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REVIEW ARTICLE

Anti-Inflammatory and Antioxidant Mechanisms of GLP-1 Receptor Agonists: Molecular Pathways and Therapeutic Implications

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as important therapeutic agents in type 2 diabetes mellitus (T2DM) and obesity, with benefits extending beyond glycaemic control and weight reduction. Growing preclinical and clinical evidence indicates that GLP-1RAs exert significant anti-inflammatory and antioxidant effects through mechanisms that are partly independent of their glucose-lowering actions. This review comprehensively examines the molecular pathways underlying these pleiotropic effects and highlights their translational relevance across multiple organ systems. GLP-1RAs modulate inflammatory Signalling by inhibiting nuclear factor-kappa B (NF-κB) activation and suppressing NLRP3 inflammasome activity through cyclic AMP–protein kinase A (cAMP–PKA)-mediated pathways, thereby reducing the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. In parallel, GLP-1RAs enhance cellular antioxidant defenses by activating the Nrf2/Keap1 pathway, inhibiting NADPH oxidase activity, and improving mitochondrial function, thereby reducing oxidative stress and lipid peroxidation. These effects contribute to cardioprotective, hepatoprotective, renoprotective, and neuroprotective outcomes observed in experimental and clinical studies. Furthermore, this review integrates current biomarker evidence with mechanistic insights to provide a comprehensive overview of the interconnected inflammatory and oxidative stress pathways targeted by GLP-1RAs. Collectively, these findings support the expanding therapeutic potential of GLP-1RAs in chronic inflammatory and metabolic disorders, including non-alcoholic steatohepatitis, chronic kidney disease, neurodegenerative diseases, and cardiovascular complications.

Keywords: GLP-1 receptor, agonists, Inflammation, Oxidative stress, NF-κB, Nrf2/Keap1, cAMP–PKA pathway

INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is a 30–amino acid incretin hormone derived from post-translational processing of proglucagon in intestinal L-cells. Secreted in response to nutrient ingestion, endogenous GLP-1 has a circulating half-life of only 1-2 minutes due to rapid degradation by dipeptidyl peptidase-4 (DPP-4). Despite its brevity, GLP-1 exerts pleiotropic physiological effects through the widely distributed GLP-1 receptor (GLP-1R), a class B G protein-coupled receptor (GPCR) expressed in the pancreas, heart, kidney, liver, lung, central nervous system, and immune

cells[1, 2]. The primary physiological actions of GLP-1 include glucose-dependent stimulation of insulin secretion, suppression of glucagon release, delayed gastric emptying, and central appetite suppression. However, this classical incretin framework represents only a fraction of GLP-1R biology; receptor activation initiates a complex intracellular signalling cascade involving cyclic AMP (cAMP), protein kinase A (PKA), phosphoinositide 3-kinase (PI3K)/Akt, and mitogen-activated protein kinase (MAPK) pathways, each with downstream effects on inflammation, oxidative stress, and cell survival[1, 2]. GLP-1RAs are engineered peptides designed to resist DPP-4 degradation while retaining or enhancing GLP-1R agonism. The class spans a clinical spectrum from short-acting, meal-time agents (exenatide twice daily, lixisenatide) to long-acting weekly formulations (semaglutide, dulaglutide, albiglutide) and the first oral GLP-1RA (oral semaglutide). More recently, tirzepatide, a dual GIP/GLP-1 receptor agonist, has demonstrated superior glycaemic and weight-loss outcomes, with emerging evidence of additional anti-inflammatory effects mediated by GIP receptor co-activation[3]. Approved indications have expanded from T2DM to obesity (semaglutide 2.4 mg, liraglutide 3.0 mg) and, in select agents, primary cardiovascular risk reduction. The cardiovascular outcome trials (CVOTs) LEADER, SUSTAIN-6, HARMONY OUTCOMES, and REWIND documented significant reductions in major adverse cardiovascular events (MACE) of 13–26%, with residual benefit persisting after adjustment for glycaemic and weight changes, strongly implicating GLP-1R-specific mechanisms, including anti-inflammatory effects[4]. This narrative review was conducted using literature retrieved from PubMed, Scopus, Web of Science, and Google Scholar databases. Keywords included "GLP-1 receptor agonists," "inflammation," "oxidative stress," "NF-κB," "Nrf2," and "NLRP3 inflammasome." Articles published in English between 2005 and 2026 were considered. Priority was given to peer-reviewed mechanistic studies, randomized clinical trials, meta-analyses, and translational studies relevant to the inflammatory and antioxidant effects of GLP-1 receptor agonists.

Chronic low-grade inflammation and sustained oxidative stress are now recognised as central pathophysiological drivers in T2DM, obesity, non-alcoholic fatty liver disease (NAFLD/MASH), atherosclerosis, and diabetic nephropathy. Nuclear factor-κB (NF-κB), the master transcriptional regulator of inflammation, and the NLRP3 inflammasome, the principal innate immune complex mediating IL-1β maturation, are constitutively hyperactivated in these conditions. Simultaneously, the Nrf2 antioxidant defense system, which governs expression of heme oxygenase-1 (HO-1), superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), is functionally suppressed[5, 6]. These two axes are not independent: reactive oxygen species (ROS) activate NF-κB and prime the NLRP3 inflammasome. At the same time, inflammatory signalling upregulates NADPH oxidases (NOX2/NOX4) and iNOS, thereby generating additional ROS and creating a self-amplifying pathological feedback loop. GLP-1RAs, by virtue of their engagement with a receptor coupled to both cAMP/PKA and PI3K/Akt, are uniquely positioned to interrupt this loop at multiple nodes simultaneously[6-8]. This review provides a comprehensive mechanistic analysis of the anti-inflammatory and antioxidant properties of GLP-1RAs, organized around:

1. molecular signalling pathways
2. organ-specific manifestations
3. clinical biomarker evidence
4. therapeutic implications.

We also address the bidirectional crosstalk between oxidative stress and inflammation, the emerging pharmacology of dual- and triple-receptor agonists, and priority research gaps.

