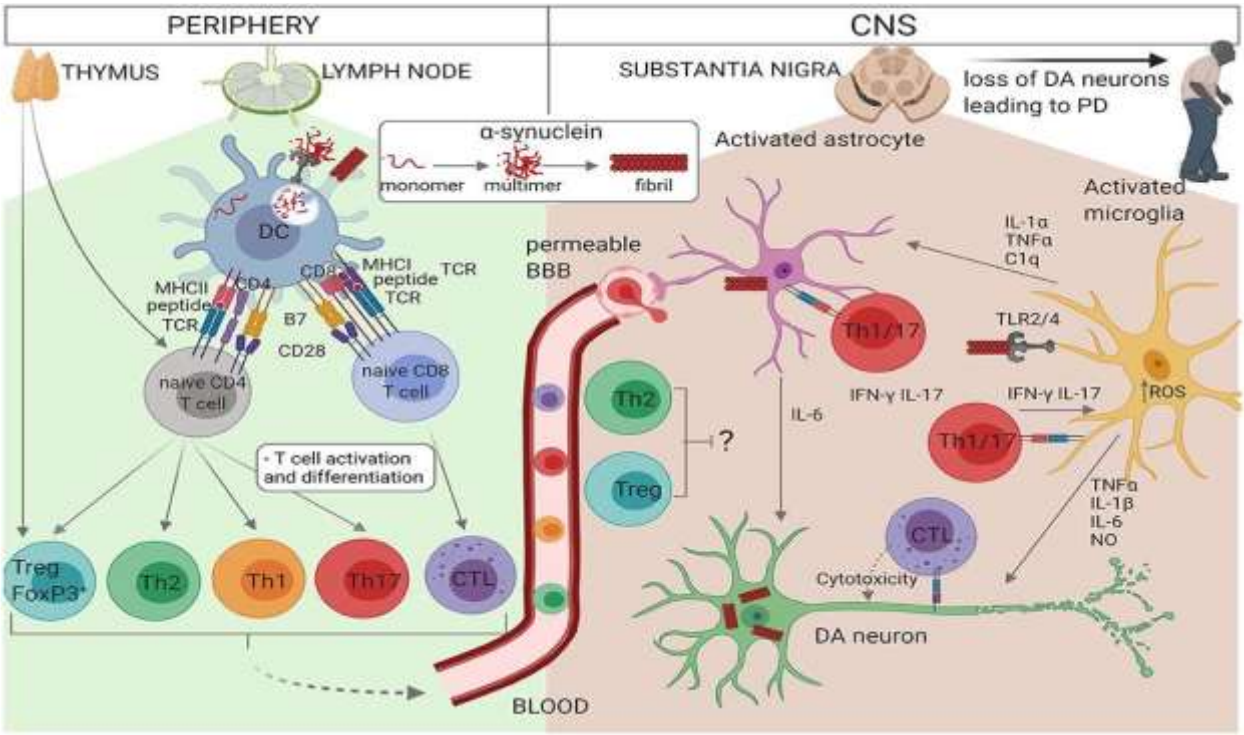
Table 1: Major Pathophysiological Mechanisms and Corresponding Therapeutic Targets in Parkinson's Disease

Mechanism	Pathological Process	Representative Molecular Targets	Potential Therapeutic Approaches
α-Synuclein Aggregation	Misfolding and prion-like propagation	α-Synuclein monomers/oligomers; SNCA gene	Passive/active immunotherapy (prasinezumab, BIIB054), aggregation inhibitors
Mitochondrial Dysfunction	Impaired energy metabolism and mitophagy	PINK1, PRKN, Complex I enzymes	Mitochondrial enhancers (nilotinib, coenzyme Q10 analogs)
Neuroinflammation	Microglial activation and cytokine release	TNF-α, IL-1β, NLRP3 inflammasome	Anti-inflammatory agents (NSAID analogs, minocycline derivatives)
Genetic Dysregulation	Mutations in LRRK2 and GBA	LRRK2 kinase, GCase enzyme	LRRK2 inhibitors (DNL201), GBA modulators (ambroxol)

Mechanism	Pathological Process	Representative Molecular Targets	Potential Therapeutic Approaches
Oxidative Stress	ROS overproduction, proteostasis failure	NRF2, DJ-1, UPS/autophagy proteins	Antioxidants, NRF2 activators, proteostasis regulators

