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REVIEW ARTICLE

Advances in PPARs Molecular Dynamics and Glitazones as a Repurposing Therapeutic Strategy through Mitochondrial Redox Dynamics against Neurodegeneration

Priya Durai[1], Narasimha M. Beeraka[2,3], Hemanth Vikram Poola Ramachandrappa[1], Prakash Krishnan[4], Pranesh Gudur,[5] Nulgumnalli Manjunathaiah Raghavendra[6] and Prashantha Kumar Bommenahally Ravanappa[1,*]

[1]Department of Pharmaceutical Chemistry, JSS College of Pharmacy, Mysuru 570 015, India and JSS Academy of Higher Education & Research, Mysuru, Karnataka, India; [2]Center of Excellence in Regenerative Medicine and Molecular Biology (CEMR), Department of Biochemistry, JSS Medical College, JSS Academy of Higher Education & Research, Mysuru 570 015, Karnataka, India; [3]I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow 119146, Russia; [4]Independent Researcher, JP Nagar, Mysuru 570 015, India; [5]Swamy Vivekananda Yoga Anusandhana Samsthana Deemed University, Bengaluru 560 105; [6]Department of Pharmaceutical Chemistry, Acharya & BM Reddy College of Pharmacy, Bengaluru 560 107, India

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Abstract: Peroxisome proliferator-activated receptors (PPARs) activity has significant implications for the development of novel therapeutic modalities against neurodegenerative diseases. Although PPAR-α, PPAR-β/δ, and PPAR-γ nuclear receptor expressions are significantly reported in the brain, their implications in brain physiology and other neurodegenerative diseases still require extensive studies. PPAR signaling can modulate various cell signaling mechanisms involved in the cells contributing to on- and off-target actions selectively to promote therapeutic effects as well as the adverse effects of PPAR ligands. Both natural and synthetic ligands for the PPARα, PPARγ, and PPARβ/δ have been reported. PPARα (WY 14.643) and PPARγ agonists can confer neuroprotection by modulating mitochondrial dynamics through the redox system. The pharmacological effect of these agonists may deliver effective clinical responses by protecting vulnerable neurons from Aβ toxicity in Alzheimer's disease (AD) patients. Therefore, the current review delineated the ligands' interaction with 3D-PPARs to modulate neuroprotection, and also deciphered the efficacy of numerous drugs, *viz*. Aβ aggregation inhibitors, vaccines, and γ-secretase inhibitors against AD; this review elucidated the role of PPAR and their receptor isoforms in neural systems, and neurodegeneration in human beings. Further, we have substantially discussed the efficacy of PPREs as potent transcription factors in the brain, and the role of PPAR agonists in neurotransmission, PPAR gamma coactivator-1α (PGC-1α) and mitochondrial dynamics in neuroprotection during AD conditions. This review concludes with the statement that the development of novel PPARs agonists may benefit patients with neurodegeneration, mainly AD patients, which may help mitigate the pathophysiology of dementia, subsequently improving overall the patient's quality of life.

Keywords: PPARs, glitazones, neurodegeneration, mitochondrial dynamics, neuroinflammation, Alzheimer's disease.

1. INTRODUCTION

The pathophysiology of neurodegenerative diseases is progressive and typically characterized by dysregulated transcription, mitochondrial abnormalities, and alterations in energy metabolism [1]. Mainly, the mitochondrial dysfunction can induce the generation of reactive oxygen species (ROS), a significant factor that causes progressive damage to neuronal cells as aging occurs [2]. Furthermore, oxidative stress, functional impairment of mitochondrial function, neuroinflammation, blockade of autophagy, and proteosomal dysfunction are key factors, which may invoke neurodegeneration in aging adults [1].

The Center for Disease Control and Prevention (CDC) and World Health Organization (WHO) declared Alzheimer's disease (AD) as one of the most devastating neurodegenerative disorders in older adults. AD is an irreversible and progressive brain disease that begins with mild memory loss due to the substantial deterioration of cognitive function [3]. AD is accompanied by the loss of the ability to think and respond to environmental cues due to dementia. According to the 2017 WHO report, approximately 50 million people are affected by AD worldwide. The disease prevalence is projected to rise up to 82 million in 2030 and 152 million in

*Address correspondence to this author at the Department of Pharmaceutical Chemistry, JSS College of Pharmacy, Mysuru 570 015, India and JSS Academy of Higher Education & Research (JSS AHER), Mysuru, Karnataka, India; E-mail: brprashanthkumar@jssuni.edu.in

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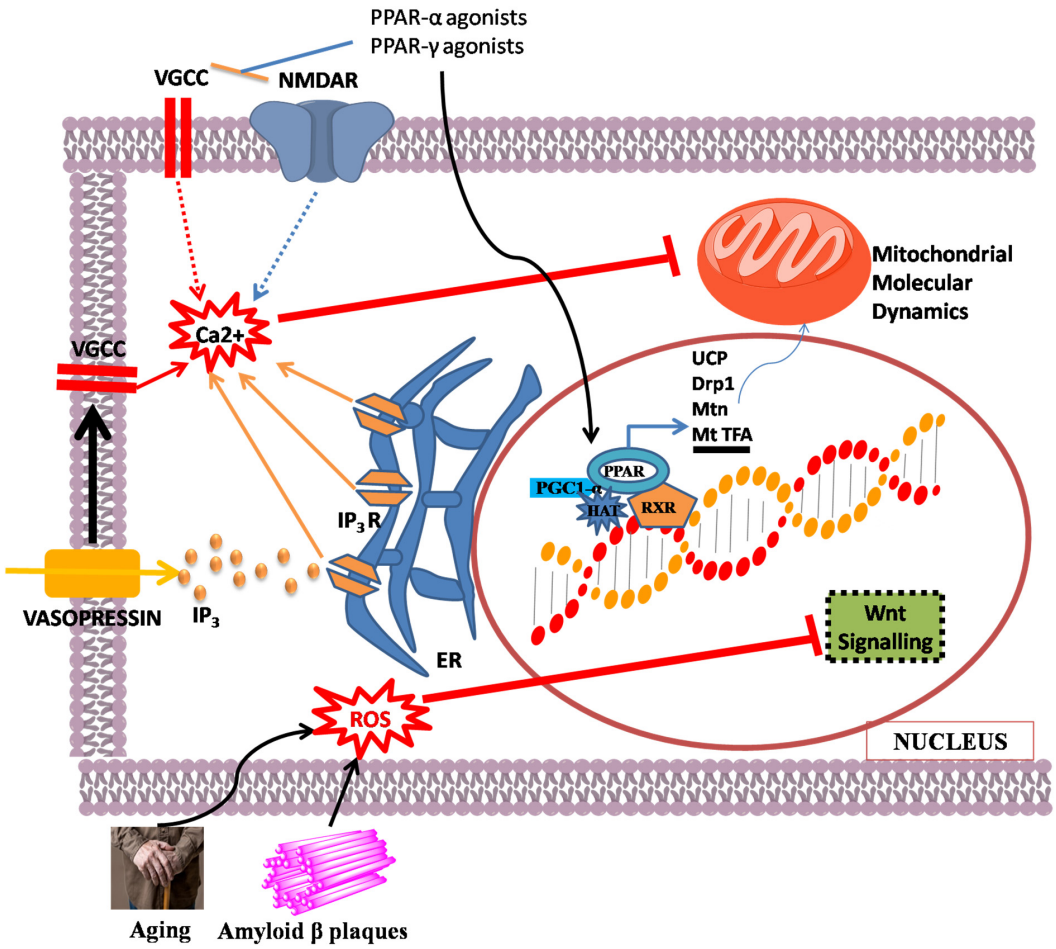