GLP-1 Receptor Structure and Tissue Distribution

The GLP-1R is a 463-amino acid class B GPCR characterized by a large extracellular N-terminal domain that forms the primary peptide-binding site. Upon GLP-1 or GLP-1RA engagement, the receptor undergoes conformational changes that promote Gαs coupling and subsequent adenylyl cyclase activation. GLP-1R expression is heterogeneous: highest in pancreatic beta cells and alpha cells, with significant expression in cardiac myocytes, vascular endothelium, renal tubular epithelium, adipocytes, macrophages, microglia, and enteric neurons. This broad distribution underpins the pleiotropic pharmacological profile of GLP-1RAs and accounts for their organ-specific anti-inflammatory effects[9-11].

Canonical cAMP/PKA Signalling Axis

The predominant signalling pathway downstream of GLP-1R activation is Gαs-mediated stimulation of adenylyl cyclase, which converts ATP to intracellular cAMP. Elevated cAMP activates two primary effectors: protein kinase A (PKA) and exchange protein activated by cAMP (Epac). PKA phosphorylates a broad spectrum of substrates with anti-inflammatory and antioxidant consequences: IKKβ (disrupting NF-κB activation), NLRP3 (preventing inflammasome assembly), CREB (inducing anti-inflammatory gene expression), and Nrf2 co-activators. Epac signalling contributes to calcium mobilization, mitochondrial quality control, and M2 macrophage polarisation[12, 13].

Table 1: Tissue Distribution of GLP-1 Receptors and Their Functional Roles

Organ/System	GLP-1R Expression Site	Physiological/Pharmacological Role
Pancreas	β-cells (high), α-cells (low)	↑ Insulin secretion, ↓ glucagon release, β-cell survival
Brain (CNS)	Hypothalamus, brainstem (NTS, area postrema)	Appetite suppression, satiety, neuroprotection
Cardiovascular	Cardiomyocytes, endothelial cells	Cardioprotection, ↑ endothelial function, ↓ inflammation
Kidney	Proximal tubules, glomerular cells	Natriuresis, ↓ oxidative stress, renal protection
Adipose Tissue	Adipocytes	↑ insulin sensitivity, ↓ inflammation, lipid metabolism
Gastrointestinal Tract	Enteric neurons, gastric mucosa	Delayed gastric emptying, gut motility regulation
Lung	Airway smooth muscle	Possible anti-inflammatory effects
Immune Cells	Macrophages, lymphocytes	↓ cytokine production, anti-inflammatory action

Non-canonical Pathways: PI3K/Akt, MAPK, and β-Arrestin

Beyond Gαs, GLP-1R activates PI3K/Akt signalling, which phosphorylates and activates Nrf2 (at Ser40 via Akt-downstream kinases) while inhibiting GSK-3β, a kinase that otherwise exports Nrf2 from the nucleus. PI3K/Akt also activates mTORC1 in a context-dependent manner and suppresses FoxO transcription factors, reducing pro-apoptotic and pro-inflammatory gene expression. ERK1/2 (MAPK) activation downstream of GLP-1R promotes cell survival and has been linked to macrophage polarisation. β-Arrestin-mediated receptor internalization, independent of G-protein Signalling, initiates a distinct wave of Signalling from endosomes, providing sustained anti-inflammatory effects beyond the initial cAMP burst[14-17].

Crosstalk with Insulin, Leptin, and Adipokine Signalling

GLP-1RA signalling intersects substantially with the insulin receptor/IRS-1/PI3K axis, leptin receptor JAK-STAT signalling, and adiponectin signalling. GLP-1RAs enhance insulin sensitivity, in part, through anti-inflammatory mechanisms. TNF-α and IL-6 are canonical inducers of IRS-1 serine phosphorylation and insulin resistance. By suppressing these cytokines, GLP-1RAs reduce an important driver of metabolic inflammation. Simultaneously, GLP-1RAs increase circulating adiponectin, which itself activates AMPK and exerts anti-inflammatory and antioxidant effects, creating a reinforcing feed-forward loop[18, 19].

1) Anti-Inflammatory Mechanism

NF-κB Signalling Inhibition:

NF-κB is the master transcriptional regulator of inflammation, governing expression of over 150 target genes, including TNF-α, IL-1β, IL-6, IL-8, COX-2, iNOS, MCP-1, VCAM-1, ICAM-1, and E-selectin. In the canonical pathway, pro-inflammatory stimuli (LPS, TNF-α, free fatty acids, hyperglycemia, AGEs) activate the IκB kinase (IKK) complex, which phosphorylates inhibitory IκBα, leading to its ubiquitination and proteasomal degradation. Released NF-κB p65/p50 dimers translocate to the nucleus and drive inflammatory gene transcription[12, 15].

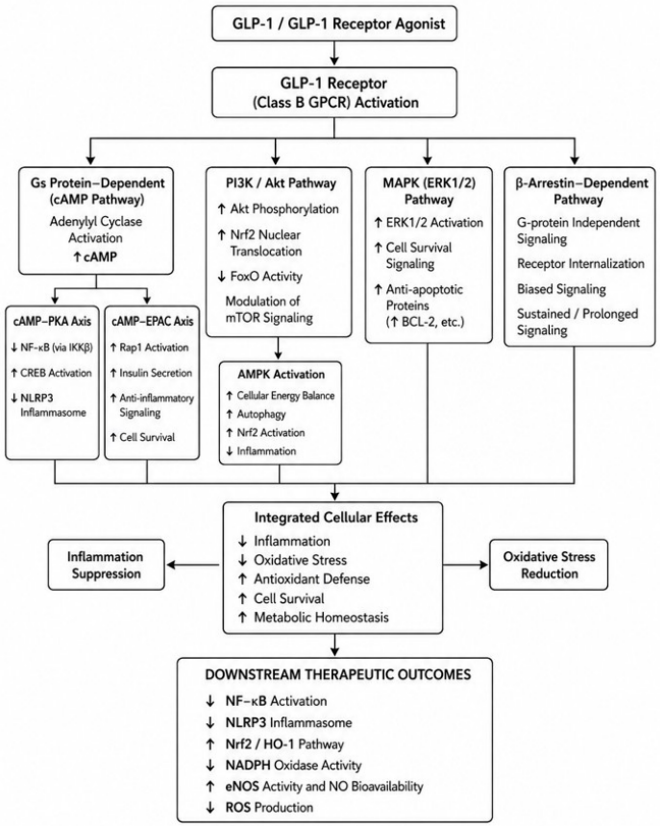

Fig. 1: Schematic representation of the GLP-1 receptor signalling cascade illustrating activation of cAMP/PKA, PI3K/Akt, and related downstream pathways involved in the regulation of inflammation, oxidative stress, and cellular survival. These signalling mechanisms collectively contribute to reduced NF-κB and NLRP3 inflammasome activation, enhanced Nrf2/HO-1 antioxidant responses, decreased ROS generation, and improved therapeutic outcomes across multiple tissues

GLP-1RAs interrupt this pathway at multiple steps. PKA directly phosphorylates IKKβ at Ser177 and Ser181, suppressing kinase activity and stabilizing IκBα.

