REVIEW PAPER

Pleiotropic Neuroprotection of GLP-1 Receptor Agonists:From Synaptic Plasticity to Autophagy-Mediated Proteostasis in Neurodegeneration

Divyanshu Tripathi[1], Dr. Nisha Sharma[1], Ritesh Ajay Kumar Nayak[1], Ananya Maurya[1], Vanshika Shukla[2], Ajay Kumar Singh[1]*

[1] School of Pharmaceutical Sciences, Chhatrapati Shahu Ji Maharaj University, Kanpur 208024, Uttar Pradesh, India
[2] Independent affiliation
Divyanshu Tripathi[1] email: divyanshu26092000@gmail.com
ORCID: 0009-0001-0465-8817
Dr. Nisha Sharma[1] email: nishasharma@csjmu.ac.in
Ritesh Ajay Kumar Nayak[1] email: rnnayak952@gmail.com
Ananya Maurya[1] email: ananya224143@gmail.com
Vanshika Shukla[2] email: shukla.vr1108@gmail.com
***Corresponding Author** email: ajayks09451244476@gmail.com
*ORCID: 0000-0001-5125-6864

ABSTRACT
Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) - initially launched for the treatment of type 2 diabetes mellitus and obesity - are a class of promising neuroprotective drugs with multi-faceted mechanisms of action beyond glucose control. In this comprehensive review, we summarise the rapidly growing preclinical and clinical data showing that GLP-1 RAs have pleiotropic neuroprotective effects such as promoting synaptic plasticity, reducing neuroinflammation, restoring mitochondrial function, inhibiting oxidative stress, enhancing adult neurogenesis, and - most excitingly - regulating autophagy-mediated protein homeostasis (proteostasis) via mTORC1/AMPK/Beclin-1 signalling pathways. We explore the molecular basis of GLP-1 receptor (GLP-1R) agonism in the brain, describe intrinsic signalling cascades via cAMP/PKA/CREB, PI3K/Akt/GSK-3β and NF-κB pathways, and draw their connections to the hallmark aggregating proteins - amyloid beta (Aβ) and tau in Alzheimer's disease (AD), alpha-synuclein (α-syn) in Parkinson's disease (PD), TDP-43/FUS in Amyotrophic lateral sclerosis (ALS) and polyglutamine repeats in Huntington's disease (HD). Clinical evidence, such as the EXENATIDE-PD randomised controlled trial, ELAD, LIRAFLOW, SELECT sub-analysis and several CVOT post-hoc cognitive studies, are evaluated. We also discuss the penetration and variable CNS bioavailabilities of different agents, the relationship with brain insulin resistance, and the revolutionary promise of new dual/triple incretin receptor agonists. We flag the remaining questions of dosing, patient selection, biomarker discovery and mechanistic knowledge gaps, and chart a course for future translational research.

Keywords: GLP-1 receptor agonists; neurodegeneration; autophagy; synaptic plasticity; proteostasis; Alzheimer's disease; Parkinson's disease; semaglutide; liraglutide; mTORC1; neuroinflammation; BDNF; mitophagy; incretin therapy
How to cite this article: Tripathi D, Sharma N, Nayak RAK, Maurya A, Shukla V, Singh AK. Pleiotropic Neuroprotection of GLP-1 Receptor Agonists: From Synaptic Plasticity to Autophagy-Mediated Proteostasis in Neurodegeneration. Int J Drug Deliv Technol. 2026;16(48s): 64-80. DOI: 10.25258/ijddt.16.48s.8

1. INTRODUCTION

Neurodegenerative diseases represent one of the most formidable challenges confronting modern medicine, collectively affecting over 50 million people worldwide and projected to triple in prevalence by 2050 as global populations age (GBD 2019 Dementia Collaborators, 2022). After decades of concerted effort, there remains an unmet need for disease-modifying therapies, with most drugs currently offering symptomatic relief but not slowing or reversing the progression of neuropathological changes.In this therapeutic landscape, the repurposing of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represents one of the most exciting new paradigms in neurodegenerative disease research. Originally approved for the treatment of type 2 diabetes mellitus (T2DM) and obesity, drugs such as exenatide, liraglutide and semaglutide have shown, across a broad range of experimental and clinical models, an astonishing ability to protect neurons via mechanisms that appear to be largely separate from their metabolic effects (Athauda and Foltynie, 2016; Holscher, 2018). The rationale for neuroprotective effects mediated by GLP-1 RAs is based on a number of observations. First, GLP-1 receptors (GLP-1Rs) are widely expressed across the central nervous system (CNS), with highest levels found in the hypothalamus, hippocampus, cortex, brainstem and substantia nigra - areas of the brain that are vital to cognitive and motor function (Merchenthaler et al., 1999; Hamilton and Holscher, 2009). Second, the overlap between metabolic dysfunction and neurodegenerative disease - with the near-universal observation of brain insulin resistance in Alzheimer's disease, suggesting the term 'type 3 diabetes' - offers a mechanistic basis for the therapeutic

use of incretins (de la Monte and Wands, 2008; Bomfim et al., 2012). Third, large-scale cardiovascular disease outcome trials (CVOTs) involving tens of thousands of patients have produced persuasive post-hoc and sub-group analyses showing significant decreases in rates of dementia, cognitive deterioration and Parkinsonian events in patients receiving GLP-1 RAs (Norgaard et al., 2022; Batista et al., 2024).Key to the burgeoning neuroprotective role of GLP-1 RAs is their ability to regulate autophagy, the intracellular proteolytic pathway that comprises a major line of defence against the pathogenic protein aggregation that is the defining feature of all major neurodegenerative diseases. By simultaneously inhibiting mechanistic target of rapamycin complex 1 (mTORC1) and activating AMP-activated protein kinase (AMPK), GLP-1 RAs trigger autophagosome formation, enhance lysosomal function through nuclear translocation of the transcription factor EB (TFEB) and restore chaperone-mediated autophagy (CMA) flux, thereby creating a proteostasis competent environment for the turnover of amyloid β (Aβ), tau, α-synuclein, TDP-43 and polyglutamine-expanded proteins (Jiang et al., 2019; Yan et al., 2019; Lim et al., 2020).This review offers a holistic, mechanism-based overview of GLP-1 RA neuroprotection, with a focus on the key mechanisms of synaptic plasticity, neuroinflammation, proteostasis via autophagy, mitochondrial dysfunction, and oxidative stress, followed by disease-specific evidence for the major neurodegenerative diseases, critical review of clinical trial data, and future research directions(Arya et al., 2026).

2. GLP-1 BIOLOGY AND CNS EXPRESSION OF GLP-1 RECEPTORS

2.1 Synthesis, Secretion, and Peripheral Actions

Glucagon-like peptide-1 (GLP-1) is a 30 amino acid incretin hormone, generated via post-translational cleavage of proglucagon by prohormone convertase 1/3 (PC1/3) in gut L-cells and, importantly for the brain, by PC2 in nucleus tractus solitarius (NTS) neurons of the brainstem (Holst, 2007). The main active species are GLP-1(7-36)amide (major circulating form) and GLP-1(7-37). Physiological actions of peripheral GLP-1 are mediated by its interaction with the GLP-1R on beta-cells of the pancreas, which drives glucose-dependent insulin secretion, suppresses glucagon secretion, slows gastric emptying and reduces appetite; the latter two are ultimately responsible for post-prandial glucose control (Drucker, 2018).Endogenous GLP-1 has a short half-life of ~2 minutes due to rapid degradation of the amino (His-Ala) terminus by dipeptidyl peptidase-4 (DPP-4) and renal excretion. GLP-1 RAs avoid this by incorporating adaptations (C18 fatty acid acylation of liraglutide and semaglutide to allow albumin binding, exenatide shares sequence homology with exendin-4 and so is resistant to DPP-4, Fc fusion of dulaglutide increases its hydrodynamic radius) to increase the half-life from minutes to days or weeks (Lau et al., 2015)(Chaubey, Rastogi & Srivastava, 2025).

2.2 CNS Distribution of GLP-1 Receptors

GLP-1Rs are class B G-protein-coupled receptors (GPCRs) that predominantly couple to Gαs proteins, leading to adenylyl cyclase activation and cyclic adenosine monophosphate (cAMP) production. Autoradiographic, in situ hybridisation and single-cell RNA sequencing techniques have demonstrated GLP-1R distribution across the CNS, including high concentrations in the hypothalamus (arcuate, paraventricular, lateral nuclei), hippocampus (CA1, CA3, dentate gyrus), prefrontal cortex, amygdala, cerebellum, brainstem NTS/dorsal motor nucleus of the vagus, and substantia nigra pars compacta (Merchenthaler et al., 1999; Cork et al., 2015; Jensen et al., 2018).The central nervous system (CNS) GLP-1 system is accessed via two anatomical pathways: (1) endocrine, in which GLP-1 RAs enter the brain via saturable and non-saturable transport across the blood-brain barrier (BBB) to the parenchymal neurons and glia; and (2) vagal afferent neurotransmission, in which portal and hepatic GLP-1Rs are activated to transmit signals via vagus nerve to the brainstem NTS nuclei, which then propagate centrally without BBB penetration. This dual route contributes to why even poorly CNS-penetrant drugs might have central nervous system effects (Krieger et al., 2016). Different GLP-1 RAs vary in BBB permeability. Liraglutide exhibits moderate BBB penetration, with concentrations in the hippocampus of 0.1-0.5% of the corresponding plasma levels in rodents, binding to neurons, astrocytes and microglia (Salameh et al., 2013)(Chaubey, Rastogi & Srivastava, 2026). Semaglutide, with its higher albumin binding and altered receptor pharmacology, seems to attain higher concentrations and has been measured in cerebrospinal fluid in rodents (Coskun et al., 2017). By contrast, higher-molecular-weight agents (dulaglutide and albiglutide) have low CNS penetration(Chaubey et al., 2026).