Fig. (1). Pathophysiology of Amyloid β plaques in the aging adults accompanied by the induction of reactive oxygen species (ROS), which can impair Wnt signaling involved in neuroprotection. Furthermore, the activation of vasopressin and glutamate-mediated NMDA receptors could have a significant effect on voltage-gated calcium channels (VGCC) to enhance intracellular calcium overload with the simultaneous release of IP3 and its activity on rhynodine receptors of the endoplasmic reticulum. Intracellular calcium overload can impair mitochondrial dynamics. Administration of PPAR agonists can mitigate damage to mitochondrial dynamics by enhancing the transcription to foster the signaling of PGC-1α and RXR, which subsequently induce UCP-1, Mtn, DRP-1, and MtTFA. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

2050. The management of AD is predominantly a complicated task due to its intricate pathophysiology [3]. Hence, the novel drug discovery and development process in this area requires extensive studies. The current therapeutic modalities against AD are constrained by the limited efficacy due to nonselective pharmacological actions and adverse effects. Accordingly, there is a critical requirement for the development of new remedies for AD [3]. The current review describes a promising role of PPARs as novel therapeutic targets in order to design novel therapeutic modalities against AD. PPARs have been significantly reported to be involved in modulating the mitochondrial dysfunction, proteasomal dysfunction, oxidative stress, and neuroinflammation, which are major underlying pathophysiological causes of AD.

2. ALZHEIMER DISEASE: INTRICATE PATHOLOGY AND AGING

The major neuropathological hallmarks in the AD are the formation of amyloid plaques, comprising overwhelmingly of the Aβ peptide and neurofibrillary tangles (NFTs) produced by hyperphosphorylated tau protein [4]. Aβ can accumulate in the veins of the meninges and cerebral cortex, which is termed as cerebral amyloid angiopathy [5]. Postmortem studies on human brain specimens, *in vitro* as well as *in vivo*, have uncovered the significant role of extracellular amyloid plaques, intracellular NFTs, oxidative stress, mitochondrial (structural and functional) variations, inflammatory reactions, and senescence or aging-induced neurological changes during the progression of AD [6].

The amyloidogenic pathway is also activated due to the mutations, which consequently facilitates the damage to neurons; in this pathway, the sequential breakdown of amyloid precursor protein (APP) occurs by β-secretase followed by γ-secretase activity [7], subsequently generating C- and N-terminal fragments of APP often considered as Aβ plaques [8]. These plaques are made up of small peptides with 39-43 amino acids in length. Mainly, Aβ (1-42) is referred to as the key player in the initiation of AD [3]. APP is crucial for neuron growth, survival, and post-injury repair. Aging has a significant influence on the development of amyloid plaques

that in turn invoke AD and AD-induced dementia [9]. During the conditions of AD, APP undergoes enzymatic fragmentation through proteolysis. One of these fragments can promote the synthesis of beta-amyloid fibrils, which can form clump deposition outside the neurons in dense formations often referred to as senile plaques [3]. Accumulation of Aβ in the brain generates oxidative stress and facilitates neurotoxicity through several cell signaling downstream cascades, which adds to the impedance on individual psychological capacities. The underlying pathophysiology of AD involves loss of calcium homeostasis, endoplasmic reticulum stress, oxidative pressure and inflammation due to the formation of Aβ aggregates [3] (Fig. **1**). Regardless of the role of Aβ in AD, just amyloid-course theory is not adequate to clarify AD pathogenesis, since the therapeutic strategies to impair Aβ synthesis have not mitigated AD pathology fully [10].

Tau is an intracellular microtubule protein, and the hyperphosphorylated tau protein has a neurotoxic impact on the aging brain. Hyperphosphorylated tau could foster the development of NFTs, dystrophic neuritis, and neuropil strings [11]. The phosphorylated tau stabilizes the microtubules, thus being called a microtubule-associated protein, and mitigates the movement of nutrient molecules within the neurons [12]. AD is also considered as a tauopathy, which was named due to abnormal aggregation of the tau protein. In addition, Tau protein undergoes hyperphosphorylation and pairs with other threads, creating NFTs, which can disintegrate the neuron's transport system [13]. The accumulation of hyperphosphorylated tau tangles can lead to the loss of neuronal function, and confer to the neuronal apoptosis [14]. Still, the pathophysiology and underlying causes of abnormal tau hyperphosphorylation have not been fully explored. For instance, the cdk5, a tau kinase, is upregulated in the brain of AD patients [15], but this conclusion has been challenged by several scientific communities [14, 16, 17]. The PP2A (protein phosphatase-2A) expression is significantly downregulated in AD brain and it is due to the deregulation of PP2A inhibitors, such as I_1^{PP2A} and I_2^{PP2A} [18]. Other proteins, such as MAP1B, β-tubulin, neurofilaments, and β-catenin, are also hyperphosphorylated during AD conditions, mainly during the deregulation of PP2A [14, 19]. Thus, Aβ and tau are two significant proteins with crucial implications in the pathogenesis of AD. The formation of intracellular NFTs from the hyperphosphorylated tau proteins [20] and the aggregation of extracellular amyloid plaques are the basic neuropathological changes observed in AD. Therefore, the novel therapeutic modalities in order to treat AD should act against tau hyperphosphorylation-induced AD pathophysiology by (a) impairing GSK-3β, cdk5 and other tau kinase proteins; (b) enhancing PP2A activity; (c) blocking tau O-GlcNAcylation [14].

2.1. Inflammation and AD

Inflammation cascades are characterized by edema and neutrophil attacks, which are normally not observed in the AD brain [21]. However, the immune components known to be significant members in inflammatory procedures are the steady causes of AD-induced neuropathophysiology. Astroglia serves as a critical component and plays an essential role in providing glia and neuron contact, maintaining ionic homeostasis, buffering excess of neurotransmitters, and secreting neurotrophic factors [22]. AD brain shows various neurotic anomalies, including a significant loss of neurotransmitters, bountiful receptive gliosis, microglial activation and inflammation. Neurodegeneration in AD is auxiliary to an inflammatory reaction to senile plaques (SPs) and NFTs. This aggravation triggers the development of SPs and NFTs, which can confer to the vulnerable responses that drive a self-continuing auto-destructive process of neurons in AD patients.

Epidemiological reports demonstrate the role of neuroinflammation in the pathogenesis of AD. Changes in microglia morphology from ramified (resting) to amoeboid (dynamic), and astrogliosis (showed by an expansion in the number, size, and motility of astrocytes) encompassing the senile plaques, are significant characteristic features in AD patients [23]. The pro-inflammatory function of astroglia is not as prominent as that of microglia, but the astroglia become activated in response to immunologic challenges or during brain injuries [22]. Aβ plaques and Tau NTFs can confer microglial M1-activation, consequently fostering chronic neuroinflammation through cytokines and interleukins, viz. IL-1β, IL-6, IL-18, and TNF-α, with simultaneous enhancement in the chemokine expression, *viz*. CCL2, CCR3, and CCR5. These inflammatory cascades still worsen the symptoms of AD due to local neuronal death [24-27]. The development of therapeutic modalities should focus on mitigating the brain inflammatory reactions induced through Aβ pathology (Fig. **2**) and the NFT advancement [28, 29].