Additionally, cAMP promotes IκBα resynthesis through CREB-dependent transcription, providing dual protection. PKA-activated CREB can also compete with p65 for coactivator binding to CBP/p300, further suppressing NF-κB transcriptional output. These mechanisms collectively account for the 15–40% reductions in circulating TNF-α, IL-6, IL-1β, and CRP documented in clinical trials of liraglutide, exenatide, and semaglutide[12, 20].

NLRP3 Inflammasome Suppression:

The NLRP3 inflammasome is a multiprotein complex (NLRP3, ASC, pro-caspase-1) critical for innate immune responses in cardiometabolic disease. Activated by diverse danger signals, including cholesterol crystals, fatty acids, uric acid, ATP, and ROS, NLRP3 drives caspase-1-mediated cleavage and secretion of IL-1β and IL-18, which are potent inducers of vascular and metabolic inflammation. GLP-1RAs suppress NLRP3 activation via PKA-mediated phosphorylation of NLRP3 at Ser295, thereby preventing its oligomerization and recruitment of ASCs. This direct phosphorylation is cAMP-dependent and has been demonstrated in macrophages, adipocytes, and cardiomyocytes exposed to liraglutide and semaglutide, with downstream reductions in caspase-1 activity and mature IL-1β secretion of 30–60% in preclinical models[21, 22].

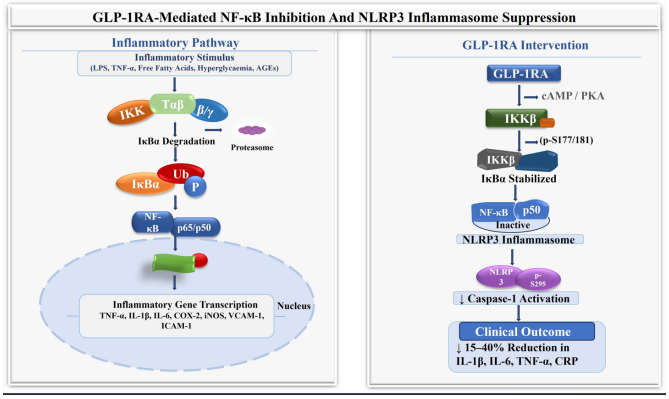

Fig. 2: GLP-1RAs suppress inflammation by inhibiting NF-κB Signalling and NLRP3 inflammasome activation through the cAMP–PKA pathway. These effects reduce pro-inflammatory cytokine production, caspase-1 activation, and IL-1β/IL-18 release, thereby attenuating inflammatory and oxidative stress responses

Macrophage Polarization M1 to M2 Phenotype Shift:

Macrophage polarisation is a critical determinant of tissue inflammation in obesity, atherosclerosis, and NAFLD. Pro-inflammatory M1 macrophages (activated by LPS and IFN-γ) produce TNF-α, IL-1β, IL-12, and reactive nitrogen species, while anti-inflammatory M2 macrophages (activated by IL-4, IL-13) secrete IL-10, TGF-β, and arginase-1. GLP-1RAs promote M1-to-M2 polarisation through cAMP/Epac-mediated PPARγ activation and AMPK phosphorylation, effects corroborated by transcriptomic studies in adipose tissue macrophages from liraglutide-treated obese mice, showing enrichment of M2-associated gene signatures and a reduction in M1 markers[23-25].

Endothelial Anti-Inflammatory Effects:

Endothelial dysfunction, characterized by upregulation of adhesion molecules (VCAM-1, ICAM-1, E-selectin) and reduced nitric oxide (NO) bioavailability, is an early and critical step in atherogenesis. GLP-1RAs directly activate endothelial GLP-1Rs, increasing cAMP, activating eNOS through PKA and Akt phosphorylation (Ser1177), and stimulating NO production. Simultaneously, NF-κB inhibition reduces adhesion molecule expression, diminishing monocyte-endothelial interactions. In human aortic endothelial cells exposed to high glucose, liraglutide treatment reduced VCAM-1 and ICAM-1 expression by 40–55%, accompanied by IκBα stabilization and preserved eNOS coupling[26, 27].

Gut Microbiome Modulation:

Intestinal dysbiosis, characterized by reduced microbial diversity, overgrowth of gram-negative LPS-producing bacteria, and impaired gut barrier integrity, drives systemic endotoxemia and low-grade inflammation in obesity and T2DM. GLP-1RAs, by slowing gastric emptying and exerting direct effects on intestinal L-cells and enteric neurons, alter the composition of the gut microbiome. Clinical studies of semaglutide and liraglutide report increased abundances of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, organisms associated with mucosal integrity and anti-inflammatory short-chain fatty acid (SCFA) production, alongside reduced circulating LPS and LPS-binding protein[28].

Central Nervous System Anti-Inflammatory Effects:

GLP-1Rs are expressed on microglia, astrocytes, hypothalamic neurons, and dopaminergic neurons of the substantia nigra. In models of neuroinflammation relevant to obesity and neurodegeneration, GLP-1RAs suppress microglial NF-κB activation, reduce TNF-α and IL-6 secretion in the CNS, and promote microglial M2 polarization. In Parkinson's disease models, liraglutide reduced dopaminergic neuron loss associated with LPS-induced neuroinflammation. Semaglutide has shown reductions in amyloid-β-induced ROS and tau hyperphosphorylation in Alzheimer's disease animal models, supporting emerging clinical trials in neurodegeneration[26, 29].