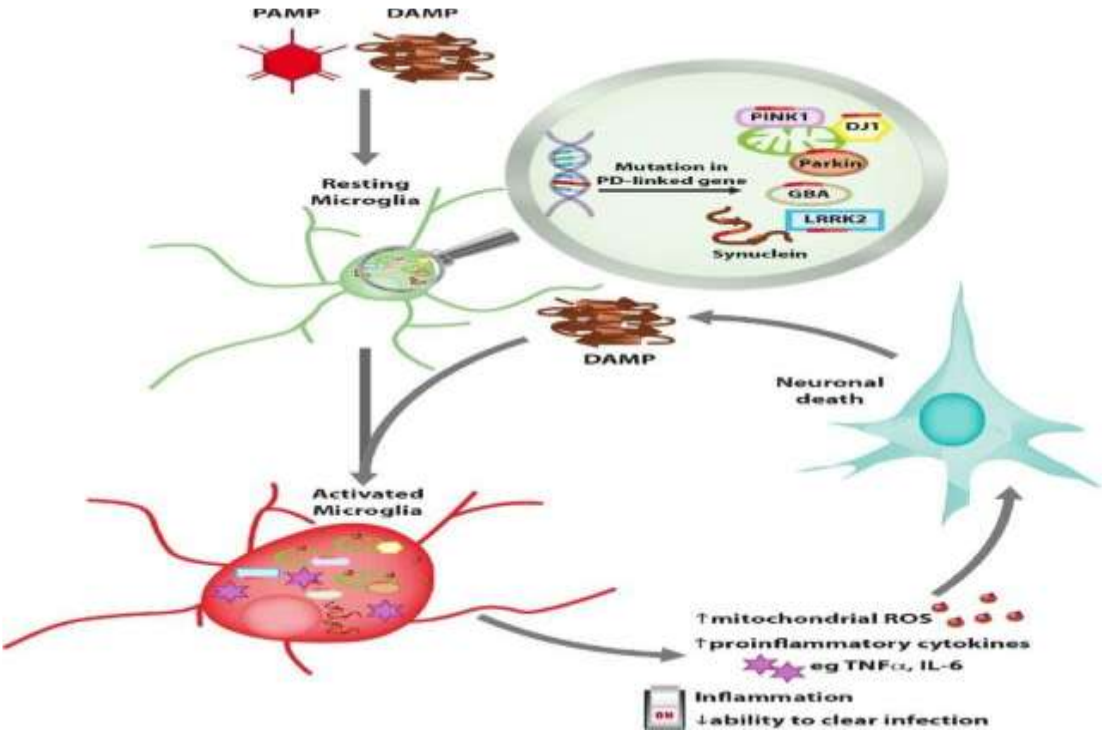
Table 2: Summary of Emerging Disease-Modifying Therapies in Early Parkinson's Disease.

Therapeutic Class	Representative Agents	Mechanism of Action	Development Stage	Key Findings (2018– 2025)
α-Synuclein Immunotherapy	Prasinezumab, BIIB054, PD01A	Neutralization of extracellular α-synuclein	Phase II completed	Safe; modest motor benefit (PASADENA trial)
LRRK2 Modulators	DNL201, DNL151	Inhibit LRRK2 kinase hyperactivity	Phase II ongoing	Target engagement; reduced kinase biomarkers
GBA Modulators	Ambroxol, GZ/SAR402671	Enhance GCase activity, improve lysosomal function	Phase II–III	Improved motor/cognitive markers
Mitochondrial Enhancers	Nilotinib, UDCA, CoQ10 analogs	Boost mitophagy and oxidative stress resilience	Phase II	Biomarker improvement; symptomatic benefit
Anti-Inflammatory Agents	Minocycline derivatives, NLRP3 inhibitors	Suppress microglial cytokine release	Preclinical– Phase I	Reduced inflammatory biomarkers
Neurotrophic Gene Therapy	AAV2-GDNF, AAV2-AADC	Promote dopaminergic survival and dopamine synthesis	Phase I–II	Safe; improved motor UPDRS scores
Stem-Cell Transplantation	iPSC-derived dopaminergic neurons	Neuronal replacement	Early clinical	Promising graft survival, needs long-term data
Microbiome Modulation	Probiotics, FMT	Regulategut–brain axis and inflammation	Exploratory	Preclinical evidence of neuroprotection