3. AD AND FAILURES OF CURRENT THERAPIES

AD is an age-related neurological condition, and it is an irreversible, progressive brain disorder that slowly destroys memory, thinking skills, and eventually, declines the ability to carry out the simplest tasks. Current therapies for AD are symptomatic and do not target the underlying Aβ pathology precisely; also, they possess minimal efficacy and offer limited protection against other important hallmarks of AD, including neuronal loss [30]. Furthermore, the aging adults associated with ApoE ε4/ε4 genotypes predominantly exhibit an enhanced incidence of AD than the individuals with ApoE ε3/ε4 genotypes [31]. Mutation in the gene encoding for triggering receptor expressed on myeloid cells 2 (TREM2) could invoke the risk of AD development [32-36]. Current therapeutic modalities, such as acetylcholinesterase inhibitors (tacrine) and anti-inflammatory drugs, are constrained by the adverse toxicity profiles. There are no specific gene therapies to modulate the mutation-induced alterations to mitigate Aβ/Tau synthesis in AD patients. Therefore, novel therapeutics with specificity and selectivity should be investigated for the targeted activity to mitigate pathophysiology of AD.

4. PPARS AND NEURODEGENERATION

PPARs belong to the ligand-regulated nuclear receptors. The PPARs contain PPAR-α, PPAR-β/δ, and PPAR-γ [37, 38]. Chromosomal genes, *viz*. PPAR-α (NR1C1), PPAR-β/δ (NUC1 or NR1C2), and PPAR-γ (NR1C3) encode for PPARs, which further encode for proteins (49-56 kDa) consisting of 468, 441, 475 and 505 amino acids. Mainly,

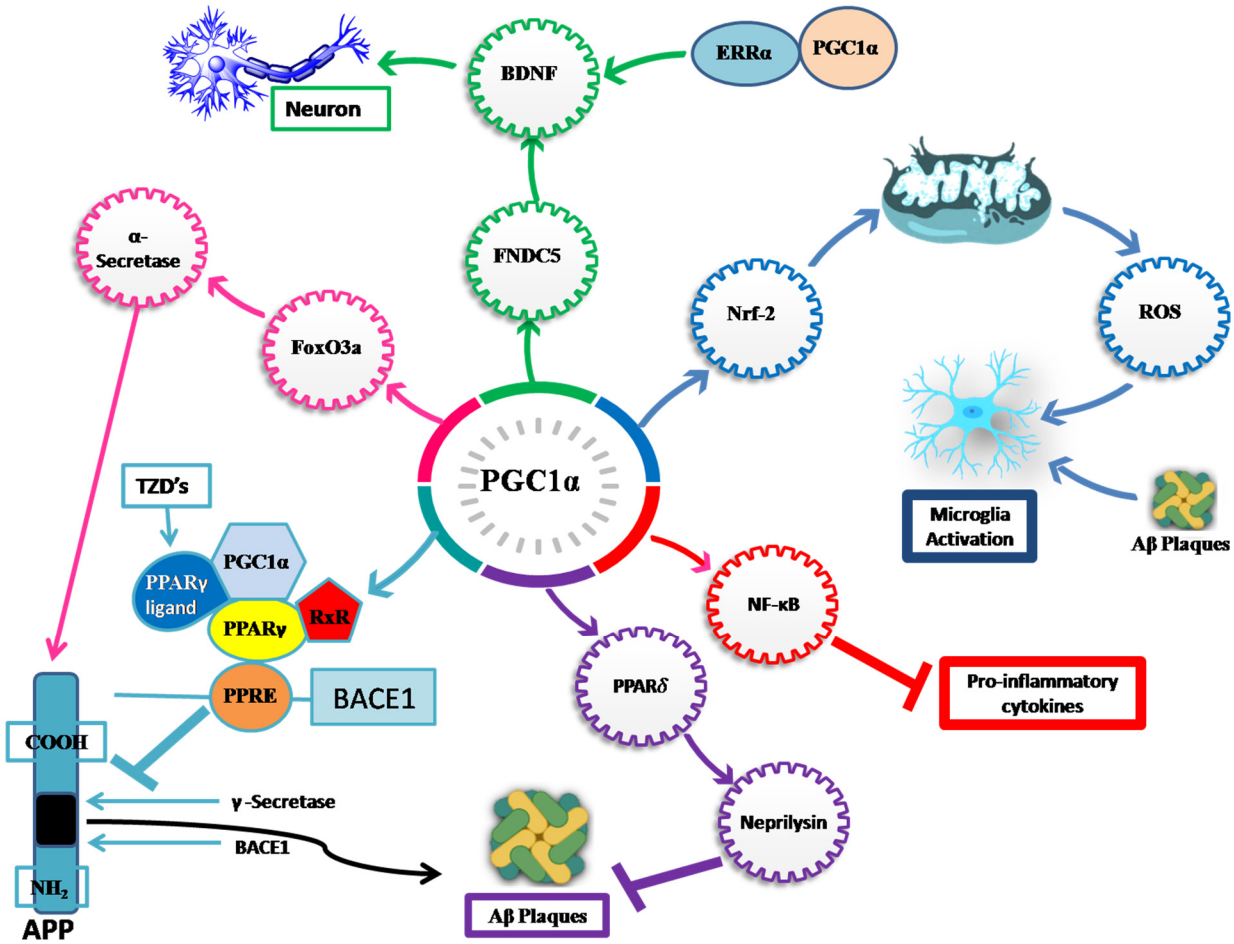

Fig. (2). Microglial activation and the functional role of PGC1α in the pathophysiology of oxidative stress in AD and its role in the mitigation of Amyloid (Aβ) plaques. Concordance between the microglia and synthesis of Amyloid (Aβ) plaques is observed in the aging adults as Aβ is produced by sequential cleavage of APP by the activity of β-APP cleaving enzyme (BACE1) and γ-secretase complex, where presenilin's activity is crucial to mediate this reaction. PPARγ binding could induce APP processing alterations by mitigating BACE1 transcription, consequently reducing Aβ production. ROS, pro-inflammatory cytokines, and BDNF factors are modulated by the PGC1α. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

PPAR-γ gene promoters can be conducive to the expression of 3 isoforms, such as γ1, γ2 and γ3 [37, 38]. PPARs can control transcription *via* several complex signaling mechanisms [39]. PPARs undergo hetero-dimerization when they interact with RXR that binds to a specific promoter of target genes. These are referred to as PPAR response elements (PPREs), which can act as transcription factors [40]. A coactivator of PPARs is PGC1-α (PPAR-γ coactivator-1 alpha), which is involved in modulating the gene expression by activating PPARs and also activating estrogen receptors or Nrf1 and Nrf2 [41] (Fig. **2**). PGC1-α plays a significant role in mitochondrial biogenesis, having implications for age-related diseases. Furthermore, these receptors could facilitate transcription regulation, lipid metabolism, and thermogenesis. PPAR-α has a functional role in the processes, such as (1) mitochondria metabolism, (2) β-fatty oxidation, (3) glucose metabolism (4) redox state and glutamate/cholinergic/dopaminergic neurotransmission. This PPAR-α is also involved in modulating the β-amyloid precursor protein (APP) in the brain, and it can also modulate the phosphorylation of Tau-protein through its engagement with β-amyloid either directly or indirectly. PPAR-β/δ can control the cell differentiation and myelination process in the brain [42]. PPAR-γ and PGC-1α together can modulate cell differentiation and mitochondrial biogenesis in neuroinflammation and neurodegeneration [43-45].

In this context, the possible hypothesis is that primarily PPAR- γ agonists bind to PPAR-γ, and cause conformational changes in the protein, where the also bound PGC-1α gets activated, consequently leading to mitochondrial biogenesis and exerting neuroprotective effects (Figs. **3**-**4**).