Table 2: Anti-Inflammatory Molecular Pathways of GLP-1 Receptor Agonists

Pathway	Molecular Mechanism	Key Mediators Affected	Primary Tissue Sites	Evidence (Agents)
NF-κB Inhibition	Blocks IKK phosphorylation; prevents IκB degradation	↓ TNF-α, IL-1β, IL-6, MCP-1, VCAM-1	Endothelium, macrophages, hepatocytes	Liraglutide, semaglutide, exenatide
NLRP3 Inflammasome Suppression	cAMP-PKA axis inhibits inflammasome assembly; blocks caspase-1	↓ IL-1β, IL-18 maturation	Macrophages, adipocytes, cardiomyocytes	Liraglutide, semaglutide
M1→M2 Macrophage Polarization	Shifts macrophage phenotype via PPARγ and AMPK activation	↑ IL-10, TGF-β, arginase-1; ↓ iNOS	Adipose tissue, liver, arterial wall	Liraglutide, dulaglutide
Endothelial Anti-Inflammation	Reduces shear stress-induced inflammatory signalling; eNOS upregulation	↓ VCAM-1, ICAM-1, E-selectin; ↑ NO	Vascular endothelium	All long-acting GLP-1RAs
Microglial Suppression	PKA-dependent downregulation of neuroinflammatory mediators	↓ TNF-α, IL-6, IL-1β in CNS	Microglia, astrocytes	Liraglutide, semaglutide
Gut Microbiome Modulation	Alters bile acid composition, SCFAs; reduces intestinal permeability	↓ LPS-driven systemic inflammation	Intestinal epithelium, gut immune cells	Semaglutide, liraglutide

Note: *NF-κB = nuclear factor-kappa B; NLRP3 = NOD-like receptor protein 3; iNOS = inducible nitric oxide synthase; eNOS = endothelial NOS; SCFAs = short-chain fatty acids; LPS = lipopolysaccharide; PPARγ = peroxisome proliferator-activated receptor gamma; AMPK = AMP-activated protein kinase.*

2) Antioxidant Mechanisms Nrf2/Keap1 Antioxidant Pathway Activation

The Nrf2 (nuclear factor erythroid 2-related factor 2) transcription factor is the central regulator of the cellular antioxidant defense system. Under basal conditions, Nrf2 is retained in the cytoplasm by its repressor Keap1 (Kelch-like ECH-associated protein 1), which promotes Nrf2 ubiquitination and proteasomal degradation with a half-life of approximately 20 minutes. Oxidative modification of Keap1 cysteine residues (Cys151, Cys273, Cys288) dissociates the complex, allowing Nrf2 to accumulate in the nucleus and bind to antioxidant response elements (AREs). GLP-1RAs activate Nrf2 through both PKA-dependent (Nrf2 Ser40 phosphorylation) and PI3K/Akt-dependent (GSK-3β inhibition, preventing Nrf2 nuclear export) mechanisms. This dual activation stabilizes nuclear Nrf2 and drives sustained expression of: HO-1 (heme oxygenase-1), NQO1 (NAD(P)H quinone oxidoreductase-1), SOD1/2 (superoxide dismutases), catalase, glutathione peroxidase (GPx), glutamate-cysteine ligase (GCL, rate-limiting for GSH synthesis), thioredoxin, and ferritin. Clinical studies document 20–45% increases in total antioxidant capacity and significant elevations in SOD and catalase activities in T2DM patients treated with liraglutide[15, 30, 31].

NADPH Oxidase Inhibition:

NADPH oxidases (NOX enzymes), particularly NOX2 and NOX4, are the primary enzymatic sources of superoxide anion in cardiovascular and inflammatory cells. NOX2 is expressed predominantly in macrophages, neutrophils, and vascular smooth muscle cells, where it forms a multiprotein complex (gp91phox, p22phox, p47phox, p67phox, p40phox, and Rac1). GLP-1RAs suppress NOX2 assembly through PKA-mediated phosphorylation of p47phox, preventing its membrane translocation and Rac1 co-activation. NOX4, constitutively active in the endothelium and kidney, is transcriptionally downregulated by Nrf2 activation and by GLP-1RA-induced reduction in ER stress, which is a major inducer of NOX4 expression[32, 33].

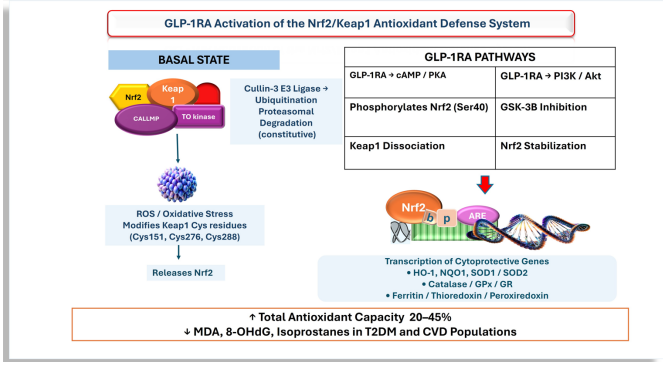

Fig. 3: GLP-1 receptor agonists activate the Nrf2/Keap1 antioxidant pathway through cAMP–PKA and PI3K/Akt Signalling, promoting Nrf2 stabilization and nuclear translocation. This enhances the transcription of cytoprotective antioxidant genes, including HO-1, NQO1, SOD, catalase, and GPx, thereby reducing oxidative stress markers and improving total antioxidant capacity

Table 3: Antioxidant Mechanisms of GLP-1 Receptor Agonists: Molecular Targets and Evidence

Antioxidant Mechanism	Molecular Mechanism	Key Mediators / Markers	Primary Tissue Sites	Evidence (Agents)
Nrf2/Keap1 Pathway Activation	PKA/PI3K-Akt phosphorylates Nrf2; Keap1 dissociation; nuclear translocation	↑ HO-1, NQO1, SOD1/2, catalase, GPx, GSH	Hepatocytes, cardiomyocytes, neurons	Liraglutide, exenatide, semaglutide
NADPH Oxidase Inhibition	PKA-mediated suppression of NOX2/NOX4 subunit assembly; Rac1 inhibition	↓ Superoxide anion (O_2^-), H_2O_2	Endothelium, macrophages, and the kidney	Liraglutide, dulaglutide
Mitochondrial ROS Attenuation	Preserves electron transport chain integrity; activates UCP2; reduces Complex I leak	↓ Mitochondrial superoxide; ↑ ATP efficiency	Cardiomyocytes, hepatocytes, beta cells	All GLP-1RAs
Mitophagy & Mitochondrial Biogenesis	PGC-1α/TFAM upregulation; PINK1-Parkin pathway activation; AMPK-dependent autophagy	↑ mtDNA content; ↓ damaged mitochondria	Skeletal muscle, liver, cardiac tissue	Liraglutide, semaglutide
Lipid Peroxidation Reduction	Attenuates 4-HNE, MDA formation; reduces oxLDL production; lipoxygenase modulation	↓ Isoprostanes, MDA, 4-HNE, oxLDL	Vascular wall, liver, adipose tissue	Liraglutide, exenatide, semaglutide
ER Stress Mitigation	Reduces unfolded protein response (UPR); modulates IRE1α, PERK, ATF6 branches	↓ GRP78, CHOP, XBP-1s; improved proteostasis	Beta cells, hepatocytes, macrophages	Liraglutide, exenatide
AGE/RAGE Axis Suppression	Reduces advanced glycation; downregulates RAGE receptor expression and signalling	↓ AGEs, sRAGE binding; ↓ oxidative burst	Kidney, retina, vascular endothelium	Liraglutide, semaglutide