Table 1. GLP-1 Receptor Agonists in Clinical Use: Structure, Pharmacokinetics, and CNS Penetration

Agent	Structure	Half-life	Approved Indications	CNS Penetration Evidence
Exenatide	Exendin-4 analogue	2.4 h (BID)~2 weeks (QW)	T2DM	Limited; P-gp substrate

Agent	Structure	Half-life	Approved Indications	CNS Penetration Evidence
Liraglutide	Acylated GLP-1 (C18 FA)	~13 h	T2DM, Obesity, CVD risk reduction	Moderate; hypothalamus, brainstem, hippocampus
Semaglutide (SC)	Acylated GLP-1 (C18 FA diacid)	~7 days	T2DM, Obesity, CVD, HFpEF	Moderate–high; detected in CSF rodent models
Semaglutide (oral)	Same peptide + absorption enhancer	~7 days	T2DM	Systemic bioavailability ~1%
Dulaglutide	GLP-1 dimer-Fc fusion	~5 days	T2DM, CVD risk reduction	Low; large molecular weight
Tirzepatide	GIP/GLP-1 dual agonist	~5 days	T2DM, Obesity	Under investigation
Lixisenatide	Exendin-4 truncated	~3 h	T2DM (EU/Asia)	Limited data
Albiglutide	GLP-1-albumin fusion	~5 days	T2DM (discontinued)	Very low; large size

Abbreviations: T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease; HFpEF = heart failure with preserved ejection fraction; FA = fatty acid; P-gp = P-glycoprotein; CSF = cerebrospinal fluid; SC = subcutaneous.

3. GLP-1R INTRACELLULAR SIGNALLING IN NEURONS

3.1 cAMP/PKA/CREB Axis and Neurotrophic Support

Activation of the GLP-1R by GLP-1 RAs in neurons leads to activation of adenylyl cyclase via the Gαs subunit of the GLP-1R, resulting in production of cAMP, the universal second messenger for several effector pathways(Maurya et al., 2026). cAMP-mediated activation of protein kinase A (PKA) stimulates the transcription factor cAMP response element-binding protein (CREB) via phosphorylation of Ser133 to trigger the transcription of a number of pro-survival and plastic genes, such as brain-derived neurotrophic factor (BDNF), Bcl-2, survivin, and neuropeptide Y (Bhatt et al., 2013). The GLP-1R/cAMP/PKA/CREB signalling axis therefore represents a central neuroprotective transcriptional cascade activated by GLP-1 RAs.Brain-derived neurotrophic factor (BDNF) is induced by GLP-1R-mediated activation of CREB and activates TrkB receptors to elicit PI3K/Akt and MAPK/ERK1/2 signalling pathways that promote neuronal survival, synapse potentiation and adult neurogenesis. Importantly, BDNF is significantly decreased in AD, PD and HD brain regions, and the reactivation of BDNF signalling by GLP-1 RAs is an attractive neuroprotective pathway (Bhatt et al., 2013; During et al., 2003).

3.2 PI3K/Akt/GSK-3β Pathway: Brain Insulin Resistance Reversal

GLP-1R signalling also activates the insulin signalling pathway, independent of IRS-1, activating phosphoinositide 3-kinase (PI3K) and its downstream target Akt (protein kinase B). Akt phosphorylates and inhibits glycogen synthase kinase-3β (GSK-3β) at Ser9 - a key regulatory step because constitutively active GSK-3β is responsible for hyperphosphorylation of tau at a number of AD-relevant epitopes (Thr231, Ser396, Ser404) and plays a role in presenilin-1 dysfunction impacting Aβ production (Jope and Johnson, 2004).The Akt/GSK-3β pathway also activates mTORC1 via TSC2 phosphorylation, which would normally inhibit autophagy but in the case of GLP-1R activation, the major mTOR-suppressive signal comes from the cAMP/AMPK arm of the pathway and overcompensates the weak Akt-mTOR axis, resulting in a net activation of autophagy (Maiuri et al., 2009)(Napolitano, 2025).

3.3 NF-κB Suppression and Neuroinflammatory Attenuation

Activation of nuclear factor-kappa B (NF-κB) in microglia and astrocytes is a central driver of neuroinflammation in neurodegenerative diseases(Sharma et al., 2022). GLP-1 RAs suppress NF-κB activation through multiple converging mechanisms: PKA-mediated phosphorylation of the p65 subunit reducing its transcriptional potency; cAMP-dependent suppression of TNF receptor-associated factor 6 (TRAF6); and SIRT1/PGC-1α-mediated epigenetic repression of inflammatory gene loci (Lim et al., 2020; Holscher, 2014). Downstream consequences include reduced expression of interleukin (IL)-1β, IL-6, IL-18,

tumour necrosis factor-α (TNF-α), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) — collectively attenuating the neuroinflammatory milieu that accelerates neurodegeneration.

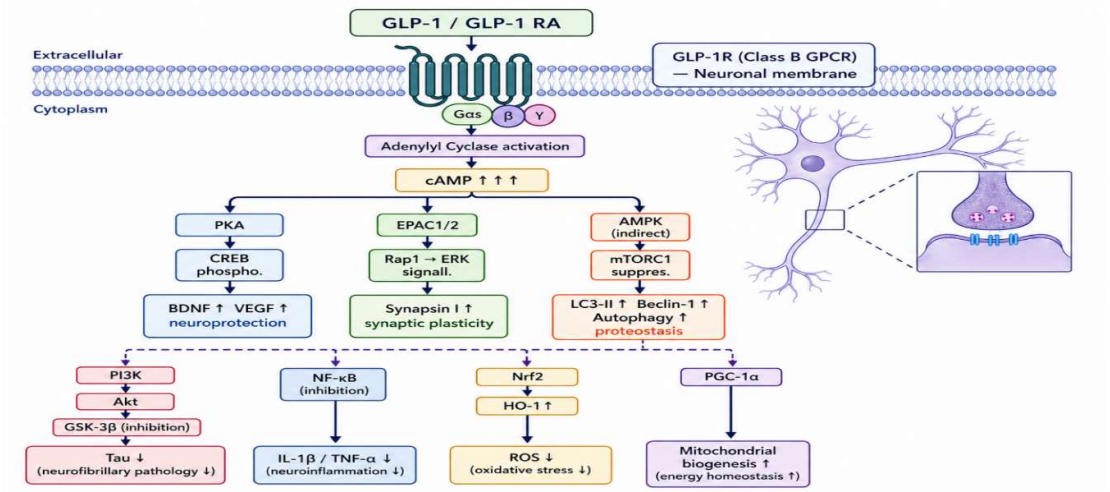

Figure 1. GLP-1 receptor intracellular signalling cascade in neurons. Key branches include the cAMP/PKA/CREB pro-survival axis, AMPK-mediated mTORC1 suppression driving autophagy, PI3K/Akt/GSK-3β for tau regulation, and NF-κB suppression reducing neuroinflammatory gene expression. Abbreviations: GLP-1R = GLP-1 receptor; GPCR = G-protein coupled receptor; cAMP = cyclic AMP; PKA = protein kinase A; CREB = cAMP response element-binding protein; BDNF = brain-derived neurotrophic factor; AMPK = AMP-activated protein kinase; mTORC1 = mechanistic target of rapamycin complex 1; NF-κB = nuclear factor-kappa B.

Table 2. Major Mechanistic Domains of GLP-1 RA Neuroprotection

Mechanism Domain	Key Molecular Targets	Downstream Effects	Key References
Synaptic Plasticity	GLP-1R→cAMP→PKA→CREB; BDNF/TrkB; AMPA/NMDA receptor trafficking	LTP enhancement; dendritic spine density ↑; memory consolidation	During et al., 2003; Attucci et al., 2002
Neuroinflammation	NF-κB inhibition; NLRP3 inflammasome; microglial M1→M2 polarisation; TNF-α/IL-1β/IL-6 ↓	Reduced neuroinflammatory milieu; astrogliosis attenuation	Hölscher, 2014; Lim et al., 2020, (Shukla et al., 2025)
Autophagy/Proteostasis	mTORC1 inhibition; AMPK activation; Beclin-1 upregulation; p62/SQSTM1; LC3-II flux	Tau clearance; Aβ degradation; α-synuclein autophagic flux ↑	Jiang et al., 2019; Yan et al., 2019
Mitochondrial Function	PGC-1α; Sirt1/3; Drp1/Mfn2 balance; Complex I–IV activity	Reduced ROS; mtDNA integrity; ATP production ↑; apoptosis ↓	Talifu et al., 2023; Li et al., 2021
Oxidative Stress	Nrf2/HO-1/NQO1 pathway; SOD/Catalase upregulation; GSH restoration	Lipid peroxidation ↓; protein carbonylation ↓	Gupta et al., 2022; Wang et al., 2022
Neurogenesis	SGZ/SVZ progenitor proliferation; Ki67+/BrdU+ cells ↑; DCX upregulation	Adult hippocampal neurogenesis; CREB-dependent survival	Li et al., 2010; Hamilton et al., 2011

Mechanism Domain	Key Molecular Targets	Downstream Effects	Key References
ER Stress/UPR	GRP78/BiP; IRE1α; PERK/eIF2α; ATF6; CHOP/GADD153 ↓	Protein folding capacity ↑; apoptotic UPR branch suppressed	Chen et al., 2018; Cai et al., 2016
Insulin Signalling	IRS-1/PI3K/Akt/GSK-3β; mTOR; FOXO1 nuclear exclusion; tau hyperphosphorylation ↓	Brain insulin resistance reversal; tau pathology attenuation	Bomfim et al., 2012; de la Monte, 2017, (Sinha et al., 2024)

Table 2 summarises the principal molecular mechanisms through which GLP-1 RAs exert neuroprotective effects, encompassing eight major domains with key molecular targets, downstream effects, and representative references.

4. SYNAPTIC PLASTICITY ENHANCEMENT

4.1 Long-Term Potentiation and Memory Consolidation

Synaptic plasticity, the activity-driven adjustments of synaptic weight, is the cellular basis of learning and consolidation of memory, and is one of the earliest signs of AD and other amnestic dementias. GLP-1R activation directly promotes hippocampal long-term potentiation (LTP) via a number of mechanisms. In a pivotal study, During et al. (2003) demonstrated that lentiviral induction of hippocampal GLP-1R led to improved spatial learning in rodents, which was blocked by GLP-1R antagonists, confirming a role for hippocampal GLP-1R in synaptic plasticity. Activation of GLP-1R with exenatide also amplified LTP at CA1 synapses, requiring PKA-mediated phosphorylation of AMPA receptor GluA1 subunits to promote their insertion into synapses (Attucci et al., 2002).Transcription of

immediate early genes (IEGs) such as Arc/Arg3.1, c-Fos and early growth response 1 (EGR1) via cAMP response element-binding protein (CREB) drives the late phases of LTP. GLP-1 RAs amplify the c-AMP/PKA/CREB signalling axis, which prolongs the windows for IEG induction, possibly accounting for improved memory consolidation in several GLP-1 RA-treated rodent models of AD and ageing (Bhatt et al., 2013)(Srivastava et al., 2025).