5. STRUCTURE ACTIVITY RELATIONSHIP (SAR), LIGAND-PPARS INTERACTIONS AND IMPLICATIONS IN NEUROPROTECTION

The A/B, C, D, and E are the unique domains reported in these subtypes. For instance, the N-terminal A/B domain is comparatively distinct in terms of length and amino acids and composed of AF-1 that mediates its activity even in the absence of ligand binding [46]. This domain significantly differs in the sequence from other nuclear receptors inside neurons and plays a crucial role in regulating PPAR activity by modulating phosphorylation and interdomain communication [47].

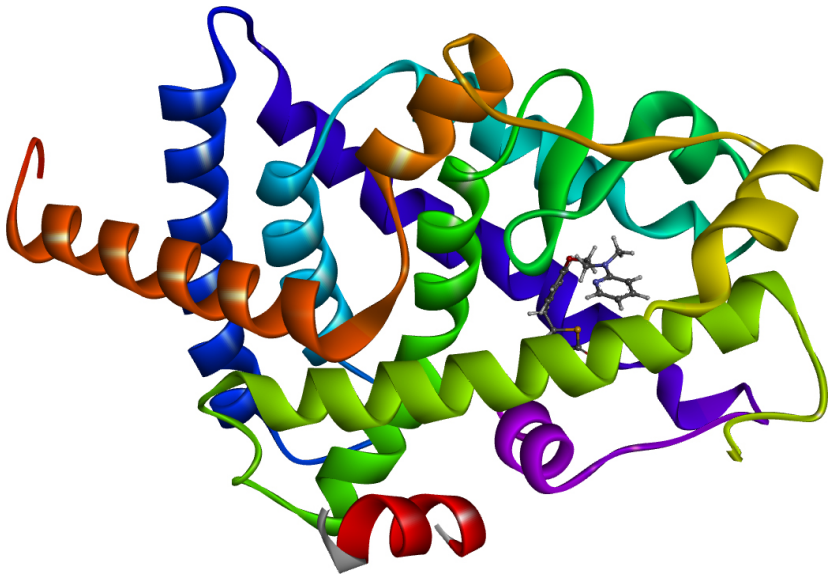

Fig. (3). PPAR-γ agonist Rosiglitazone (ball and stick representation) bound to the PPAR-γ at its active site and PPAR-γ bound to the PGC-1α (red ribbon at the bottom). PDB ID: 3CS8 visualized in Discovery Studio Visualizer. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

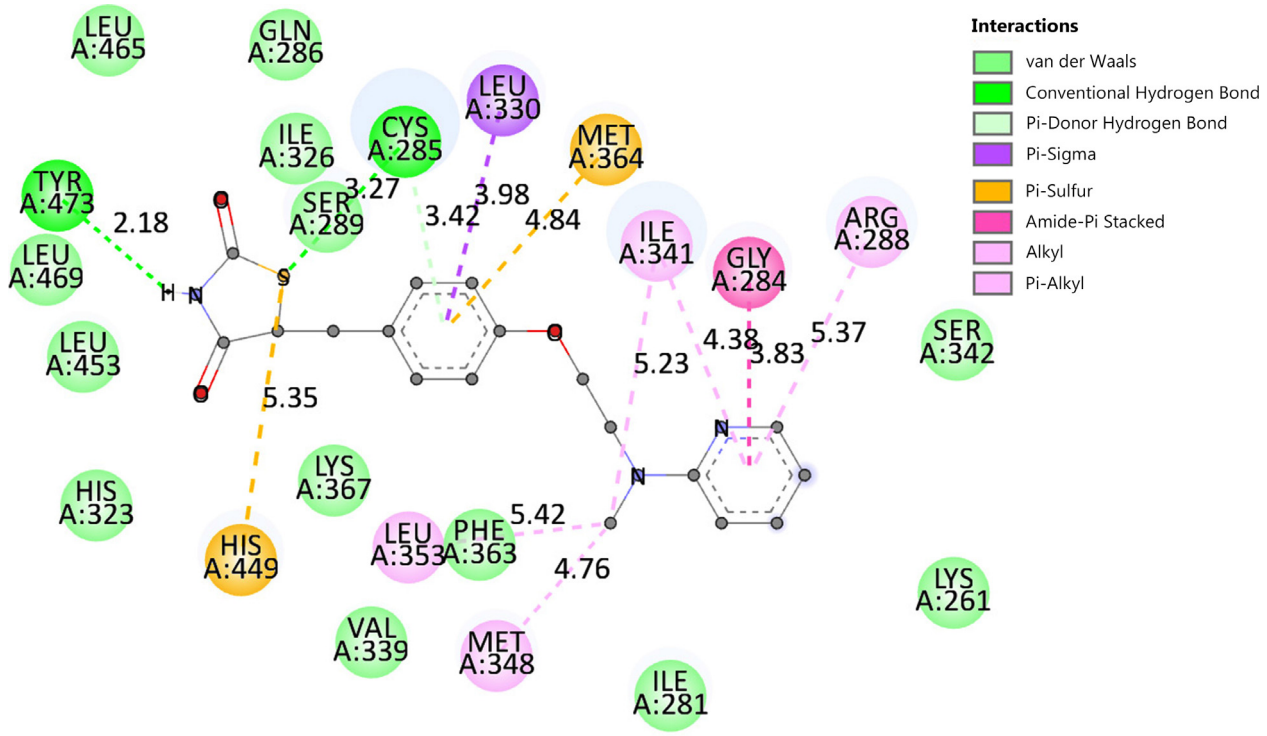

Fig. (4). Molecular interactions between rosiglitazone and PPAR-γ protein for the structure-based drug design. First, thiazolidinedione represents the head group and hydrogen bond interactions. Benzyl represents the body and hydrophobic interactions, and two-carbon linker and hydrophobic pyridine moiety represent tail and hydrophobic interactions. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

The C-domain of this PPAR is composed of 70 amino acids and encodes the DNA binding domain (DBD) to enable the binding of PPREs in the promoter region of the target gene. This domain is referred to as the conserved domain composed of two zinc fingers. The D-hinge region is a prominent region that enables the interaction of DBD with the ligand-binding domain. This region is considered as the significant docking domain region. The E terminal domain contains two major regions with conserved amino acid sequences similar to the conserved sequences located in other nuclear receptors [46].

LBD domain is predominantly involved in regulating the ligand specificity and binding of the PPAR to PPRE in order to regulate gene expression for neuroprotection. Hence, this region could be considered as the significant domain that

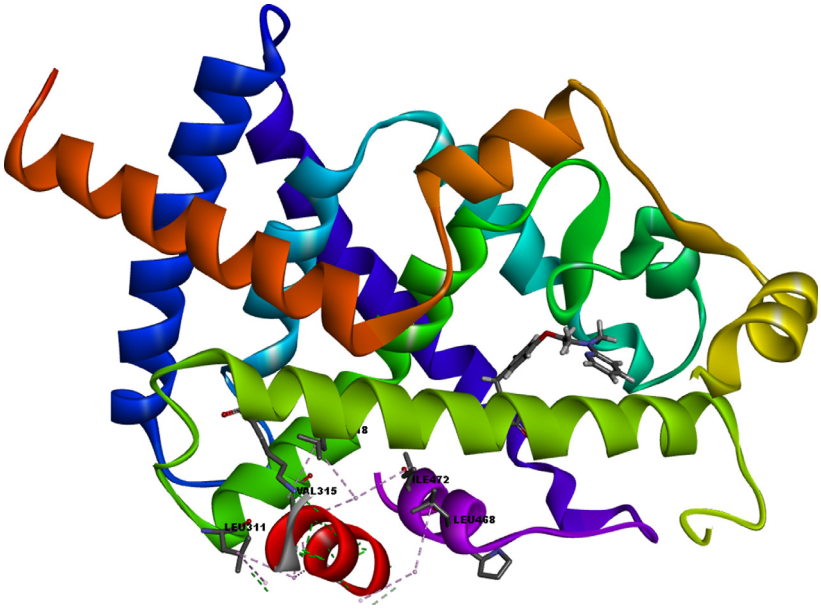

Fig. (5). Schematic depiction of 3D interactions between PPAR- γ and PGC-1α. PDB ID: 3CS8 visualized in Discovery Studio Visualizer. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