Note: *HO-1 = heme oxygenase-1; NQO1 = NAD(P)H: quinone oxidoreductase 1; SOD = superoxide dismutase; GPx = glutathione peroxidase; GSH = glutathione; MDA = malondialdehyde; 4-HNE = 4-hydroxynonenal; AGE = advanced glycation end-product; RAGE = receptor for AGE; ER = endoplasmic reticulum; ROS = reactive oxygen species; UPR = unfolded protein response.*

Mitochondrial Control and Biogenesis:

Dysfunctional mitochondria are a major source of intracellular ROS via electron leakage from Complexes I and III of the electron transport chain. GLP-1RAs promote mitochondrial health through multiple convergent mechanisms. PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha), the master regulator of mitochondrial biogenesis, is upregulated by cAMP/CREB and AMPK signalling downstream of GLP-1R activation. AMPK activation also promotes mitophagy through ULK1 phosphorylation and induction of the PINK1-Parkin pathway, selectively eliminating depolarized, ROS-generating mitochondria. In diabetic cardiomyopathy models, liraglutide treatment preserved mitochondrial membrane potential, increased mtDNA copy number by 35%, and reduced 4-hydroxynonenal (4-HNE) protein adducts, a marker of lipid peroxidation-driven mitochondrial damage[34, 35].

Lipid Peroxidation and AGE Reduction:

Lipid peroxidation, the oxidative degradation of polyunsaturated fatty acids by ROS, generates reactive aldehydes (MDA, 4-HNE, acrolein) that form protein adducts, disrupt membrane function, and amplify inflammation. GLP-1RAs reduce lipid peroxidation markers (MDA, isoprostanes) by 25–45% in clinical studies, attributable to direct ROS scavenging via Nrf2-induced antioxidant pathways, reduced substrate availability through weight loss, improved lipid profiles, and decreased lipoxygenase and cyclooxygenase activity via NF-κB suppression. Advanced glycation end-products (AGEs), formed by non-enzymatic glycation of proteins and lipids in hyperglycaemic conditions, activate the RAGE receptor to generate ROS and induce NF-κB. GLP-1RAs reduce AGE formation through glycaemic control and independently downregulate RAGE expression in endothelial and renal cells[36-39].

Organ-Specific Therapeutic Implications

1) Cardiovascular System

The cardiovascular anti-inflammatory effects of GLP-1RAs are among the best-characterized, supported by both mechanistic studies and large CVOTs. In the vascular wall, GLP-1RAs reduce macrophage foam cell formation by suppressing cholesterol crystal-induced NLRP3 activation and promoting ABCA1-mediated cholesterol efflux. They attenuate VCAM-1 and ICAM-1-mediated monocyte recruitment, reducing plaque macrophage density. In the myocardium, GLP-1RAs provide ischemia-reperfusion protection through cAMP-mediated activation of the RISK (Reperfusion Injury Salvage Kinase) pathway and opening of mitochondrial KATP channels, effects demonstrated in both rodent and porcine cardiac models. The LEADER trial (liraglutide, n=9,340) and SUSTAIN-6 (semaglutide, n=3,297) each documented significant reductions in MACE, with post hoc analyses indicating associations between

reductions in CRP and reductions in CV event risk, suggesting that anti-inflammatory mechanisms contribute incrementally to cardioprotection beyond glycaemic improvement[40].

2) Liver NAFLD and Non-Alcoholic Steatohepatitis

GLP-1Rs are expressed on hepatic stellate cells and, at low levels, on hepatocytes, with significant indirect hepatic effects mediated by reduced adipose tissue lipolysis and central appetite suppression. In NAFLD/NASH models, GLP-1RAs reduce hepatic steatosis by suppressing de novo lipogenesis (via SREBP-1c downregulation). At the same time, anti-inflammatory effects include reduced Kupffer cell TNF-α and MCP-1 secretion, hepatic NF-κB activity, and hepatic stellate cell activation (TGF-β, α-SMA). The LEAN trial (liraglutide, 72 weeks) demonstrated histological improvement in NASH in 39% vs 9% of placebo patients. The phase 3 semaglutide NASH trial (n=320) reported NASH resolution in 59% vs 17% in controls, with a reduction in liver inflammation score of 2.1 points vs 0.8 points. Mechanistically, hepatic oxidative stress markers (MDA, 8-OHdG) decreased significantly and correlated with upregulation of Nrf2 and HO-1 in paired liver biopsies[41, 42].

3) Kidney Diabetic Nephropathy

Diabetic nephropathy (DKD) is driven by a combination of glomerular hemodynamic stress, inflammation, and oxidative injury to tubular and mesangial cells. GLP-1Rs are expressed on renal proximal tubular cells and medullary collecting ducts, enabling direct renal effects beyond systemic glycaemic improvement. GLP-1RAs reduce glomerular macrophage infiltration, mesangial NF-κB activity, and tubular ICAM-1 expression in DKD models. Oxidative stress biomarkers (8-OHdG and MDA in urine and renal tissue) are significantly reduced, accompanied by increased expression of catalase and SOD2. The REWIND trial (dulaglutide, n=9,901) demonstrated a 15% reduction in the composite renal outcome (sustained macroalbuminuria, eGFR decline, renal death), extending prior data from LEADER and SUSTAIN-6. A notable fraction of the renal benefit appeared to be independent of glycaemic control, consistent with direct anti-inflammatory and antioxidant effects on the kidney[43, 44].