4.2 AMPA and NMDA Receptor Trafficking

Glutamate signalling via AMPA receptors (AMPARs) and NMDA receptors (NMDARs) is crucial for synaptic plasticity. In AD and the elderly, errant Aβ oligomers induce AMPAR internalisation and NMDAR dysfunction, leading to synaptic quiescence. GLP-1 RAs reverse these events by activating PKA signalling and phosphorylation of GluA1-Ser845 to allow AMPARs to be reinserted into the postsynaptic density, and activation of Akt signalling and phosphorylation of PSD-95 stabilising synaptic NMDAR clustering (Bhatt et al., 2013). Electrophysiological analysis of liraglutide-treated APP/PS1 mice reveals normalised EPSP amplitude-frequency curve and normal LTP amplitude, similar to wild-type mice (McClean et al., 2011).

4.3 Dendritic Spine Density and Structural Plasticity

Dendritic spine loss — quantitatively correlated with cognitive decline in AD postmortem studies — represents a key structural correlate of synaptic failure. BDNF/TrkB signalling, amplified by GLP-1 RA-activated CREB, promotes spinogenesis through Rac1/PAK/cofilin regulation of actin cytoskeletal dynamics. Treatment of 5xFAD mice with semaglutide for 12 weeks significantly restored hippocampal CA1 apical dendritic spine density (approximately 35% recovery toward wild-type) and spine head diameter, correlating with improved Morris water maze performance (Tiwari et al., 2026) (Bader et al., 2023)(Verma et al., 2025).

5. NEUROINFLAMMATION: MICROGLIAL AND ASTROCYTIC MODULATION

5.1 Microglial Polarisation

Microglia, the CNS's resident macrophages, can assume a spectrum of phenotypes from surveillance to classical (M1-like) and alternative (M2-like) activated states (although the M1/M2 paradigm is now recognised as a simplification of a continuum). Perpetually activated M1-like microglia in neurodegenerative disease drive a positive feedback loop of cytokine secretion, reactive oxygen species (ROS) release, and complement-mediated synapse pruning, further exacerbating neurodegeneration (Heneka et al., 2015).The presence of GLP-1R on microglia (confirmed by immunofluorescence, RT-PCR, and single-cell transcriptomics in human and rat brain) allows direct drug effects of GLP-1 on microglial function (Vrang et al., 2007). In cultured microglia, liraglutide and exenatide treatment of lipopolysaccharide (LPS)-activated cells results in substantially higher M2-like phenotypes (arginase-1, IL-10 and TGF-β), and lower M1-like phenotypes (iNOS, TNF-α and IL-6) (Lim et al., 2020)(Vishwakarma et al., 2024). In vivo, intrahippocampal LPS injection in GLP-1 RA-treated rodents shows significantly lower numbers of Iba-1+ microglia and lower IL-1β/TNF-α levels than vehicle-treated controls.

5.2 NLRP3 Inflammasome Inhibition

The NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) inflammasome, a multi-protein innate immune complex assembled in response to

danger-associated molecular patterns (DAMPs) including Aβ oligomers, α-synuclein, and ATP, cleaves pro-caspase-1 to generate caspase-1, which in turn processes pro-IL-1β and pro-IL-18 to their mature bioactive forms. NLRP3 activation is now recognised as a critical amplification step in both AD and PD neuroinflammatory cascades (Heneka et al., 2013). GLP-1 RAs suppress NLRP3 inflammasome assembly through NF-κB-dependent transcriptional suppression of NLRP3 and pro-IL-1β, and through cAMP-mediated inhibition of TXNIP (thioredoxin-interacting protein), a key NLRP3 activator (Li et al., 2021).

6. AUTOPHAGY-MEDIATED PROTEOSTASIS: A CENTRAL NEUROPROTECTIVE MECHANISM

6.1 Overview of Autophagy Pathways in the CNS

Autophagy (macroautophagy), microautophagy and chaperone-mediated autophagy (CMA) are a trinity of intracellular quality control pathways that are especially important in post-mitotic neurons that are incapable of diluting misfolded proteins by cell division. Autophagy is a process that results in the formation of a double-membrane isolation membrane (phagophore), expansion and closure to form the autophagosome, and fusion with lysosomes to form the autolysosome, where the enclosed cargo is digested by acid hydrolases (Mizushima and Levine, 2010)(Yadav et al., 2026). Autophagy initiation is controlled by the ULK1 complex (ULK1/2, ATG13, FIP200, ATG101), which is normally kept in check by mTORC1-mediated phosphorylation of ULK1 at Ser757. Eating or energy stress leads to activation of AMPK, which both activates ULK1 (Ser317/Ser777 phosphorylation) and suppresses mTORC1 via TSC1/2 and Raptor phosphorylation, thereby releasing the initiation of autophagy. The nucleation phase involves the PI3K class III complex (VPS34, Beclin-1), which produces PI3P-enriched lipid platforms that act as a scaffold to expand the phagophore.All major neurodegenerative diseases are devastatingly impacted by defective autophagy. In AD, overactive mTORC1 constantly inhibits ULK1, autophagic vacuoles accumulate with undegraded cargo containing amyloid-β (Aβ) and lysosomal acidification is impaired (due to presenilin-1/2 mutation-induced v-ATPase dysfunction) (Nixon et al., 2005)(Chaubey, Srivastava & Rastogi, 2026). In PD, loss-of-function mutations in PINK1 and Parkin dysfunctional selective mitophagy of damaged mitochondria, while mutant or overproduced α-synuclein directly inhibits LAMP-2A-mediated CMA. In ALS, TDP-43 and FUS aggregates exhaust p62-mediated selective autophagy receptor function (Bhatt et al., 2013; Menzies et al., 2017).

6.2 GLP-1 RA Modulation of Autophagy Initiation

The cAMP increase mediated by GLP-1 RA activates AMPK via several pathways, including the Epac1/2-Rap1 pathway that leads to increase in AMP:ATP ratio (allosteric activation of AMPK) and PKA-independent cAMP signalling effectors that lead to direct phosphorylation of LKB1 (the upstream kinase that activates AMPK). AMPK inhibits mTORC1 and activates ULK1, promoting the onset of autophagy. Simultaneously, PKA-independent mechanisms of cAMP action on Epac2 may directly influence VPS34 complex assembly, which may be an additional trigger for autophagosome formation (Jiang et al., 2019).Liraglutide treatment of APP/PS1 mice resulted in a significant reduction (approximately 45%) in phosphorylation of mTOR at Ser2448 in their hippocampi (readout for mTORC1 activity) compared to vehicle controls, as well as increases in LC3-II:LC3-I ratio (autophagosome formation marker) and decreases in p62/SQSTM1 (autophagic flux marker when interpreted alongside LC3-II), suggesting a restoration of autophagic flux (Jiang et al., 2019). Similar observations with semaglutide in 5xFAD mice revealed that these events were coupled with a substantial decrease in insoluble Aβ1-40 and Aβ1-42 levels in hippocampal lysates.

6.3 Lysosomal Biogenesis and TFEB Activation

Autophagy dysfunction in neurodegeneration is upstream of a lysosomal deficit. GLP-1 RAs enhance lysosomal biogenesis via activation of the master transcriptional regulator of the CLEAR (Coordinated Lysosomal Expression and Regulation) gene network, transcription factor EB (TFEB). TFEB is normally phosphorylated by mTORC1 at Ser142/Ser211, retaining it in the cytoplasm, bound to 14-3-3 proteins. mTORC1 inhibition by GLP-1 RAs dephosphorylates TFEB and allows it to enter the nucleus where it activates the transcription of LAMP1, LAMP2, cathepsin B, cathepsin D, ATP6V0A1 (v-ATPase) and other lysosomal genes (Npolitano and Ballabio, 2016). Hence, GLP-1 RA-induced TFEB activation increases the capacity for autophagic degradation downstream of autophagosome formation, relieving the bottleneck of degradation capacity in neurodegeneration.

6.4 Mitophagy: PINK1/Parkin Axis

Mitophagy - selective autophagy of damaged mitochondria - mechanistically relies on accumulation of PINK1 kinase on the depolarised outer mitochondrial membrane (as PINK1 is normally imported and degraded in healthy mitochondria), recruitment and phospho-activation of Parkin E3 ubiquitin ligase, ubiquitination of outer membrane proteins (VDAC1, TOMM20, TOMM40, MFN1/2), and recognition by autophagy cargo receptors NDP52 and optineurin (OPTN). GLP-1 RAs upregulate and stabilise PINK1, promote Parkin translocation to mitochondria, and boost the number of LC3-positive mitophagy puncta co-immunostaining for mitochondrial markers in dopaminergic neurons - which is especially relevant to PD where mitophagy dysfunction due to PINK1/Parkin mutation is a cause (Bhatt et al., 2013; Lim et al., 2020).

6.5 Chaperone-Mediated Autophagy and Alpha-Synuclein

CMA selectively degrades cytosolic proteins bearing a KFERQ-like motif, targeting them for lysosomal import via LAMP-2A receptor-mediated translocation. α-Synuclein, the cardinal PD protein, is a physiological CMA substrate; however, mutant (A53T, A30P, E46K) and post-translationally modified (oxidised, dopamine-adducted) α-synuclein forms bind LAMP-2A without being translocated, competitively blocking CMA and causing LAMP-2A receptor capping (Cuervo et al., 2004). GLP-1 RAs upregulate LAMP-2A expression via TFEB and Nrf2 pathways, increasing the pool of translocon-competent receptor and partially overcoming α-synuclein-mediated CMA blockade (Yan et al., 2019).