plays a crucial role in dimerization and nuclear localization. Furthermore, the AF-2 is activated upon the ligand binding and promotes PPAR cofactor recruitment. However, these domains have a variable sequence compared to the sequences in nuclear receptors and share a similar mode of activity, which involves heterodimerization with RXR receptors. For instance, the binding of small molecule agonists could invoke the strengthened interaction of coactivators with PPAR, which results in conformation changes and triggers gene expression to modulate both protein (for instance, beta-amyloid) and lipid metabolism [48]. Thus, the PPARs exhibit both induction and repression of gene transcription involved in several cellular functions through three main divergent pathways: (1) ligand-dependent transactivation, (2) ligand-independent repression, and (3) ligand-dependent transpression.

Therefore, the development of novel small molecule inhibitors or already existing small molecule agonists (*e.g.*, glitazone derivatives) may display multitarget capacities by modulating the activity of PPARs selectively in order to invoke neuroprotection (Fig. **5**).

5.1. Thiazolidinedione Scaffolds as Dual PPAR-α and PPAR-γ Agonists, Pharmacophore Features, and Structure-Activity Relationships (SAR)

Compounds that contain thiazolidinedione scaffolds are known as glitazones. These are the drugs of choice for treating insulin resistance in type 2 diabetes mellitus (T2DM). Glitazones can bind to both PPAR-α and PPAR-γ, but the selectivity of the binding is more towards the PPAR-γ. The synthesis of glitazones can be performed from fibrates (Fig. **6**) as anti-diabetics, but their SAR has not been unraveled for neuroprotection during neurodegeneration by examining their efficacy for binding to PPARs. Glitazones binding to PPAR-γ can exhibit glycemic control, whereas binding to the PPAR-α can promote the modulation of the triglycerides.

The pharmacophore features of glitazones consist of thiazodinedione (TZD) rings which constitute the acidic head group. It is responsible for the head group interactions with PPAR-γ receptors; especially it participates in hydrogen bonding interactions with His323 and His449 at an optimal distance of 2A°. These hydrogen bond interactions are also crucial for glitazones to orient in the active site pocket of PPAR-γ. The benzyloxy group constitutes the trunk portion of glitazones, which takes part in hydrophobic interactions with many hydrophobic amino acids of PPAR-γ. Subsequently, two carbon linkers connecting the trunk portion of glitazones to the lipophilic tail are also displayed during the interaction. Two carbon linkers fit body and tail portions of glitazones to the binding pocket of PPAR-γ. The structural representation of pharmacophore features is provided in Fig. (**7**).

Ciglitazone is a primitive glitazone reported in 1980. Later, the US FDA approved troglitazone, which was the first glitazone introduced in the market in 1997. However, within 6 weeks of introduction by GlaxoWellcome, it was recalled from the UK market due to the adverse fatal idiosyncratic hepatotoxicity. Later, rosiglitazone and pioglitazone were developed and introduced to the market by SmithKline and Takeda as insulin sensitizers for the management of T2DM [49, 50]. The clinically approved glitazones have been provided in Fig. (**8**).

5.1.1. Structure-activity Relationships

SAR for the glitazones primarily requires an acidic TZD ring system to exhibit optimal hydrogen bonds with the histidine residues of PPAR-γ receptors. This constitutes the head group of thiazolidinediones (TZD). Bioisosteric replacement of TZD with rhodanine can reduce the activity due to the disruption of hydrogen bonds with histidine residues, subsequently limiting the glitazone to orient optimally in the active site pocket of PPAR-γ [50]. The benzyloxy trunk portion is important for exhibiting hydrophobic

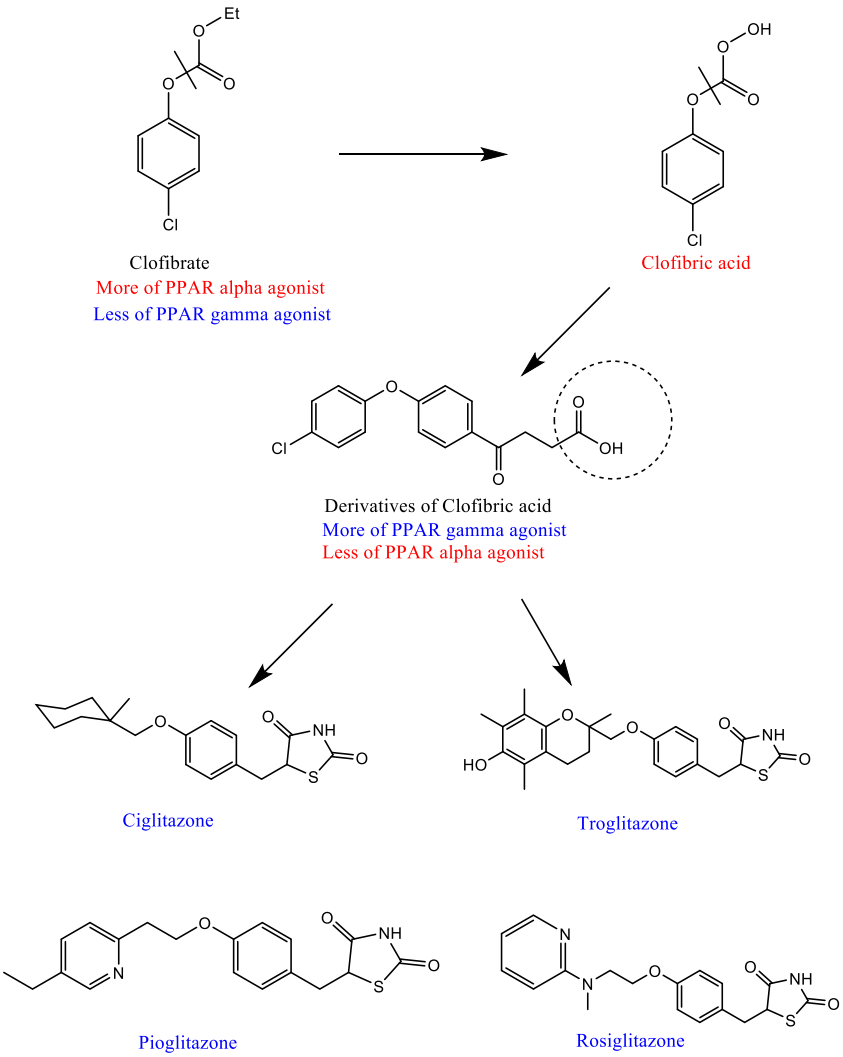

Fig. (6). Synthesis of several glitazones and their substantial efficacy as PPAR-γ agonists and minimal efficacy as PPAR-α agonists.