4) Adipose Tissue

Adipose tissue inflammation, characterized by crown-like structures of macrophages surrounding dead adipocytes, elevated MCP-1 and leptin levels, and reduced adiponectin levels, is a key driver of insulin resistance and systemic inflammation in obesity. GLP-1RAs reduce adipose macrophage infiltration, shift adipose tissue macrophages from M1 to M2 phenotype, and restore adiponectin secretion by 15–25%. Adipocyte ROS are reduced through improved mitochondrial function and attenuated lipid peroxidation, effects associated with improved insulin Signalling (IRS-1 Ser→Tyr phosphorylation ratio) and GLUT4 translocation[45, 46].

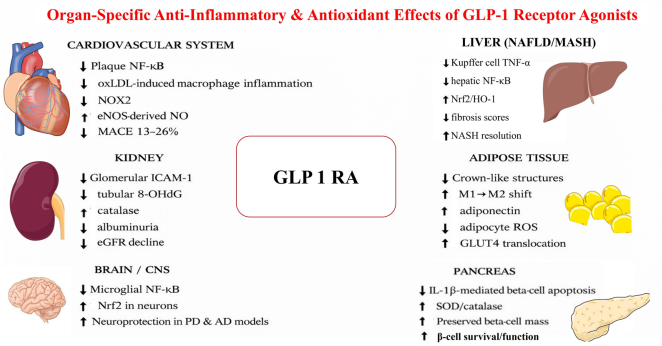

Fig. 4: Organ-specific protective effects of GLP-1 receptor agonists are mediated through anti-inflammatory and antioxidant mechanisms across the cardiovascular system, liver, kidney, adipose tissue, brain, and pancreas. GLP-1RAs reduce inflammatory signalling, oxidative stress, and tissue injury while improving metabolic and cellular functions in multiple organ systems

5) Brain and Neurodegenerative Disease

The neuroprotective potential of GLP-1RAs represents a rapidly evolving area of investigation. GLP-1Rs expressed on dopaminergic neurons, microglia, and hippocampal neurons mediate anti-apoptotic and anti-inflammatory effects. In murine MPTP models of Parkinson's disease, liraglutide reduced microglial NF-κB activation and IL-6 secretion in the substantia nigra by 40–60%, while preserving tyrosine hydroxylase-positive neuronal density and improving motor function. Semaglutide similarly reduced amyloid-β-induced ROS and tau phosphorylation in 5xFAD Alzheimer's mice. Clinical trials of semaglutide in mild cognitive impairment (EVOKE) and Parkinson's disease (NCT04154072) are ongoing, with early biomarker data suggesting reductions in CSF IL-6 and 8-isoprostane[47, 48].

6) Pancreatic Beta Cells

Beta-cell loss in T2DM is mediated in part by IL-1β-induced apoptosis, ER stress, and mitochondrial ROS. GLP-1RAs exert direct beta-cell protective effects through: inhibition of NLRP3-derived IL-1β in islet macrophages, CREB-dependent upregulation of anti-apoptotic genes (BCL-2, BCL-XL, MCL-1), improvement of mitochondrial quality, and reduction of ER stress-induced CHOP expression. These effects collectively preserve beta-cell mass and function in animal models of T2DM, with clinical correlates including preserved C-peptide response and improved beta-cell function indices (HOMA-B) after liraglutide and semaglutide treatment[49, 50].

Table 4: Organ-Specific Anti-Inflammatory and Antioxidant Effects of GLP-1 Receptor Agonists

Organ / System	Anti-Inflammatory Effects	Antioxidant Effects	Clinical / Functional Outcomes	Evidence Level
Cardiovascular	↓ VCAM-1, ICAM-1; ↓ macrophage infiltration in plaque; ↓ foam cell formation	↓ NOX2; ↑ eNOS; ↓ lipid peroxidation in plaque	↓ MACE 13–26%; ↓ CV death (LEADER, SUSTAIN-6)	Clinical RCTs
Liver (NASH/MASH)	↓ Hepatic NF-κB; ↓ Kupffer cell activation; ↓ TNF-α, MCP-1	↑ Nrf2/HO-1; ↓ NADPH oxidase; ↓ lipid peroxidation; ↓ ALT/AST	↓ Fibrosis score; resolution of NASH in 59% (sema trial)	Clinical RCTs
Kidney	↓ Renal NF-κB; ↓ macrophage infiltration; ↓ ICAM-1 in glomeruli	↓ 8-OHdG; ↓ MDA in tubular cells; ↑ catalase/SOD	↓ Albuminuria; ↓ eGFR decline (REWIND, CREDENCE analysis)	Clinical RCTs
Adipose Tissue	↓ Macrophage crown-like structures; M1→M2 shift; ↓ MCP-1, leptin	↑ Adiponectin; ↓ adipocyte ROS; ↓ 4-HNE in AT	↓ Waist circumference; improved adipokine profile	Clinical RCTs
Brain / CNS	↓ Microglial activation; ↓ TNF-α, IL-6 in CSF and brain parenchyma	↑ Nrf2/HO-1 in neurons; ↓ amyloid-β-induced oxidative stress	Emerging: Parkinson's, Alzheimer's, cognitive function	Preclinical/Early
Pancreatic Beta Cells	↓ IL-1β-induced apoptosis; ↓ ER stress; preservation of beta-cell mass	↑ SOD/catalase; ↓ ROS-induced apoptosis; ↓ mitochondrial depolarization	Preserved insulin secretion; beta-cell mass in animal models	Preclinical

Note: *MACE = major adverse cardiovascular events; NASH = non-alcoholic steatohepatitis; eGFR = estimated glomerular filtration rate; PD = Parkinson's disease; AD = Alzheimer's disease; AT = adipose tissue; NOX2 = NADPH oxidase 2; eNOS = endothelial nitric oxide synthase; 8-OHdG = 8-hydroxy-2'-deoxyguanosine.*

Table 5: Clinical Biomarker Evidence for Anti-Inflammatory and Antioxidant Effects of GLP-1 Receptor Agonists