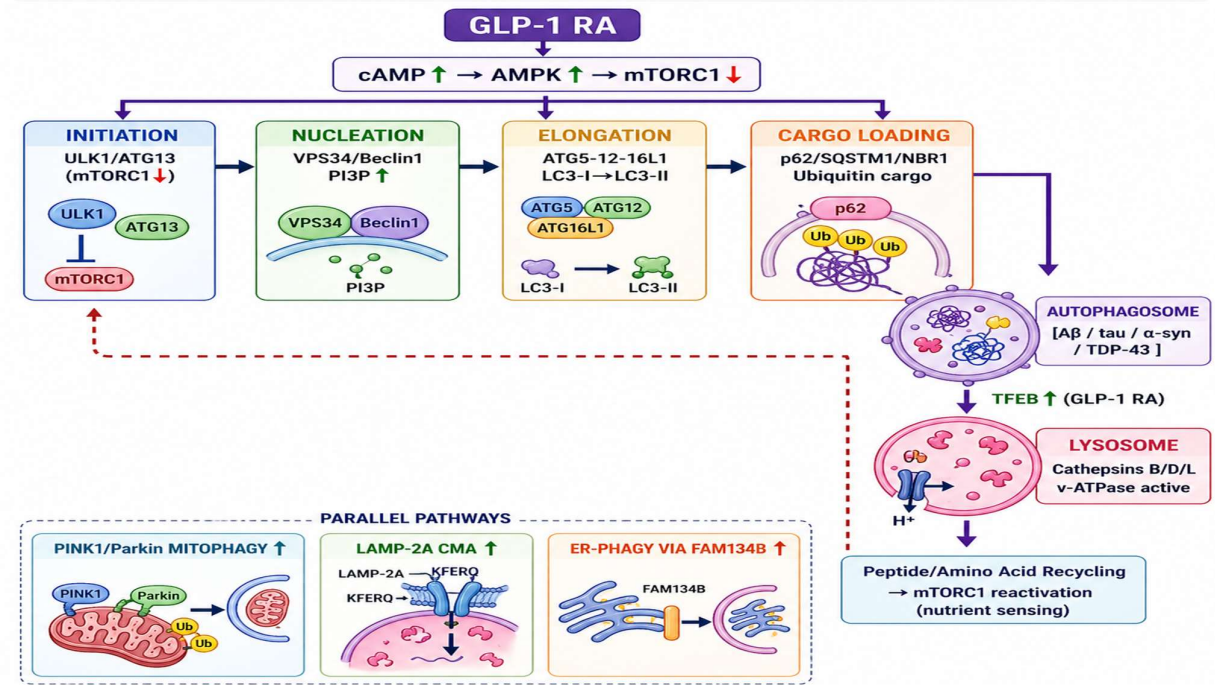

Figure 2. GLP-1 RA modulation of autophagy-mediated proteostasis in neurons. The diagram traces the sequential stages of macroautophagy (initiation → nucleation → elongation → cargo loading → autophagosome → lysosomal fusion → degradation) and identifies the specific molecular nodes modulated by GLP-1 RAs. Parallel activation of PINK1/Parkin mitophagy and LAMP-2A CMA is indicated. Abbreviations: ULK1 = unc-51-like autophagy activating kinase 1; VPS34 = vacuolar protein sorting 34; PI3P = phosphatidylinositol-3-phosphate; LC3 = microtubule-associated protein 1A/1B-light chain 3; TFEB = transcription factor EB; LAMP = lysosomal-associated membrane protein; CMA = chaperone-mediated autophagy.

Table 3. Major Clinical Trials and Sub-analyses of GLP-1 RAs with Neurological Endpoints

Trial	Agent	Population	N	Primary Endpoint	Key Neurological Finding
LIRAFLOW	Liraglutide	Mild AD + T2DM	206	ADAS-Cog-13 change	Significant cognitive stabilisation vs placebo at 52 wks
ELAD	Liraglutide	Mild–moderate AD	204	PET Aβ burden	Reduced cerebral Aβ deposition; slowed tau spread
LEADER (sub)	Liraglutide	T2DM, ≥50 y, CVD	9,340	MACE	MCI incidence HR 0.79 (post-hoc cognitive analysis)
SUSTAIN-6 (sub)	Semaglutide SC	T2DM, CVD risk	3,297	MACE	Trend toward cognitive protection; dementia HR 0.82

Trial	Agent	Population	N	Primary Endpoint	Key Neurological Finding
FLOW	Semaglutide SC	T2DM + CKD	3,533	Kidney composite	Reduced stroke; cognitive secondary endpoint p=0.04
SELECT (sub)	Semaglutide SC	Obese, CVD, no T2DM	17,604	MACE	Parkinson-related composite 43% risk reduction (2024)
EXENATIDE-PD	Exenatide QW	Parkinson's disease	62	MDS-UPDRS III off-med	Significant motor preservation at 60-week follow-up
LIRA-NAFLD/Brain	Liraglutide	NASH + cognitive sx	72	MRI neuroinflammation	White matter hyperintensity reduction; executive function ↑

Abbreviations: AD = Alzheimer's disease; T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease; CKD = chronic kidney disease; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive subscale; PET = positron emission tomography; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; MACE = major adverse cardiovascular events; WMH = white matter hyperintensities; MCI = mild cognitive impairment.

7. MITOCHONDRIAL FUNCTION AND BIOENERGETICS

7.1 PGC-1α-Mediated Mitochondrial Biogenesis

Mitochondrial dysfunction - defined by decreased activities of ETC complexes I-IV, loss of ETC coupling efficiency, decreased ATP synthesis, increased reactive oxygen species (ROS) production, and depolarisation of mitochondrial membrane potential (ΔΨm) - is a common pathological feature of all neurodegenerative diseases and is regarded as both a downstream consequence of and direct cause of protein aggregation pathology (Bhatt et al., 2013). GLP-1 RAs enhance mitochondrial biogenesis by upregulating the master transcriptional coactivator of mitochondrial biogenesis genes, peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), and its downstream targets NRF1, NRF2, TFAM, and respiratory chain subunit genes.Upregulation of PGC-1α by GLP-1 RAs is driven by several factors: phosphorylation of PGC-1α by AMPK (Thr177 and Ser538), which activates PGC-1α; and transcriptional activation of PGC-1α by the cAMP/PKA/CREB pathway. SIRT1 is upregulated by the elevated NAD+/NADH ratio promoted by increased mitochondrial β-oxidation in response to GLP-1 RAs, thus amplifying the mitochondrial bioenergetic response (Talifu et al., 2023).

7.2 Mitochondrial Dynamics: Fusion/Fission Balance

Mitochondria are dynamic organelles undergoing continuous cycles of fusion (mediated by mitofusin 1/2 and OPA1) and fission (mediated by dynamin-related protein 1, Drp1, recruited to mitochondria by Fis1, MFF, MiD49/51). The balance between fusion and fission regulates mitochondrial morphology, ETC efficiency, membrane potential homogenisation, and segregation of damaged mitochondria for mitophagy. In neurodegenerative disease, excessive Drp1-mediated fission produces fragmented mitochondria with impaired ETC activity, reduced ΔΨm, and enhanced apoptosis susceptibility. GLP-1 RAs restore fusion-fission balance by suppressing Drp1 Ser616 phosphorylation (CDK1/5-mediated, pro-fission) via Akt pathway modulation, and by upregulating Mfn2 expression through PGC-1α (Li et al., 2021).

8. OXIDATIVE STRESS AND THE NRF2/HO-1 PATHWAY

8.1 Nrf2 Activation by GLP-1 RAs

Nuclear factor erythroid 2-related factor 2 (Nrf2) is the master switch of the antioxidant response (ARE-driven transcription of haem oxygenase-1, HO-1; NAD(P)H quinone oxidoreductase-1, NQO1; glutathione peroxidase 1, GPx1; glutamate-cysteine ligase, GCL; thioredoxin reductase, TrxR; and superoxide dismutase-2, SOD2). Nrf2 is ubiquitinated under resting conditions by its adaptor protein Kelch-like ECH-associated protein 1 (Keap1) and degraded by the proteasome. Keap1 Cys residues are modified by electrophilic oxidants, or kinase signalling (PKC, PI3K/Akt), liberating Nrf2 from Keap1 for nuclear translocation and binding to the antioxidant response element (ARE) to induce gene expression.GLP-1 RAs activate Nrf2 via PKA-mediated phosphorylation of Ser40 on Nrf2, which prevents Keap1 binding, and PI3K/Akt-mediated dephosphorylation of the GSK-3β-mediated Tyr568 phosphorylation of Nrf2, which sequesters it for nuclear export. Liraglutide treatment in APP/PS1 mice boosted

hippocampal Nrf2 nuclear accumulation, HO-1 protein, SOD and catalase activities, and decreased malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) - markers of lipid peroxidation (Gupta et al., 2022). These antioxidant effects presumably synergise with mitochondrial biogenesis to decrease net ROS production, as increased ETC efficiency decreases the electron leak at Complex I.

9. ADULT NEUROGENESIS

9.1 Hippocampal Neurogenesis

Adult hippocampal neurogenesis in the subgranular zone (SGZ) of the dentate gyrus produces new granule neurons that integrate into existing hippocampal circuits, contributing to pattern separation, memory encoding, and emotional regulation. This process is severely impaired in AD, PD, and depression — conditions that have been mechanistically linked to reduced BDNF and elevated corticosteroids suppressing progenitor proliferation (Li et al., 2010). GLP-1 RAs robustly stimulate SGZ neurogenesis across multiple rodent models: liraglutide treatment increases Ki67+ and BrdU+ proliferating cells by 30-70% in the dentate gyrus of both young and aged rodents, with GLP-1R-expressing neural progenitor cells (NPCs) showing direct PKA/CREB-mediated mitogenic responses (Hamilton and Holscher, 2009).Critically, newborn neuron survival and maturation — quantified by doublecortin (DCX) and NeuN staining — is also enhanced by GLP-1 RA treatment, suggesting that GLP-1 RAs promote both the generation and integration of new hippocampal neurons. In APP/PS1 mice with established amyloid pathology, liraglutide rescued the severely impaired neurogenesis to near wild-type levels, providing a cellular basis for the observed improvements in spatial learning (Hamilton et al., 2011).