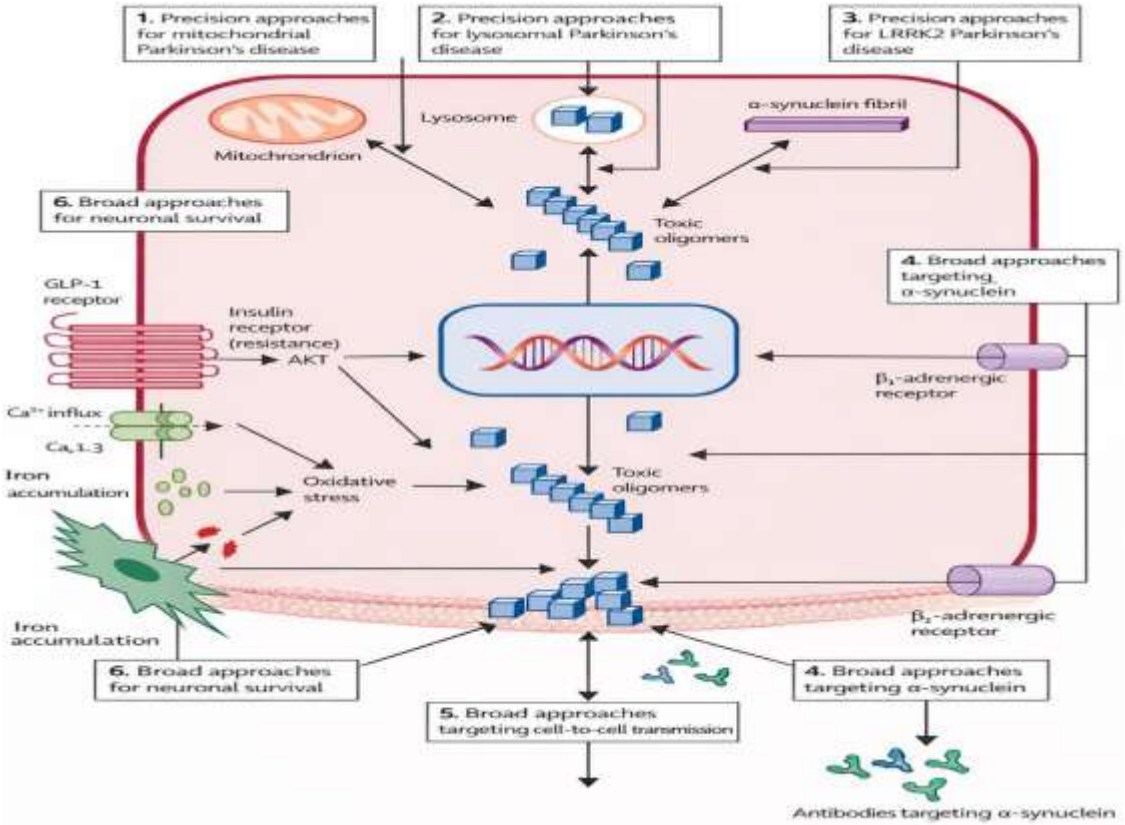
Schematic Representation of The Interactions Between Glial Cells and Immune Cells in PD

Figure 1 Schematic Representation of The Interactions Between Glial Cells and Immune Cells in PD



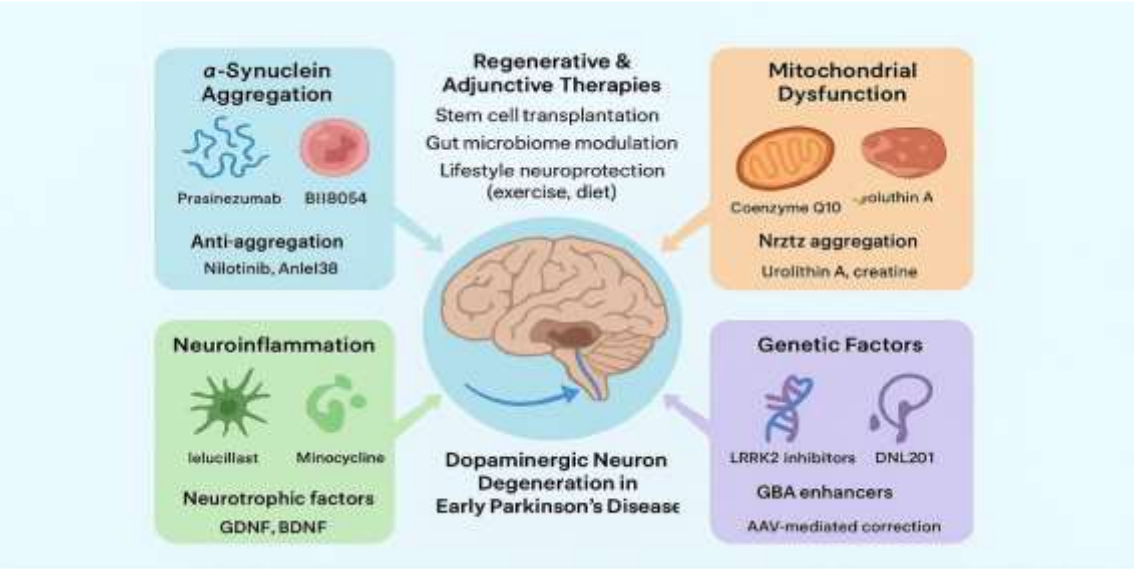
Inflammation is Genetically Implicated in Parkinson's Disease