Biomarker	Category	Effect Size	Key Agent(s)	Patient Population	Strength
hsCRP	Inflammation	↓ 20–40%	Liraglutide, semaglutide	Obese T2DM, NASH, CVD	High
IL-6	Inflammation	↓ 15–35%	Liraglutide	T2DM, obesity	High
TNF-α	Inflammation	↓ 10–30%	Exenatide, liraglutide	T2DM, adiposity	High
Adiponectin	Anti-inflam.	↑ 15–25%	Liraglutide, sema.	T2DM, obesity	High
MDA	Oxidative stress	↓ 25–45%	Liraglutide, exenatide	T2DM, CKD	High
8-Isoprostane	Oxidative stress	↓ 20–40%	Liraglutide	T2DM, atherosclerosis	Moderate
8-OHdG	DNA oxidation	↓ 20–35%	Liraglutide, exenatide	T2DM, CKD	High
SOD / GPx	Antioxidant defense	↑ 10–30%	Exenatide, liraglutide	T2DM, CVD	High
NOX2 (serum)	ROS production	↓ 20–35%	Liraglutide	CVD, obesity	Moderate
Nrf2 (tissue)	Antioxidant signalling	↑ 2–5 fold	Liraglutide, exenatide	Preclinical models	Low

Clinical Evidence and Biomarker Landscape

1) Inflammatory Biomarkers

High-sensitivity C-reactive protein (hsCRP), an acute-phase reactant driven by hepatic IL-6 signalling, is the most widely assessed inflammatory biomarker in GLP-1RA clinical trials. Across 14 randomized controlled trials (n > 18,000 patients), liraglutide and semaglutide consistently reduced hsCRP by 20–40% relative to placebo, with the magnitude of reduction correlating with weight loss in some but not all analyses, suggesting a weight-independent component. TNF-α reductions of 10–30% and IL-6 reductions of 15–35% have been documented in shorter-duration metabolic studies, while adiponectin, an anti-inflammatory adipokine inversely related to obesity, increases 15–25% with liraglutide treatment. Notably, the LEADER trial reported significant reductions in hsCRP and fibrinogen at 36 months of liraglutide treatment, with post hoc analyses suggesting that patients with higher baseline hsCRP levels derived proportionally greater MACE benefit, implicating baseline inflammatory burden as a modifier of cardiovascular efficacy[38, 51].

2) Oxidative Stress Biomarkers

Circulating MDA (malondialdehyde, assessed by TBARS assay) and urinary 8-isoprostane (a stable prostaglandin-like compound produced by free radical-mediated lipid peroxidation) represent the most clinically validated oxidative stress markers. In T2DM patients treated with liraglutide for 24–52 weeks, MDA fell by 25–45% and 8-isoprostane by 20–40%, with parallel increases in SOD and GPx activity (10–30%). Urinary 8-OHdG, a marker of oxidative DNA damage particularly relevant to DKD, was

significantly reduced in a prospective study of liraglutide in T2DM patients with early nephropathy (−32%, p<0.001), with reductions correlating with preserved eGFR trajectory[38, 51].

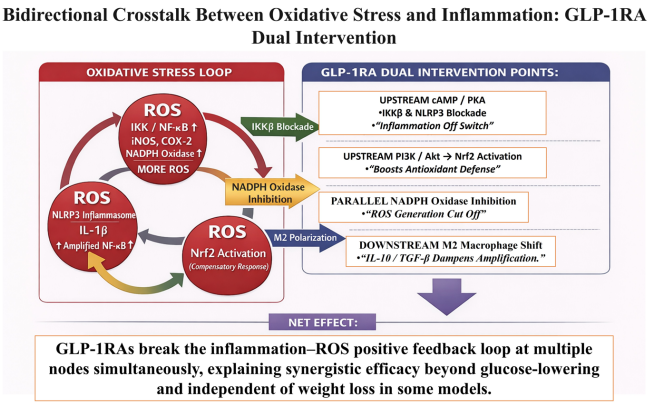

Fig. 5: Dual modulation of oxidative stress and inflammatory pathways by GLP-1 receptor agonists through inhibition of NF-κB, NLRP3 inflammasome activation, and NADPH oxidase activity, alongside activation of Nrf2-mediated antioxidant defenses and M2 macrophage polarization. These coordinated actions disrupt the inflammation–ROS positive feedback loop and contribute to organ-protective effects beyond glucose lowering

Current Limitations and Future Research Directions

Key priority research directions identified in this review include the need for tissue-specific mechanistic studies using human biopsy samples (such as liver, adipose tissue, and coronary arteries) to validate the in vivo engagement of pathways such as Nrf2, NF-κB, and NLRP3. There is also a need for head-to-head randomized controlled trials comparing anti-inflammatory biomarker profiles among GLP-1 receptor agonists while controlling for equivalent weight loss. Further, dedicated clinical trials should explore the role of GLP-1RAs in non-diabetic inflammatory conditions, including NASH, Parkinson's disease, and inflammatory arthritis, with clearly defined mechanistic endpoints such as Nrf2 activation, NLRP3 activity, and macrophage polarization. Additionally, combination strategies involving GLP-1RAs with agents like NLRP3 inhibitors (e.g., colchicine, MCC950) or Nrf2 activators (e.g., bardoxolone methyl) should be investigated to determine whether their effects are additive or redundant. Pharmacogenomic studies are also essential for identifying genetic variations in GLP-1R Signalling pathways that may influence individual anti-inflammatory responses. Finally, further research is needed to determine optimal dosing and timing strategies to maximize anti-inflammatory benefits, including whether these effects persist at lower glycemia-equivalent doses or require higher, dose-dependent exposure[26, 52-54].

Although GLP-1 receptor agonists demonstrate significant anti-inflammatory and antioxidant benefits, concerns remain regarding the long-term consequences of chronic immune modulation. Prolonged suppression of inflammatory pathways may potentially alter normal immune responses and increase susceptibility to infections or immune imbalance in susceptible individuals. Common adverse effects, such as gastrointestinal intolerance (nausea, vomiting, and diarrhoea), may also affect long-term adherence. In addition, rare concerns related to pancreatitis, gallbladder disease, and pancreatic safety continue to require careful monitoring. Current evidence regarding long-term immunological safety is still limited, particularly in non-diabetic populations receiving higher-dose therapy for obesity or chronic inflammatory conditions. Therefore, further long-term clinical and mechanistic studies are necessary to establish the safety and tolerability profile of GLP-1RAs during chronic use[55, 56].