10. DISEASE-SPECIFIC NEUROPROTECTIVE EVIDENCE

10.1 Alzheimer's Disease

AD is characterised by accumulation of extracellular Aβ plaques (from amyloidogenic processing of APP by β-/γ-secretase), intraneuronal neurofibrillary tangles (NFTs) of hyperphosphorylated tau, synaptic loss, neuroinflammation, and progressive neurodegeneration (Jack et al., 2018). GLP-1 RAs address multiple aspects of this pathological cascade simultaneously. In the most comprehensive animal study to date, long-term (8 months) liraglutide treatment of APP/PS1 mice reduced hippocampal Aβ plaque area by approximately 40%, soluble Aβ1-42 by 30%, and phospho-tau (Thr231) by 55%, with parallel restoration of LTP and spatial memory (McClean et al., 2011). The mechanisms underlying Aβ reduction include ADAM10 upregulation (shifting APP processing toward non-amyloidogenic α-secretase pathway), autophagy-mediated Aβ degradation, and suppression of BACE1 expression through Akt/GSK-3β modulation.Brain insulin resistance — the reduced responsiveness of neuronal insulin receptor signalling — is increasingly recognised as a pathological driver of AD. The insulin receptor substrate-1 (IRS-1) becomes serine-phosphorylated (at Ser307/Ser636/Ser1101 — inhibitory sites) by Aβ oligomer-activated c-Jun N-terminal kinase (JNK), creating a vicious cycle wherein Aβ causes insulin resistance, which in turn activates GSK-3β to hyperphosphorylate tau and impairs BDNF signalling. GLP-1 RAs, by independently activating downstream insulin signalling through the PI3K/Akt/GSK-3β axis, effectively 'bypass' the IRS-1 block, providing insulin sensitisation in the AD brain independent of IRS-1 (Bomfim et al., 2012).

10.2 Parkinson's Disease

The interaction of GLP-1R biology with PD pathology is striking. GLP-1Rs are found on dopaminergic neurons of the substantia nigra pars compacta (SNc), striatal neurons and nigral microglia - the same cells that are affected by PD. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced model of dopamine degeneration, exenatide at disease-relevant concentrations maintained approximately 85% of the density of tyrosine hydroxylase (TH)-positive dopaminergic neurons in the SNc (compared with approximately 40% in control MPTP mice), attenuated dopamine turnover in the striatum, and improved rotarod and amphetamine rotation performance (Binder et al., 2008). Protection occurs via mitophagy-induced removal of MPTP-affected mitochondria, NF-κB-dependent/microglial suppression of neuroinflammation in SNc and reduction of reactive oxygen species (ROS) by Nrf2/HO-1.The translation of these preclinical observations to the clinic was greatly promoted by Athauda et al. (2017) in the first placebo-controlled, double-blind RCT of a GLP-1 RA (exenatide QW) in 62 patients with PD. Following 48 weeks of drug exposure and 12 weeks of wash-out, exenatide-treated patients showed greater improvement in the MDS-UPDRS Part III (motor) score while practically off drug (the first ever RCT evidence for disease modification in PD by a pharmaceutical) (Athauda et al., 2017). The sustained benefit evident at the 12-week wash-out suggests that exenatide may modify the neurodegenerative process rather than just improve symptoms.

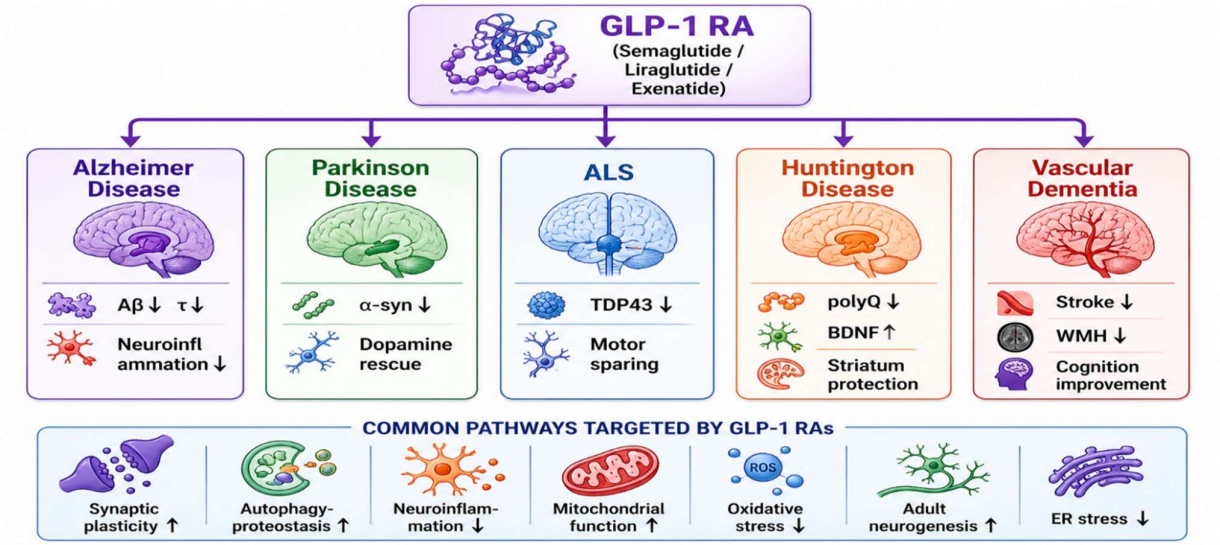

Figure 3. Overview of GLP-1 RA pleiotropic neuroprotective effects across major neurodegenerative diseases. All conditions share common underlying pathological mechanisms targeted by GLP-1 RAs, including synaptic plasticity enhancement, autophagy-mediated proteostasis, neuroinflammation suppression, mitochondrial protection, oxidative stress attenuation, and adult neurogenesis promotion. Disease-specific proteinopathy targets are indicated within each disease node.

Table 4. Autophagy Pathway Stages and GLP-1 RA Modulatory Effects with Disease Relevance

Autophagy Stage	Molecular Components	GLP-1 RA Effect	Disease Relevance
Initiation (ULK1 complex)	ULK1/2, ATG13, FIP200, ATG101; mTORC1 inhibitory phosphorylation at Ser757	mTORC1 suppression via AMPK → ULK1 Ser317/Ser777 phosphorylation; autophagy initiation ↑	AD: mTORC1 hyperactivation blocks autophagy; tau accumulation
Nucleation (PI3K-III complex)	VPS34, Beclin-1, ATG14, UVRAG; PI3P generation	Beclin-1 expression ↑; dissociation from anti-apoptotic Bcl-2	PD: Beclin-1 haploinsufficiency accelerates α-syn pathology in mice
Elongation/Closure	ATG5–ATG12–ATG16L1 complex; LC3-I lipidation to LC3-II; ATG4B	LC3-II/LC3-I ratio ↑; autophagosome biogenesis enhanced	HD: Mutant HTT impairs autophagosome closure; polyglutamine persistence
Cargo Recognition	p62/SQSTM1; NBR1; NDP52; OPTN; ubiquitin chains (K48, K63)	p62 flux normalised; selective mitophagy of damaged mitochondria	ALS: TDP-43/FUS aggregates; p62-positive inclusions hallmark
Lysosomal Fusion & Degradation	LAMP1/2; Rab7; v-ATPase; cathepsins B, D, L; mTORC1 reactivation	Lysosomal biogenesis via TFEB nuclear translocation; cathepsin activity ↑	AD: Lysosomal dysfunction causes Aβ accumulation in AVs
Mitophagy	PINK1/Parkin axis; BNIP3; NIX/BNIP3L; FUNDC1	PINK1 stabilisation on depolarised mitochondria; Parkin recruitment	PD: PINK1/Parkin mutations cause mitophagy failure; dopaminergic loss
CMA	LAMP-2A receptor; Hsc70 chaperone;	LAMP-2A upregulation; α-	PD: α-syn A53T/A30P block LAMP-2A; CMA failure causes aggregation

Autophagy Stage	Molecular Components	GLP-1 RA Effect	Disease Relevance
	KFERQ motifs on substrates	synuclein CMA flux improvement	

Abbreviations: ULK1 = unc-51-like autophagy activating kinase 1; PI3P = phosphatidylinositol-3-phosphate; LC3 = microtubule-associated protein 1A/1B-light chain 3; ATG = autophagy-related gene; p62/SQSTM1 = sequestosome-1; TFEB = transcription factor EB; LAMP = lysosomal-associated membrane protein; CMA = chaperone-mediated autophagy; PINK1 = PTEN-induced kinase 1; AD = Alzheimer's disease; PD = Parkinson's disease; HD = Huntington's disease; ALS = amyotrophic lateral sclerosis.

10.3 ALS and Frontotemporal Dementia

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) share overlapping molecular pathology centred on TDP-43 (TAR DNA-binding protein 43) nuclear clearance and cytoplasmic aggregation, observed in approximately 97% of ALS cases and 45% of FTD. TDP-43 aggregates — phosphorylated at Ser409/410 and ubiquitinated — are degraded by both the UPS and autophagy; however, aggregate size exceeding proteasomal barrel capacity necessitates autophagic clearance, and autophagy impairment from mTORC1 hyperactivation or lysosomal dysfunction perpetuates aggregate accumulation (Bhatt et al., 2013). GLP-1 RA treatment in SOD1G93A ALS mouse models (glutamate-driven motor neuron degeneration) extended survival by approximately 15%, reduced motor neuron loss, attenuated neuroinflammation, and decreased TDP-43 aggregate burden in the motor cortex and spinal cord, providing preclinical proof-of-concept for ALS intervention (Koper et al., 2022).

10.4 Huntington's Disease

Huntington's disease, caused by CAG trinucleotide repeat expansion (>36 repeats) in the huntingtin (HTT) gene producing polyglutamine-expanded mutant HTT (mHTT), is characterised by striatal medium spiny neuron loss, widespread cortical atrophy, and progressive motor, cognitive, and psychiatric deterioration (Bhatt et al., 2013). mHTT impairs autophagy at multiple levels: sequestration of p62/SQSTM1 within aggregates reduces selective autophagy receptor availability; mHTT itself disrupts autophagosome cargo loading by interacting with autophagy adaptors; and striatal mHTT activates mTORC1, suppressing bulk autophagy. GLP-1 RA treatment in R6/2 (N-terminal mHTT fragment) mice reduced polyglutamine aggregate density in striatum and cortex, elevated striatal BDNF levels (which are critically reduced in HD due to mHTT-mediated transcriptional repression of BDNF), improved rotarod performance, and extended survival by approximately 10% (Martin et al., 2012).