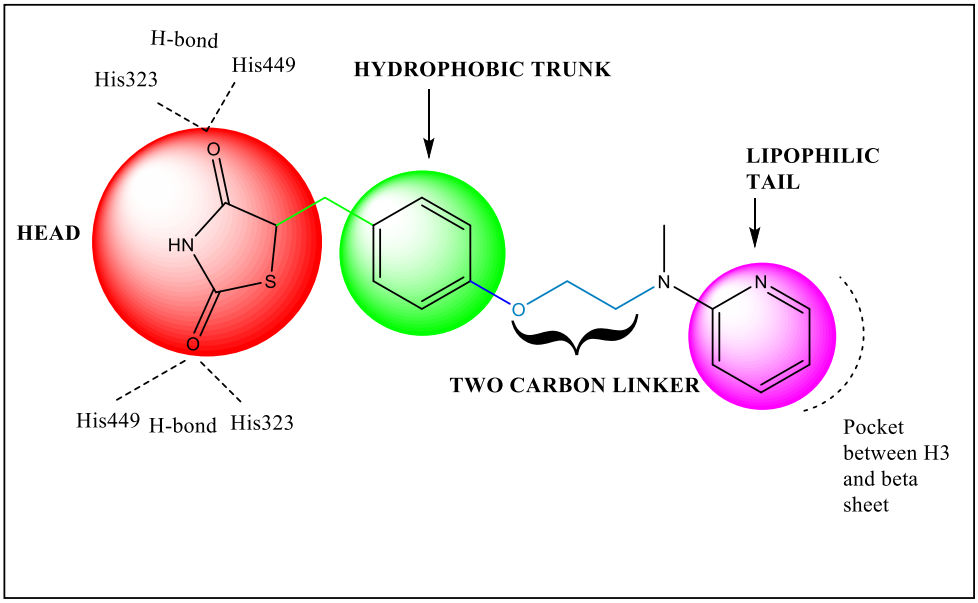

Fig. (7). Schematic depiction of glitazone pharmacophore, which binds to the PPAR-γ receptors.

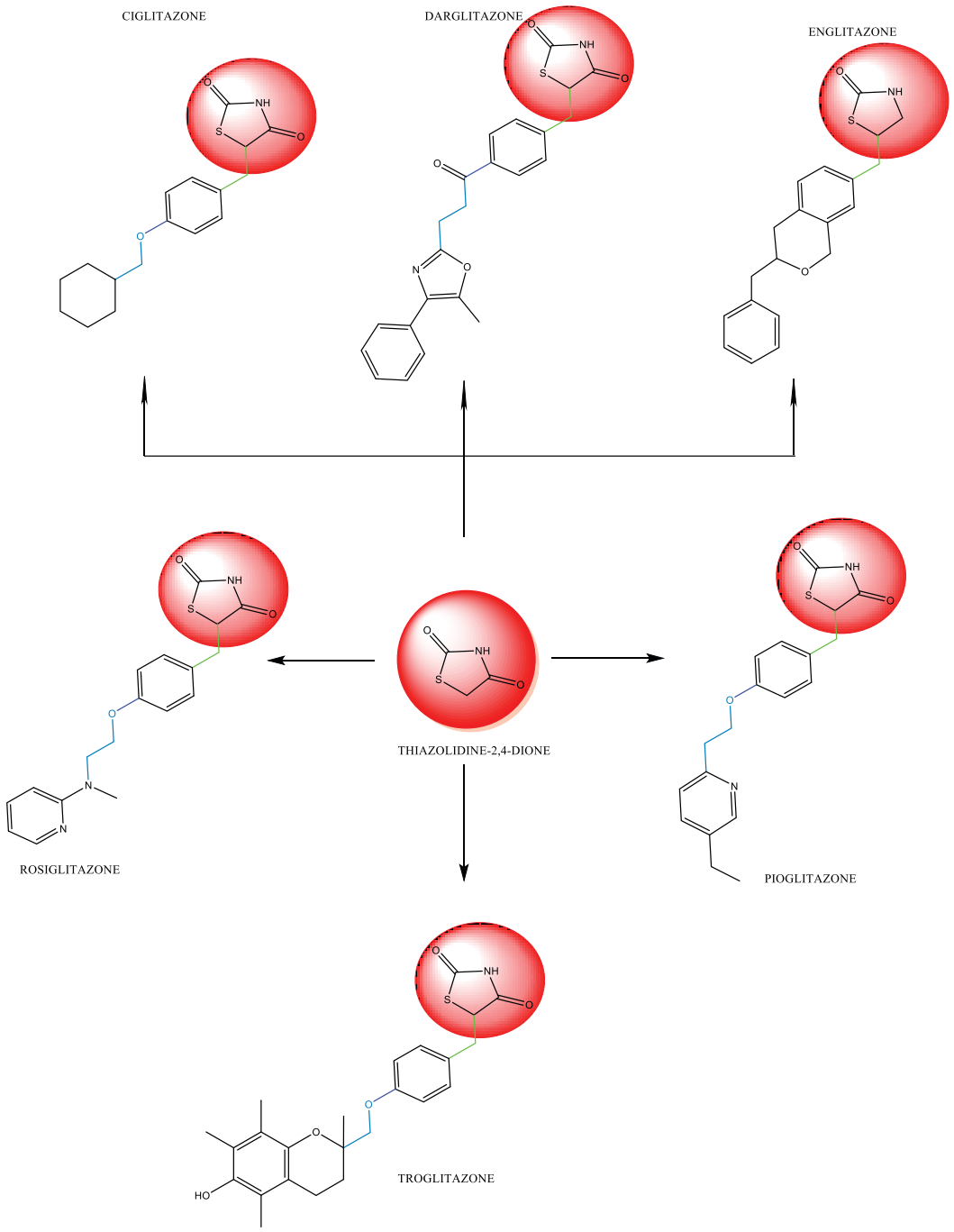

Fig. (8). Schematic depiction of various clinically approved glitazones for diabetic patients.

interactions with PPAR-γ receptors. The lipophilic tail is also crucial for mediating hydrophobic interactions; these interactions occur mainly due to the presence of pyridine in pioglitazone and rosiglitazone, and benzene and cyclohexyl rings in englitazone and ciglitazone. Optimally, a two-linker is essential for connecting the hydrophobic trunk and lipophilic tail, which can fit these two fragments in the active site pocket of PPAR-γ.

5.2. Why are PPARs Agonists as Targets for AD?

Activation of PPARα using specific agonists could lower the fatty substance level and enhance neuronal homeostasis. Activation of PPARγ also can invoke insulin refinement and boost glucose metabolism, while the activation of PPARβ/δ improves unsaturated fats absorption [51]. PPARs are involved in modulating different epigenetic pathways, and nuclear and enzymatic pathways in the liver and skeletal muscles [52]. These pathways are typically reported to be altered in metabolic disease conditions and induce irregular metabolic vitality in AD patients. Therefore, the intercession of PPARs can provide remedial factors for plenty of ailments, such as dyslipidemia, diabetes, neurodegeneration, and cancer malignancy. PPARs activation in the brain can exert neurotrophic and anti-inflammatory effects, and their agonistic receptor activity has significant implications for decreasing the rate of Aβ aggregation and deposition [1, 53-55].