CONCLUSION

In conclusion, GLP-1 receptor agonists represent a unique therapeutic class that extends beyond glycaemic control to exert significant anti-inflammatory and antioxidant effects through coordinated modulation of NF-κB, NLRP3, and Nrf2 pathways. These pleiotropic mechanisms contribute to their demonstrated benefits across cardiovascular, hepatic, renal, and neurological conditions. As evidence continues to evolve, the anti-inflammatory pharmacology of GLP-1RAs may prove to be as important as their metabolic actions, supporting their expanding role in the management of complex chronic diseases.

Summary: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are increasingly recognized for their therapeutic effects beyond glycaemic control in type 2 diabetes mellitus and obesity. This review comprehensively summarizes the anti-inflammatory and antioxidant mechanisms of GLP-1RAs, focusing on their modulation of key molecular pathways, including NF-κB, NLRP3 inflammasome, and Nrf2/Keap1 signaling. Through activation of cAMP/PKA and PI3K/Akt pathways, GLP-1RAs reduce pro-inflammatory cytokine production, suppress oxidative stress, improve mitochondrial function, and enhance endogenous antioxidant defenses. The review further highlights organ-specific protective effects in the cardiovascular system, liver, kidneys, adipose tissue, brain, and pancreatic beta cells, supported by biomarker-based clinical and preclinical evidence. Additionally, emerging therapeutic implications in non-alcoholic steatohepatitis, chronic kidney disease, neurodegenerative disorders, and cardiovascular risk reduction are discussed. Overall, this review provides an integrated mechanistic and translational perspective on the pleiotropic actions of GLP-1RAs and emphasizes their potential role in managing chronic inflammatory and oxidative stress-related diseases.

LIST OF ABBREVIATIONS

Abbreviation	Full Form
4-HNE	4-Hydroxynonenal
8-OHdG	8-Hydroxy-2'-deoxyguanosine
AGE	Advanced Glycation End-product
Akt	Protein Kinase B
ALT	Alanine Aminotransferase
AMPK	AMP-Activated Protein Kinase
ARE	Antioxidant Response Element
ASC	Apoptosis-Associated Speck-like Protein Containing a CARD
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
BCL-2	B-cell Lymphoma 2
BCL-XL	B-cell Lymphoma-extra Large
cAMP	Cyclic Adenosine Monophosphate
CBP	CREB-Binding Protein
CHOP	C/EBP Homologous Protein
CKD	Chronic Kidney Disease
CNS	Central Nervous System
COX-2	Cyclooxygenase-2
CRP	C-Reactive Protein
CREB	cAMP Response Element-Binding Protein
CV	Cardiovascular
CVD	Cardiovascular Disease
CVOT	Cardiovascular Outcome Trial
DKD	Diabetic Kidney Disease
DPP-4	Dipeptidyl Peptidase-4
eGFR	Estimated Glomerular Filtration Rate
eNOS	Endothelial Nitric Oxide Synthase
Epac	Exchange Protein Activated by cAMP
ER	Endoplasmic Reticulum
ERK	Extracellular Signal-Regulated Kinase
GCL	Glutamate-Cysteine Ligase
GIP	Glucose-Dependent Insulinotropic Polypeptide
GLP-1	Glucagon-Like Peptide-1
GLP-1R	Glucagon-Like Peptide-1 Receptor
GLP-1RA	Glucagon-Like Peptide-1 Receptor Agonist
GPCR	G Protein-Coupled Receptor
GPx	Glutathione Peroxidase
GSH	Glutathione
GSK-3β	Glycogen Synthase Kinase-3 Beta
HOMA-B	Homeostatic Model Assessment for Beta-Cell Function
HO-1	Heme Oxygenase-1
hsCRP	High-Sensitivity C-Reactive Protein
ICAM-1	Intercellular Adhesion Molecule-1
IFN-γ	Interferon Gamma
IKK	IκB Kinase
IL	Interleukin
IL-1β	Interleukin-1 Beta
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-12	Interleukin-12
IL-18	Interleukin-18
iNOS	Inducible Nitric Oxide Synthase
IRS-1	Insulin Receptor Substrate-1
JAK	Janus Kinase
Keap1	Kelch-like ECH-Associated Protein 1
LKB1	Liver Kinase B1
LPS	Lipopolysaccharide
MACE	Major Adverse Cardiovascular Events
MAPK	Mitogen-Activated Protein Kinase
MASH	Metabolic Dysfunction-Associated Steatohepatitis
MCP-1	Monocyte Chemoattractant Protein-1
MDA	Malondialdehyde
MCL-1	Myeloid Cell Leukemia-1
mtDNA	Mitochondrial DNA
mTOR	Mammalian Target of Rapamycin
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NF-κB	Nuclear Factor-Kappa B
NLRP3	NOD-Like Receptor Protein 3
NO	Nitric Oxide
NOX	NADPH Oxidase
NOX2	NADPH Oxidase 2
NOX4	NADPH Oxidase 4
NQO1	NAD(P)H Quinone Oxidoreductase-1
Nrf2	Nuclear Factor Erythroid 2-Related Factor 2
oxLDL	Oxidized Low-Density Lipoprotein
PERK	Protein Kinase RNA-like Endoplasmic Reticulum Kinase
PI3K	Phosphoinositide 3-Kinase
PGC-1α	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha
PINK1	PTEN-Induced Kinase 1
PKA	Protein Kinase A
PPARγ	Peroxisome Proliferator-Activated Receptor Gamma
RAGE	Receptor for Advanced Glycation End-products
RCT	Randomized Controlled Trial
ROS	Reactive Oxygen Species
RISK	Reperfusion Injury Salvage Kinase
SC	Subcutaneous
SCFA	Short-Chain Fatty Acid
SOD	Superoxide Dismutase

Abbreviation	Full Form
SOD1/2	Superoxide Dismutase 1 and 2
STAT3	Signal Transducer and Activator of Transcription 3
SURPASS	Tirzepatide Clinical Trial Program
T2DM	Type 2 Diabetes Mellitus
TBARS	Thiobarbituric Acid Reactive Substances
TFAM	Mitochondrial Transcription Factor A
TGF-β	Transforming Growth Factor Beta
TNF-α	Tumor Necrosis Factor Alpha
TRPC6	Transient Receptor Potential Canonical 6
ULK1	Unc-51 Like Autophagy Activating Kinase 1
UPR	Unfolded Protein Response
VCAM-1	Vascular Cell Adhesion Molecule-1

DISCLOSURE

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