Figure 2 Inflammation is Genetically Implicated in Parkinson's Disease



Progress Towards Therapies for Disease Modification in Parkinson's Disease

Figure 3 Progress Towards Therapies for disease Modification in Parkinson's Disease



Mechanistic Overview of Emerging Disease-Modifying Strategies for Early Parkinson's Disease

Figure 4 Mechanistic Overview of Emerging Disease-Modifying Strategies for Early Parkinson's Disease

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DISCUSSION

This narrative review examined the evolving landscape of disease-modifying therapies (DMTs) in Parkinson's disease (PD) and interpreted current evidence in the context of established and emerging pathogenic frameworks. Collectively, the findings reflected a clear paradigm shift from purely symptomatic management toward mechanistic, neurodegeneration-oriented strategies. Advances in molecular neuroscience over the last decade have substantially clarified the roles of α-synuclein aggregation, mitochondrial dysfunction, neuroinflammation, lysosomal impairment, and genetic susceptibility, thereby enabling the rational development of targeted interventions (9). However, despite strong biological plausibility and encouraging preclinical data, translation into consistent clinical benefit remained limited, highlighting the complexity of modifying disease trajectory in a heterogeneous neurodegenerative disorder. Immunotherapies directed against α-synuclein represented one of the most extensively studied approaches. Clinical trials demonstrated acceptable safety profiles and evidence of target engagement, with some biomarker-level improvements observed. Nevertheless, the lack of robust or sustained improvement in motor and functional outcomes suggested that intervention may have occurred too late in the disease course, when irreversible neuronal loss had already accumulated (10). These findings were consistent with earlier literature indicating that α-synuclein pathology likely begins years before clinical diagnosis, thereby limiting the therapeutic window for disease modification using aggregation-targeted strategies alone. The implication is not a failure of the biological target per se, but rather a need for earlier identification, improved stratification, and more sensitive outcome measures.

Genetic pathway modulation emerged as a relative strength within the current DMT pipeline. Therapies targeting LRRK2 kinase hyperactivity and GBA-related lysosomal dysfunction showed favorable pharmacokinetic, pharmacodynamic, and mechanistic signals, particularly in genetically defined subgroups. Improvements in lysosomal activity and α-synuclein clearance suggested that precision medicine approaches could yield more consistent effects than broadly applied therapies (11,12). At the same time, the limited proportion of patients carrying these mutations constrained generalizability, emphasizing the need to determine whether downstream pathway modulation can benefit idiopathic PD populations with similar molecular signatures. Mitochondrial enhancers and bioenergetic modulators demonstrated moderate promise, especially in improving cellular resilience and reducing oxidative stress. Agents such as nilotinib and ursodeoxycholic acid showed biomarker-based neuroprotective signals, supporting the concept that mitochondrial dysfunction represents both a driver and amplifier of neurodegeneration (13). However, variable clinical outcomes across studies underscored ongoing uncertainty regarding optimal targets, dosing, and combination strategies. These therapies appeared more plausible as adjunctive components within multimodal regimens rather than as standalone disease-modifying agents. Neuroinflammation-targeted strategies highlighted an important area of debate. Substantial experimental evidence supported the role of microglial activation and inflammasome signaling in disease progression, and pharmacological suppression of these pathways reduced neurotoxicity in preclinical models (14). In clinical contexts, however, balancing neuroprotection against systemic immune suppression remained challenging. The mixed outcomes observed to date suggested that timing, target specificity, and disease stage were critical determinants of therapeutic success, rather than blanket anti-inflammatory suppression.