5.3. PPARs Functions

PPARs comprise a DNA binding domain in the N-terminal and a ligand binding domain (LBD) in the C-terminal [56, 57]. The homo PPAR structures heterodimerize with another class of receptors, retinoid X receptors (RXR). During unstimulated conditions, the heterodimer complex correlates with corepressors (NCoR and SMRT), consequently invoking the suppression of gene transcription [58]. The binding of ligands to the hydrophobic pocket of LBD receptor can activate the conformational changes and release corepressors NCoR/SMRT, which further modulate gene transcription individually. The binding of PPAR agonists can release the corepressor and stabilize LBD, which results in the binding of coactivators (CBP/P300, p160/SRC-1) with vitamin D receptor-interacting protein (DRIP) or thyroid hormone receptor-associated protein (TRAP), subsequently activating PPAR. The activated PPAR/RXR heterodimer can consequently stimulate PPRE in the promoter locale of the target gene. These molecular interactions can invoke alterations in the histone acetyl transferases and the gene transcription machinery (RNA polymerase complex) to initiate chromatin relaxation for targeting the gene transcription [59]. Coactivator PGC-1α induced gene expression has a significant impact for producing the ameliorative effects against AD. In addition, it can control mitochondrial biogenesis, oxidative metabolism, unsaturated fat oxidation, and gluconeogenesis. These mitochondrial consequences, in turn, can improve cerebrum function [60]. Thus, the modulation of PPAR-γ activity may deliver effective therapeutic modalities, thereby decreasing the pathophysiology of neurodegeneration in AD conditions.

5.4. PPAR Alpha

PPAR-α is substantially expressed in the muscles, liver, heart, and kidney, and mostly modulates genes associated with the metabolism of lipids and lipoproteins. PPAR-α regulates the β-oxidation of fatty acids, ketogenesis and gluconeogenesis. Specifically, PPAR-α can control the auto-inflammatory mechanisms and prevent metabolic disorders. PPAR-α is abundant in astrocytes and neurons. PPAR-α is additionally expressed in the hippocampus where it is associated with synaptic versatility and memory by controlling the expression of cAMP- response-element binding protein (CREB), a basic transcription factor involved in memory development [61]. PPAR-α has also been reported to be engaged in controlling glutamate homeostasis, cholinergic and dopaminergic signaling. Only the PPAR-α receptor assumes a noteworthy function in the transcription of genes encoding for proteins involved in neurotransmission. In mitochondria, PPAR-α is also reported to be involved in modulating the role of components pertaining to fatty acids and energy metabolism. The anti-inflammatory functions of PPAR-α in the brain models are well documented; for instance, PPAR-α mediated neuronal immune modulation has emerged as an advanced therapeutic approach for the treatment of AD. It appears now that PPAR-α could be a promising target to design the novel therapeutic modalities against AD as well as other neurodegenerative diseases and neurodevelopmental disorders.

Zhang *et al.* reported the effect of PPAR-α agonism using fenofibrate and GW7647 by regulating the PI3-K pathway, which reduces the APP metabolism in the transgenic mice model. The PPAR-α agonists can decrease the BACE-1 and consequently mitigate the release of Aβ42 [62]. The non-amyloidogenic pathway can be enhanced by gemfibrozil, a PPAR-α agonist, through the upregulation of neuronal α-secretase expression (Table **2**). Cisternas *et al.* reported the relationship between PPAR-α activation and the Wnt-signaling in AD brain models. This effect can enhance glucose utilization (glycolysis). WY14643, a PPAR-α agonist, can enhance the peroxisomal catalytic function, which results in peroxide-induced oxidative stress. Peroxides can regulate the cytokines expression through protein kinase activation, and also promote the PPAR-α transcription. This clearly indicates the relationship between oxidative stress, inflammation, and PPAR-α mediated inflammatory regulation [62, 63].

5.5. PPAR beta/delta

PPAR β/δ is abundantly expressed throughout the body, but its levels are comparatively low in the liver. PPAR β/δ emerged as an important regulator of lipid and glucose metabolism, inflammation, cell proliferation, and differentiation [64, 65], and energy balance primarily in adipose tissue, skeletal muscle, and the heart. A few studies have shown that PPAR-δ agonists can decrease the brain Aβ burden and offer neuroprotective effects in transgenic mice expressing mutant forms of human APP [66-69]. PPAR-δ is widely expressed throughout the brain and is enriched in brain areas involved in energy homeostasis [70]. PPAR-δ expression is substantially observed inside the hippocampus and dentate gyrus/CA1. Oral administration of PPAR-δ agonists in a transgenic mouse model expressing a mutant form of human APP significantly reduced the plaque burden and brain inflammation, and increased the expression of plaque degrading enzymes [66, 71]. PPAR-δ agonists can increase gene expression of the antioxidant enzymes, such as catalase and SOD, which suppress inflammation evoked by Aβ-amyloid peptides and inhibit astrocyte and microglia activation [66]. PPAR-δ activation also stimulates the production of acetylcholine, a key neurotransmitter involved in learning and memory. It is still enigmatic whether hippocampal PPAR-δ activation could protect neurons against Aβ1–42-mediated neurotoxicity.

T3D-959,a dual PPAR delta/gamma agonist, significantly enhanced spatial learning and memory as indicated by the decreased levels of oxidative stress and Aβ, and controlled the expression of phospho-tau, choline acetyltransferase, and myelin-associated glycoprotein. T3D-959 can enhance motor performance, preserving cortical and white matter structure by decreasing the expression of multiple pro-inflammatory cytokines [72, 73].

5.6. PPAR Gamma

PPARγ protein exists in two isoforms: PPARγ1, abundantly expressed in adipose tissue, large intestine, and hematopoietic cells; PPARγ2 expression is predominantly restricted to the adipose tissue under physiological conditions [74]. A plethora of studies delineate that the administration of PPARγ ligands could mitigate the pathophysiology of neurodegeneration occurring in AD, Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis [75]. In addition, PGC-1α