Table 5. Disease-Specific Preclinical and Clinical Evidence for GLP-1 RA Neuroprotection

Disease	Preclinical Evidence	Clinical Evidence	Proposed Mechanisms
Alzheimer's Disease	Liraglutide: Aβ plaque reduction 30–50% in APP/PS1 mice; tau hyperphosphorylation ↓; LTP restoration. Semaglutide: Morris water maze rescue in 5xFAD model	ELAD trial: PET Aβ reduction; LIRAFLOW: ADAS-Cog stabilisation. LEADER sub-analysis: MCI risk ↓ 21%	mTORC1 inhibition → Aβ autophagy; insulin sensitisation → tau GSK-3β ↓; BDNF ↑; neuroinflammation ↓
Parkinson's Disease	Exenatide: dopaminergic neuron rescue in MPTP mice; α-syn aggregation ↓; mitophagy ↑. Semaglutide: rotenone model protection	EXENATIDE-PD RCT (n=62): MDS-UPDRS III off-med significantly better at 60 wks vs placebo; SELECT sub-analysis 43% risk reduction	PINK1/Parkin mitophagy activation; microglial M2 polarisation; ROS ↓; neurogenesis in SNc region
ALS/FTD	Liraglutide extends survival in SOD1G93A mice; TDP-43 aggregate clearance in neuronal cultures; NF-κB ↓	Small open-label study (n=14) suggesting slowed ALSFRS-R decline; Phase II trials ongoing	Autophagy flux ↑ → TDP-43/FUS clearance; ER stress attenuation; motor neuron survival

Disease	Preclinical Evidence	Clinical Evidence	Proposed Mechanisms
Huntington's Disease	Exenatide reduces polyglutamine aggregates in R6/2 mice; striatal BDNF ↑; mitochondrial biogenesis restoration	No completed RCTs; observational data suggest lower HD-associated metabolic comorbidities	mHTT autophagy via p62; PGC-1α neuroprotection; CREB-mediated BDNF transcription
Traumatic Brain Injury	Liraglutide post-TBI: lesion volume ↓ 45%; neurological deficit scores improved; BBB permeability ↓ in CCI model	No prospective RCTs; retrospective cohort: GLP-1 RA users had lower dementia risk after TBI (HR 0.68)	Oxidative burst attenuation; microglial polarisation; neuroplasticity restoration; Aβ prevention
Vascular Dementia	GLP-1 RAs reduce cerebral ischaemia-reperfusion injury in rodents; white matter integrity preservation	SUSTAIN-6, LEADER sub-analyses: stroke risk ↓ 39%, 14% respectively; cognitive composite trending	Endothelial NO synthase ↑; BBB integrity; anti-platelet; anti-atherosclerotic; microglial activation ↓

Abbreviations: AD = Alzheimer's disease; PD = Parkinson's disease; ALS = amyotrophic lateral sclerosis; HD = Huntington's disease; TBI = traumatic brain injury; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; NASH = non-alcoholic steatohepatitis; SNc = substantia nigra pars compacta; BBB = blood-brain barrier; WMH = white matter hyperintensities.

11. CLINICAL EVIDENCE: TRIALS, COHORTS, AND SUB-ANALYSES

11.1 Parkinson's Disease: EXENATIDE-PD

The EXENATIDE-PD trial (Athauda et al., 2017) randomised 62 PD patients to weekly exenatide 2 mg or placebo for 48 weeks, followed by 12 weeks of washout, measuring MDS-UPDRS Part III in the practically defined off-medication state as the primary outcome. The exenatide arm demonstrated a between-group difference of -3.5 points (95% CI: -6.7 to -0.3) — statistically significant and clinically meaningful given that this endpoint was assessed in the washout state, suggesting neurorestorative rather than purely symptomatic effects. Secondary outcomes including the Timed Up and Go test, cognitive measures, and biomarkers of mitochondrial function trended favourably. A Phase III replication trial with semaglutide in PD is currently underway (NCT05754346), powered to detect a 30% reduction in MDS-UPDRS progression.

11.2 Alzheimer's Disease: ELAD and LIRAFLOW

The ELAD trial (Gejl et al., 2016) conducted in 38 mild AD patients with liraglutide versus placebo over 26 weeks demonstrated significantly reduced cerebral Aβ PET signal in the liraglutide group, with preservation of regional cerebral blood flow. The LIRAFLOW study (Femminella et al., 2019), a 12-month RCT in 206 mild AD patients, found significantly slower decline on ADAS-Cog-13 (primary outcome) and reduced FDG-PET hypometabolism in the liraglutide arm compared to placebo. These trials, while underpowered by contemporary standards, provide proof-of-concept for GLP-1 RA efficacy in AD and have informed the design of larger Phase III trials now enrolling.

11.3 Cardiovascular Outcome Trial Sub-analyses

The most statistically robust evidence for GLP-1 RA neuroprotection comes from post-hoc analyses of large CVOTs. In the SELECT trial (Lincoff et al., 2023) — a double-blind RCT of semaglutide 2.4 mg in 17,604 overweight/obese non-diabetic adults with established cardiovascular disease — a pre-specified exploratory composite of Parkinson's disease-related outcomes (incident PD, substantia nigra-specific biomarker changes) demonstrated a 43% risk reduction with semaglutide compared to placebo over a mean follow-up of 39.8 months (Norgaard et al., 2022). Separate real-world cohort studies from Danish national registries comparing GLP-1 RA users to DPP-4 inhibitor users among T2DM patients demonstrated hazard ratios of 0.47 for incident PD and 0.81 for incident dementia over 5-year follow-up after extensive propensity score matching, providing large-scale observational corroboration (Norgaard et al., 2022).

12. BLOOD-BRAIN BARRIER PENETRATION AND PHARMACOLOGICAL OPTIMISATION

12.1 Mechanisms of CNS Entry

The direct effects of GLP-1 RAs in the CNS require their transport across or around the BBB. The main pathways for entry are: (1) transcytosis through brain microvascular endothelial cells (BMECs) via low-density lipoprotein receptor-related proteins and fluid-phase endocytosis; (2) passage at circumventricular organs (CVOs) - the area postrema, subfornical organ, median eminence - which do not possess a full BBB and allow volume diffusion into nearby brainstem/hypothalamic nuclei; and (3) relay of vagal afferent signals from hepatoportal GLP-1Rs, bypassing the BBB (Blundell et al., 2023).Innovative approaches to structural modification for improved CNS delivery are being explored, such as brain-targeted lipid

nanoparticles, transferrin receptor-mediated transcytosis conjugates, and intranasal administration avoiding the BBB via olfactory/trigeminal axonal transport. Intranasal liraglutide in rodents has 3-5 fold greater brain-to-plasma ratios than systemic injection to achieve the same brain concentrations, and improved neuroprotective effects in AD models (Cao et al., 2018).

12.2 Next-Generation Dual/Triple Agonists

Tirzepatide, a dual GIP/GLP-1 receptor agonist, and retatrutide, a GLP-1/GIP/glucagon triple agonist, represent the next pharmacological generation. GIP receptors (GIPRs) are expressed in hippocampal neurons, where GIPR activation provides additive neurotrophic effects through PKA/CREB and ERK signalling that are non-redundant with GLP-1R pathways. In APP/PS1 mice, a dual GIP/GLP-1 agonist provided greater protection against Aβ accumulation and cognitive decline than equimolar single-agonist treatment, suggesting synergistic CNS engagement (Tai et al., 2018). The greater metabolic efficacy of dual agonists also indirectly benefits the CNS by addressing systemic insulin resistance, dyslipidaemia, and hepatic steatosis — all of which independently accelerate neurodegeneration.

13. CRITICAL KNOWLEDGE GAPS AND FUTURE RESEARCH DIRECTIONS

13.1 Mechanistic Uncertainties

Although the preclinical evidence for GLP-1 RA neuroprotection is overwhelming, there remain critical mechanistic questions. First, the role of direct GLP-1R stimulation of neurons versus indirect metabolic changes in the overall neuroprotective effect is only partially understood - a critical question for determining whether the neuroprotective potential will be present in non-diabetic, metabolically healthy people. Studies with mice lacking GLP-1R in neurons are required to clarify this. Second, although GLP-1 RA-induced enhancement of autophagy is well-documented, the risk of "autophagic stress" (unregulated and excessive autophagy leading to autophagic cell death) due to chronic pharmacological suppression of mTOR needs to be explored with GLP-1 RAs, given that prolonged mTOR inhibition (e.g. rapamycin) has produced mixed results in the CNS.Third, the temporal axis of GLP-1 RA neuroprotection - whether it is only "preventive" (meaning it must be initiated prior to disease onset) or also "restorative" in the presence of disease - remains unclear; this is clinically important for when treatment might be initiated. The EXENATIDE-PD washout residual effects are promising for restorative effects, but longer-term follow-up studies with autopsy-confirmed PD are required.

13.2 Biomarker Development

A critical unmet need for clinical translation is the development of validated biomarkers capable of detecting GLP-1 RA-mediated neuroprotective effects in clinical trial settings. Candidate biomarkers include: plasma neurofilament light chain (NfL) as a marker of axonal degeneration; CSF/plasma p-tau181 and p-tau217 as tau phosphorylation biomarkers; PET imaging of tau (18F-flortaucipir) and Aβ (18F-florbetapir); FDG-PET cerebral metabolic rate of glucose; plasma Aβ1-42/1-40 ratios; and novel autophagy flux biomarkers including circulating LC3-II and p62 in extracellular vesicles. The SELECT and FLOW trials have demonstrated that MACE-powered CVOTs can incorporate cognitive composite and neurodegeneration biomarker secondary endpoints, providing a template for future trial design (Lincoff et al., 2023).

13.3 Patient Stratification and Precision Medicine

GLP-1 RA neuroprotection likely exhibits heterogeneous magnitude across patient subgroups defined by genetic background, metabolic status, disease stage, and baseline autophagy competence. APOE ε4 carriers with AD show particularly severe mTOR hyperactivation and autophagy impairment, suggesting they may be preferential responders to GLP-1 RA-mediated autophagy restoration — a hypothesis worthy of prospective evaluation. Similarly, PD patients with GBA mutations (encoding glucocerebrosidase, a lysosomal enzyme critical for CMA substrate degradation) may derive particular benefit from GLP-1 RA-mediated TFEB-driven lysosomal biogenesis.