Regenerative approaches, including gene therapy and stem-cell-based interventions, represented the most ambitious attempts to address neuronal loss directly. Gene-based delivery of neurotrophic factors and dopamine-synthesizing enzymes demonstrated safety and modest functional benefits, while early trials of induced pluripotent stem cell-derived dopaminergic neurons showed encouraging graft survival and integration (15,16). Despite their conceptual appeal, these strategies faced substantial technical, ethical, and logistical barriers, including delivery challenges, long-term safety, immune compatibility, and scalability. Consequently, regenerative therapies were best viewed as complementary to neuroprotective strategies rather than definitive solutions. Several overarching limitations emerged across the reviewed evidence. Parkinson's disease heterogeneity—spanning genetic background, molecular pathology, symptom profile, and progression rate—complicated trial design and diluted treatment effects (17). Outcome assessment remained heavily reliant on clinical scales that primarily captured symptomatic change rather than neurobiological progression, thereby limiting sensitivity to disease modification (18). Although advances in molecular imaging, α-synuclein seeding assays, and neurofilament light chain measurement offered promise, these biomarkers required further validation before routine implementation. Timing of intervention represented a critical and recurring constraint. By the onset of classical motor symptoms, substantial dopaminergic neuronal loss had already occurred, reducing the likelihood of meaningful neuroprotection (19). Evidence increasingly supported the concept that prodromal intervention—guided by markers such as REM sleep behavior disorder, hyposmia, or subtle cognitive changes—may offer a more effective therapeutic window. Additionally, drug delivery across the blood–brain barrier remained a significant obstacle, particularly for large molecules and gene therapies, prompting exploration of novel delivery platforms including targeted transport systems, focused ultrasound, and exosome-based vectors (20).

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Despite these challenges, the overall strength of the reviewed literature lay in its convergence toward a systems-level understanding of PD. The cumulative evidence suggested that targeting a single pathogenic pathway was unlikely to yield durable disease modification. Instead, future progress appeared most plausible through multimodal and combinatorial strategies that simultaneously addressed protein aggregation, mitochondrial vulnerability, neuroinflammation, and peripheral contributors such as the gut–brain axis (21). This integrative approach aligned with emerging precision medicine frameworks, in which treatment selection would be guided by multi-omics profiling, advanced biomarker interpretation, and continuous digital monitoring of disease dynamics (22). In summary, the reviewed evidence indicated that while true disease modification in Parkinson's disease had not yet been definitively achieved, substantial progress had been made in defining actionable biological targets and therapeutic frameworks. Strengths of the current research included improved mechanistic clarity, expanding biomarker discovery, and early validation of precision-medicine concepts. Limitations centered on disease heterogeneity, late intervention, and outcome measurement constraints. Future research would benefit from earlier patient identification, standardized biomarker-driven trial designs, and combination therapies tailored to individual disease biology, ultimately supporting a transition from symptomatic treatment toward prevention and long-term disease control.

CONCLUSION

This narrative review concludes that the therapeutic focus in Parkinson's disease is progressively shifting from symptomatic control toward strategies aimed at modifying the underlying neurodegenerative process. The accumulated evidence supports the concept that Parkinson's disease is biologically multifactorial, involving protein aggregation, mitochondrial dysfunction, neuroinflammation, genetic susceptibility, and systemic contributors, which collectively limit the effectiveness of single-target therapies. Emerging disease-modifying approaches, including immunotherapies, genetic and lysosomal modulators, mitochondrial enhancers, anti-inflammatory agents, and regenerative strategies, demonstrate meaningful biological promise, particularly when applied early in the disease course. The findings underscore the critical importance of early and prodromal intervention, robust biomarker development, and precision-medicine frameworks to improve patient stratification and therapeutic responsiveness. Ultimately, the most impactful future strategies are likely to involve integrated, multimodal treatment paradigms that combine pharmacological, biological, and lifestyle-based interventions to preserve neuronal function and slow disease progression, moving Parkinson's care closer to prevention rather than late-stage management.

AUTHOR CONTRIBUTIONS

Author	Contribution
Umbreen Gull*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Faziyya Latif	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Rida Javed	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Saba Sonia	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Ayisha khalid	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published

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Author	Contribution
Abdul Rehman	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Farah Zafar	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Faiza Irshad	Writing - Review & Editing, Assistance with Data Curation

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