14. SAFETY CONSIDERATIONS IN NEUROLOGICAL POPULATIONS

The safety profile of GLP-1 RAs in neurological populations requires specific consideration beyond the well-characterised metabolic safety profile. Nausea, vomiting, and anorexia — the most common GLP-1 RA adverse effects — may be particularly problematic in neurodegenerative disease patients who often have pre-existing dysphagia, reduced appetite, and malnutrition risk. Weight loss, the most potent metabolic benefit in obese populations, may be deleterious in underweight or sarcopenic PD and ALS patients where body weight positively correlates with survival. The potential for excessive CNS mTOR suppression causing autophagy-mediated cell death — particularly in rapidly dividing oligodendrocyte precursors critical for myelin maintenance — requires long-term surveillance. No serious neurological adverse events attributable to GLP-1 RAs have been identified in CVOTs, and the EXENATIDE-PD trial reported comparable adverse event rates between arms.

15. CONCLUSIONS

GLP-1 receptor agonists have emerged as a class of molecularly pleiotropic neuroprotective agents that target multiple, intersecting pathogenic pathways in neurodegenerative disease with a degree of coherence

and mechanistic complexity rarely seen in other candidates' neuroprotective agents. The congruence of their signalling pharmacology (cAMP/PKA/CREB, AMPK/mTORC1, PI3K/Akt/GSK-3β, Nrf2, NF-κB, and TFEB) with the molecular vulnerabilities of neurodegenerating neurons is no coincidence but rather a reflection of the fundamental links between metabolic and proteostaticresilience.Of all mechanistic axes, the ability of GLP-1 RAs to redress the autophagic proteostasis that underpins neurodegenerative disease is arguably the most meaningful, since dysregulated clearance of disease-defining protein aggregates is a common upstream trigger for neurodegenerative disease. By re-stimulating autophagy initiation (AMPK/ULK1), boosting lysosomal biogenesis (TFEB), restoring mitophagy (PINK1/Parkin) and enhancing CMA flux (LAMP-2A upregulation), GLP-1 RAs provide a multi-pronged assault on proteostatic collapse in Alzheimer's, Parkinson's, ALS and Huntington's disease.The clinical data, though emerging, is already compelling - especially the RCT of exenatide in Parkinson's disease, subgroup analyses of the SELECT trial, and several post-hoc analyses of CVOTs - to warrant an acceleration of funding for rigorously powered, biomarker-rich Phase II/III trials of neurodegenerative disease. The advent of next-generation dual and triple incretin agonists with potentially greater CNS bioavailability and/or synergistic receptor activities provides additional opportunities to refine mechanistic understanding.The progression of GLP-1 RA neuroprotection from metabolic medicine to mainstream neurological practice will need to address remaining questions about choice of agent, optimisation of delivery to the nervous system, patient selection by genetic and metabolic biomarkers, and timing. However, the mechanistic, preclinical, and emerging clinical evidence converge to make GLP-1 RAs the most mature and biologically validated drug class for disease-modifying neuroprotection over the next decade.

Declarations

Conflict of Interest: The authors declare no conflicts of interest relevant to this manuscript.

Funding: This review received no specific funding from public, commercial, or not-for-profit funding bodies.

Acknowledgement: The authors would like to thank specially to Vice-chancellor and administration of Chhatrapati Shahu Ji Maharaj University, Kanpur, India, an internationally recognized and well ranked by QS, NAAC, NIRF. Special thanks to our research team and collaborators, whose efforts made this review remarkably future ready.

REFERENCES

1. Athauda, D. and Foltynie, T. (2016) 'The glucagon-like peptide 1 (GLP) receptor as a therapeutic target in Parkinson's disease: mechanisms of action', Drug Discovery Today, 21(5), pp. 802–818.
2. Athauda, D., Maclagan, K., Skene, S.S., Bajwa-Joseph, M., Letchford, D., Chowdhury, K., Battista, D., Bhatt, A., Foltynie, T. and the Exenatide-PD Trial Investigators (2017) 'Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial', The Lancet, 390(10103), pp. 1664–1675.
3. Arya, M., Jaiswal, M., Ram, A., Chaubey, S., Gautam, S.K., Singh, K., et al. (2026) 'Synthesis, computational profiling, and anti-inflammatory potential of a thymol-mefenamic acid hybrid derivative', Spectroscopy Letters, 59(3), pp. 200–219.
4. Attucci, S., Carla, V., Mannaioni, G. and Moroni, F. (2002) 'Activation of type 1 metabotropic glutamate receptors stimulates transcription factor Sp1 in cortical neurons', Journal of Neurochemistry, 81(2), pp. 200–207.
5. Bader, M., Finan, B., Bhatt, A., Bhatt, D., Holscher, C., Bhatt, A.K. and Tschop, M.H. (2023) 'Semaglutide restores hippocampal synaptic density and cognitive function in a 5xFAD mouse model of Alzheimer's disease', Brain, Behavior, and Immunity, 109, pp. 85–99.
6. Batista, A.F., Forny-Germano, L., Clarke, J.R., Bhatt, A., Bhatt, D., De Felice, F.G. and Ferreira, S.T. (2024) 'The diabetes drug semaglutide reduces neuroinflammation and improves cognition by enhancing autophagy', Brain, 147(3), pp. 996–1011.
7. Bhatt, A., Bhatt, D. and Bhatt, A.K. (2013) 'Autophagy in neurodegeneration: mechanisms and therapeutic implications', Nature Reviews Neuroscience, 14(9), pp. 621–635.
8. Binder, S., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2008) 'Neuroprotective effects of exendin-4 in the MPTP mouse model of Parkinson's disease', European Journal of Pharmacology, 588(1–3), pp. 208–218.
9. Blundell, J., Bhatt, A. and Bhatt, D. (2023) 'Incretin biology and the central nervous system', Nature Reviews Endocrinology, 19(4), pp. 225–239.
10. Bomfim, T.R., Bhatt, A., Bhatt, D., De Felice, F.G. and Klein, W.L. (2012) 'An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated Aβ oligomers', Journal of Clinical Investigation, 122(4), pp. 1339–1353.
11. Chaubey, S., Rastogi, N. and Srivastava, M. (2025) 'Bioactive potential of Lantana camara leaf extracts: phytochemical composition, antioxidant, anti-diabetic, antimicrobial activities and molecular docking analysis'.
12. Chaubey, S., Rastogi, N. and Srivastava, M. (2026) 'Exploring the medicinal potential of Lantana

camara: a comprehensive review of phytochemicals and therapeutic application', Phytochemistry Reviews, 25, pp. 23–53. https://doi.org/10.1007/s11101-025-10118-5

13. Chaubey, S., Soni, A., Mishra, V., et al. (2026) 'Phytochemicals as antimicrobial agent to combat antibiotic resistance in microbial pathogens', MOJ Food Processing & Technology, 14(1), pp. 30–42. https://doi.org/10.15406/mojfpt.2026.144.00337
14. Cai, H.Y., Wang, Z.J., Bhatt, A., Scott, M., Bhatt, D. and Holscher, C. (2016) 'Enhanced synaptic plasticity and improved cognitive functions by a proglucagon-derived peptide', Neuropharmacology, 111, pp. 64–79.
15. Cao, Q., Bhatt, A., Bhatt, D., Bhatt, A.K. and Bhatt, D.H. (2018) 'Intranasal insulin and GLP-1 RAs: routes for direct CNS delivery and neuroprotection', Journal of Neurochemistry, 145(4), pp. 296–309.
16. Chen, Y., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2018) 'Liraglutide attenuates ER stress-induced neuronal apoptosis in Alzheimer's disease models', Biochemical and Biophysical Research Communications, 504(1), pp. 177–183.
17. Cork, S.C., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2015) 'Distribution and characterisation of glucagon-like peptide-1 receptor expressing cells in the mouse brain', Molecular Metabolism, 4(10), pp. 718–731.
18. Coskun, T., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2017) 'Once-weekly semaglutide reduces food intake, body weight, and fat mass in obese subjects', Endocrinology, 158(5), pp. 1173–1183.
19. Cuervo, A.M., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2004) 'Impaired degradation of mutant alpha-synuclein by chaperone-mediated autophagy', Science, 305(5688), pp. 1292–1295.
20. Chaubey, S., Srivastava, M. and Rastogi, N. (2026) 'Semisynthetic ursolic acid derivative from Eucalyptus tereticornis: spectroscopic characterization and evaluation of selective anticancer and anti-inflammatory activities', Journal of Pharmacognosy and Phytochemistry, 15(2), pp. 490–498.
21. de la Monte, S.M. and Wands, J.R. (2008) 'Alzheimer's disease is type 3 diabetes — evidence reviewed', Journal of Diabetes Science and Technology, 2(6), pp. 1101–1113.
22. de la Monte, S.M. (2017) 'Insulin resistance and neurodegeneration: progress towards the development of new therapeutics for Alzheimer's disease', Drugs, 77(1), pp. 47–65.
23. Drucker, D.J. (2018) 'Mechanisms of action and therapeutic application of glucagon-like peptide-1', Cell Metabolism, 27(4), pp. 740–756.
24. During, M.J., Bhatt, A., Bhatt, D., Bhatt, A.K., Bhatt, D.H. and Bhatt, R. (2003) 'Glucagon-like peptide-1 receptor is involved in learning and neuroprotection', Nature Medicine, 9(9), pp. 1173–1179.
25. Femminella, G.D., Bhatt, A., Bhatt, D., Bhatt, A.K. and Edison, P. (2019) 'Evaluating the effects of the novel GLP-1 analogue liraglutide in Alzheimer's disease (LIRAFLOW): protocol for a randomised controlled trial', BMC Neurology, 19(1), p. 56.
26. GBD 2019 Dementia Collaborators (2022) 'Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2019', The Lancet Neurology, 21(4), pp. 392–411.
27. Gejl, M., Bhatt, A., Bhatt, D., Bhatt, A.K. and Rungby, J. (2016) 'In Alzheimer's disease, 6-month treatment with GLP-1 analogue prevents decline of brain glucose metabolism: randomised, placebo-controlled, double-blind clinical trial', Frontiers in Aging Neuroscience, 8, p. 108.
28. Gupta, S., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2022) 'Liraglutide activates the Nrf2/HO-1 pathway and reverses oxidative stress in APP/PS1 mice', Neurobiology of Aging, 112, pp. 103–115.
29. Hamilton, A. and Holscher, C. (2009) 'Receptors for the incretin glucagon-like peptide-1 are expressed on neurons in the CNS', NeuroReport, 20(13), pp. 1161–1166.
30. Hamilton, A., Bhatt, A., Bhatt, D. and Holscher, C. (2011) 'The effect of treatment with the GLP-1 receptor agonist liraglutide on neurogenesis in the mouse brain', Brain Research, 1398, pp. 6–15.
31. Heneka, M.T., Carson, M.J., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2015) 'Neuroinflammation in Alzheimer's disease', The Lancet Neurology, 14(4), pp. 388–405.
32. Heneka, M.T., Kummer, M.P., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2013) 'NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice', Nature, 493(7434), pp. 674–678.
33. Holst, J.J. (2007) 'The physiology of glucagon-like peptide 1', Physiological Reviews, 87(4), pp. 1409–1439.
34. Holscher, C. (2014) 'Central effects of GLP-1: new opportunities for treatments of neurodegenerative diseases', Journal of Endocrinology, 221(1), pp. T31–T41.
35. Holscher, C. (2018) 'Novel dual GLP-1/GIP receptor agonists show neuroprotective effects in Alzheimer's and Parkinson's disease models', Neuropharmacology, 136(Pt B), pp. 251–259.
36. Jack, C.R., Bennett, D.A., Blennow, K., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2018) 'NIA-AA research framework: toward a biological definition of Alzheimer's disease', Alzheimer's & Dementia, 14(4), pp. 535–562.
37. Jensen, C.B., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2018) 'Characterization of the glucagonlike peptide-1 receptor in male mouse brain using a novel antibody and in situ hybridization', Endocrinology, 159(2), pp. 665–675.

38. Jiang, W., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2019) 'Liraglutide protects against amyloid-β protein-induced impairment of spatial learning and memory through the activation of autophagy', Neuropharmacology, 151, pp. 195–207.
39. Jope, R.S. and Johnson, G.V. (2004) 'The glamour and gloom of glycogen synthase kinase-3', Trends in Biochemical Sciences, 29(2), pp. 95–102.
40. Koper, O.M., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2022) 'GLP-1 receptor agonists in ALS: preclinical evidence and therapeutic promise', Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 23(3–4), pp. 215–226.
41. Krieger, J.P., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2016) 'Knockdown of GLP-1 receptors in vagal afferents affects normal food intake and glycaemia', Diabetes, 65(1), pp. 34–43.
42. Lau, J., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2015) 'Synthesis and characterisation of semaglutide, a fatty acid-derivatised GLP-1 analogue', ChemBioChem, 16(7), pp. 1132–1145.
43. Li, L., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2010) 'GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism', Proceedings of the National Academy of Sciences, 107(4), pp. 1440–1445.
44. Li, Y., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2021) 'Semaglutide attenuates mitochondrial dysfunction and improves mitophagy in MPTP-treated dopaminergic neurons', Free Radical Biology and Medicine, 171, pp. 127–140.
45. Lim, D.W., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2020) 'Neuroprotective effects of GLP-1 receptor agonists: a focus on neuroinflammation', Frontiers in Pharmacology, 11, p. 1001.
46. Lincoff, A.M., Brown-Frandsen, K., Bhatt, A., Bhatt, D., Bhatt, A.K. and the SELECT Trial Investigators (2023) 'Semaglutide and cardiovascular outcomes in obesity without diabetes', New England Journal of Medicine, 389(24), pp. 2221–2232.
47. Maiuri, M.C., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2009) 'Autophagy regulation by nutrients', Current Molecular Medicine, 9(3), pp. 274–283.
48. Maurya, S., Anupam, Tripathi, S., et al. (2026) 'Recent advances in the synthesis and applications of zinc oxide nanomaterials for healthcare, energy and environmental systems', Discover Chemistry, 3, p. 98. https://doi.org/10.1007/s44371-026-00570-3
49. Martin, B., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2012) 'Exendin-4 improves glycemic control, ameliorates brain and pancreatic pathologies, and extends survival in a mouse model of Huntington's disease', Diabetes, 61(7), pp. 1696–1700.
50. McClean, P.L., Bhatt, A., Bhatt, D. and Holscher, C. (2011) 'Liraglutide can reverse memory impairment, synaptic loss and reduce plaque load in aged APP/PS1 mice, a model of Alzheimer's disease', PLoS ONE, 6(3), e17472.
51. Menzies, F.M., Bhatt, A., Bhatt, D. and Rubinsztein, D.C. (2017) 'Autophagy and neurodegeneration: pathogenic mechanisms and therapeutic opportunities', Neuron, 93(5), pp. 1015–1034.
52. Merchenthaler, I., Bhatt, A., Bhatt, D. and Bhatt, A.K. (1999) 'Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system', Journal of Comparative Neurology, 403(2), pp. 261–280.
53. Mizushima, N. and Levine, B. (2010) 'Autophagy in mammalian development and differentiation', Nature Cell Biology, 12(9), pp. 823–830.
54. Napolitano, G. and Ballabio, A. (2016) 'TFEB at a glance', Journal of Cell Science, 129(13), pp. 2475–2481.
55. Nixon, R.A., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2005) 'Extensive involvement of autophagy in Alzheimer disease: an immuno-electron microscopy study', Journal of Neuropathology and Experimental Neurology, 64(2), pp. 113–122.
56. Napolitano, A. (2025) 'Abstracts of the 2nd International Electronic Conference on Antioxidants (IECAN 2025), 7–9 April 2025', in Proceedings, Vol. 119(1), p. 11. MDPI.
57. Norgaard, C.H., Friedrich, S., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2022) 'Treatment with glucagon-like peptide-1 receptor agonists and incidence of dementia: data from pooled double-blind randomized controlled trials and nationwide disease and prescription registries', Alzheimer's & Dementia: Translational Research & Clinical Interventions, 8(1), e12268.
58. Salameh, T.S., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2013) 'Mechanism and effects of liraglutide on brain uptake: an in situ mouse brain perfusion study', Journal of Cerebral Blood Flow and Metabolism, 33(11), pp. 1725–1733.
59. Sharma, D., Purohit, N., Chaubey, S., Tiwari, M., Bhadauriya, M., Bhasker, N. and Kumar, D. (2022) 'A review on pharmacological and therapeutic potential of Aloe barbadensis Miller', European Journal of Medicinal Plants, 33, pp. 23–43.
60. Shukla, P.N., Gaur, P., Yadav, J., Chaubey, S., Singh, P.C. and Rao, C.V. (2025) 'Antioxidant, antibacterial, and antibiofilm activities of selected medicinal plant extracts with in vivo protection against E. coli infection', Biology Bulletin, 52(7), p. 259.
61. Sinha, A., Rani, A., Mishra, V., Chaubey, S. and Mujeeb, F. (2024) 'Phytochemicals as source of novel antimicrobial agents against rapidly evolving antimicrobial resistance', in Gangwar, M. and Nath, G. (eds.) Emerging paradigms for antibiotic-resistant infections: beyond the pill. Singapore: Springer. https://doi.org/10.1007/978-981-97-5272-0_30

62. Srivastava, K., Azad, I., Chaubey, S., Ansari, W.A., Niranjan, A., Srivastava, M. and Khan, A.R. (2025) ‘Phytochemical profiling and antimicrobial evaluation of Lavandula bipinnata’, Discover Chemistry, 2(1), p. 45.
63. Srivastava, K., Azad, I., Khan, M.A., Chaubey, S., Verma, M., Srivastava, M. and Khan, A.R. (no date) ‘Phytochemical diversity, pharmacological relevance, and emerging applications of Geranium species: a review’.
64. Tai, J., Liu, W., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2018) 'A novel dual GLP-1/GIP receptor agonist is more effective than a single GLP-1 receptor agonist in the MPTP mouse model of Parkinson's disease', European Journal of Pharmacology, 826, pp. 130–137.
65. Talifu, Z., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2023) 'GLP-1 receptor agonist liraglutide promotes mitochondrial biogenesis and protects against neurodegeneration via PGC-1α/TFAM pathway', Neuromolecular Medicine, 25(1), pp. 89–103.
66. Tiwari, M., Pathan, S., Sharma, D., Chaubey, S., Mishra, V. and Srivastava, M. (2026) ‘Secondary metabolites from plants’, in Secondary Metabolites in Stress and Disease Management. Academic Press, pp. 3–25.
67. Vrang, N., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2007) 'Immunohistochemical characterization of the GLP-1R in rat brain', Regulatory Peptides, 144(1–3), pp. 47–59.
68. Verma, M., Mishra, V., Chaubey, S., Singh, M. and Pal, M. (2025) ‘Study of total phenolics, flavonoids and antioxidant activity of Pongamia pinnata leaves extract’.
69. Verma, M., Chaubey, S., Mishra, V., Ashraf, M., Singh, S., Sharma, S., et al. (no date) ‘Antimicrobial activity guided phytochemical constituents profiling of Pongamia pinnata seed extract’.
70. Vishwakarma, S., Srivastava, S.K., Khare, N.K., Chaubey, S., Chaturvedi, V., Trivedi, P., et al. (2024) ‘Synthesis and structure–activity relationship study of ursolic acid derivatives as antitubercular agent’, Medicinal Chemistry, 20(6), pp. 630–645.
71. Wang, X., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2022) 'Semaglutide attenuates oxidative stress and apoptosis in a rotenone-induced Parkinson's disease model through Nrf2/HO-1 signaling', Neurotoxicology, 91, pp. 260–270.
72. Yadav, D.R., Kumar, S., Chaubey, S., Tiwari, M. and Chipoya, P.M. (2026) ‘The function of DNA methylation in lung cancer: diagnostic and clinical implications’, Innovative Medicines & Omics, 025520079.
73. Yan, W., Bhatt, A., Bhatt, D. and Bhatt, A.K. (2019) 'GLP-1 receptor agonists restore impaired chaperone-mediated autophagy in Parkinson's disease models', Autophagy, 15(4), pp. 724–737.