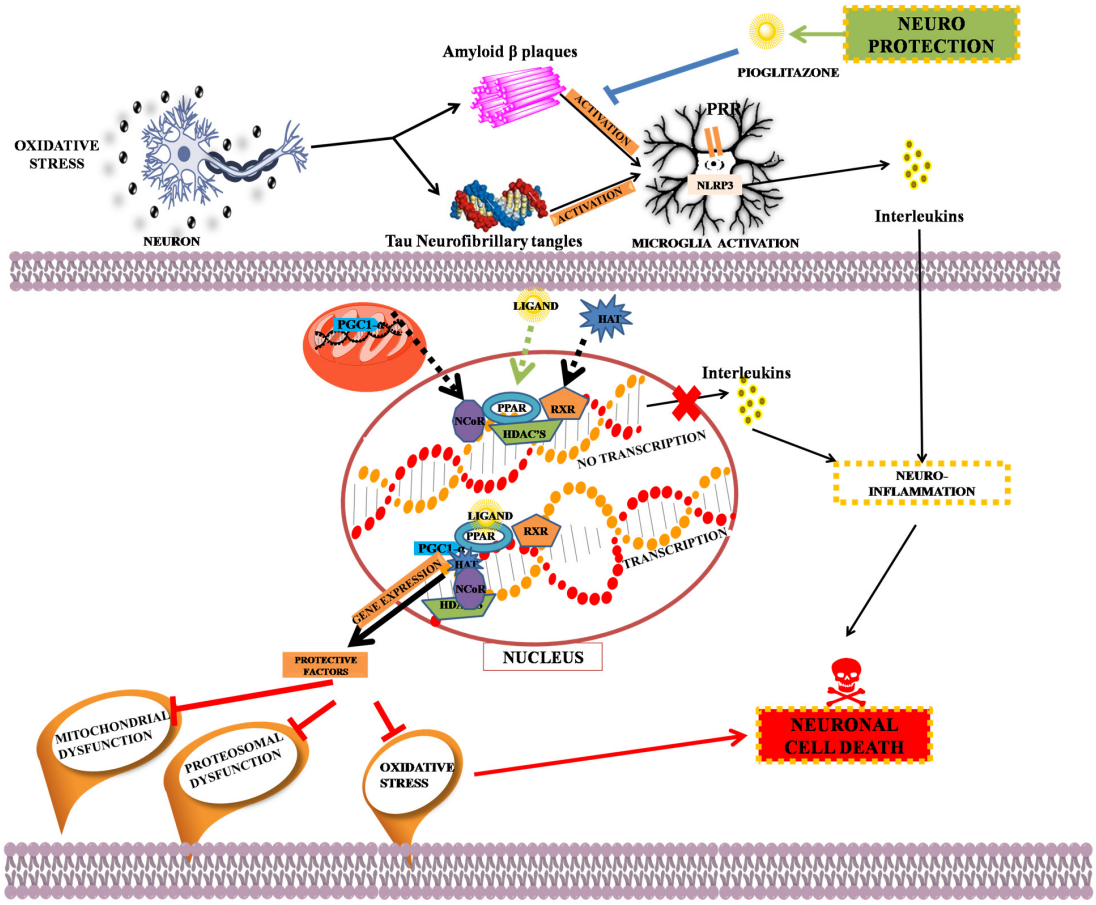

Fig. (9). Pharmacological efficacy of Thiazolidinediones (also called glitazones) in mitigating the pathophysiology of oxidative stress-induced amyloid β-plaques; Tau neurofibrillary tangles consequently inducing microglial activation and releasing inflammatory factors that cause neuroinflammation and neural cell death. Other factors, such as mitochondrial dysfunction and proteosomal dysfunction, induce neuronal cell death and neurodegeneration. Activation of PPAR through ligand binding or by glitazones could confer to the gene expression for promoting the protective factors' synthesis and inhibiting the mitochondrial dysfunction and oxidative stress. On the other hand, the binding of the PPAR ligands can also mitigate the synthesis of inflammatory factors, thereby mitigating neurodegeneration by modulating the transcription. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

inside the brain mitigates the neurodegenerative pathologies [75].

6. THE BENEFITS OF PPARS AGONISTS OVER OTHER TARGETS IN AD CONDITIONS

For instance, PGC-1α is a cofactor for transcription factors, including the PPARγ, and it is involved in the regulation of metabolic genes, oxidative phosphorylation, and mitochondrial biogenesis in several cells [75]. Since the mitochondrial dysfunction has been linked to neurodegenerative diseases, such as AD, HD and PD, the therapeutic targeting of PGC-1α can either directly or indirectly modulate the pathophysiology of these diseases *via* PPAR-γ ligand binding; this modulation can be performed by glitazones as a new class of useful drug-repurposing neuroprotectives due to their pharmacological activity [76-79]. Glitazones can bind to PPARγ in adipocytes and promote maturation of these cells and deposition of fat into the peripheral tissues. By reducing circulating fat concentrations, TZDs may improve individual insulin sensitivity in type 2 diabetes conditions. Furthermore, TZDs can effectively bind to PPARγ receptors and modulate the other signaling pathways that regulate energy metabolism; these drugs may increase memory performance and also decrease Aβ deposits, accelerating amyloid plaque clearance. Nevertheless, extensive preclinical and clinical studies are needed to confirm these pharmacological activities as a drug-repurposing strategy [76-79]. TZDs can induce mitochondrial biogenesis and enhance mitochondrial function, as indicated by a rise in the respiratory complex activities and mitigation of oxidative stress. Finally, TZDs are capable of reducing tau phosphorylation through the inhibition of different kinase activities and promoting the formation of neurofibrillary tangles in AD conditions [76-79].

PPARs can regulate the inflammatory signaling by modulating several mechanisms; for instance, PPARs can compete with NF-kB similar to several sets of co-activators, *viz*. CREB, and impair NF-kB activity. They can interact with several transcription factors and impair NF-kB binding to DNA, and modulate gene expression to mitigate the pathophysiology of neurodegeneration [80, 81]. Other PPAR-γ agonist molecules, such as pioglitazone, can enhance oxygen consumption, consequently modulating the mitochondrial DNA contents and fostering the expression of genes responsible for mitochondrial biogenesis, viz. mito-

chondrial transcription factors A (Tfam) [82]. Rosiglitazone can confer glucose uptake into the brain and promote mitochondrial biogenesis in neurons [83]. Furthermore, these drug molecules can enhance the mitochondrial membrane potential and impair neuronal cell death. PPAR isoforms may contribute to energy balance by regulating mitochondrial processes and sustaining cell metabolism in response to dietary lipid consumption, facilitating wound healing in diabetes patients [84, 85]. Thus, the PPARs can exert typically significant protective effects during cardiovascular abnormalities, fatty liver syndrome, type II diabetes, [86], cancer, and stroke [87]. The biochemical pathway associated with the pharmacological efficacy of glitazones is shown in Fig. (**9**).

Furthermore, the administration of rosiglitazone and pioglitazone could be conducive to the prevention of neural cell death, inflammation, and myelin damage during neurodegeneration [88-90], by modulating the role of PPARs. Hence, they may have potent therapeutic applications in preventing neurodegeneration in PD, AD, and other neurological diseases, such as ALS and HD. Still, several preclinical and clinical studies are required to examine the significant role of these drug molecules in triggering mitochondrial biogenesis response and their therapeutic responses in the above diseases as drug repurposing strategies.

6.1. Mitochondrial Dynamics and PPAR Agonists

Mitochondrial dysfunction is considered as the key aspect that facilitates Aβ-induced neurotoxicity [91, 92], suggesting that mitochondrial dynamics could play a significant role in mitochondrial dysfunction [93-95]. Balance in the mitochondrial fusion and fission events promotes a healthy mitochondrial population when responding to stress stimuli [95]. Extensive ROS-mediated oxidative stress can induce damage to the mitochondrial DNA, which consequently fosters the malfunction of mitochondria, and these defective organelles can be recovered by recurrent mitochondrial fusion and fission [95-97]. A study by Wada and Heneka *et al.* depicted the efficacy of PGC-1α and mitochondrial dynamics to be considered as a future therapeutic modality to ameliorate AD-induced pathophysiology. In this study, the authors observed the significant loss of PGC-1α signal after peroxide-induced mitochondrial damage, which is linked to the metabolic processes and a significant alteration in mitochondrial biogenesis [98, 99]. Furthermore, the activity of PGC-1α is linked to the PPARs, RXR, and ER-related receptor α (ERRα), which facilitate the modulation of other mitochondrial proteins, *viz*. Nrf1, Nrf2, DRP1, FIS1, and MFN2 [93, 98-101]. In this study, the authors described the loss of PGC-1α signaling and suggested the impaired expression of all these mitochondrial proteins pertaining to the mitochondrial fission-fusion, consequently affecting the balance in mitochondrial dynamics in AD models.

6.2. On- and Off-target Effects of PPAR Agonists in AD

Some PPAR-γ agonists (thiazolidinediones) are capable of interacting with other targets as diverse as nuclear receptors, like glucocorticoid receptors [102], and GPCRs [103], protein kinases [103], calcium and potassium ion channels [104, 105], and mitochondrial targets [106-109]. A report by Wright *et al.* (2014) delineated the on- and off-target effects of PPAR agonists contributing to the mechanisms involved in modulating various disease pathologies, including neurodegeneration-induced AD. Thus, PPAR ligands can interact with non-PPAR targets, modulate phosphorylation, and foster nongenomic regulation. The on- and off-target effects of mTOT, mitoNEET, and thiazolidinediones could be conducive to the assessment of the therapeutic potential of these drugs and their adverse effects, *viz*. inflammation, cardiovascular abnormalities during both metabolic diseases and neurological diseases. During the unliganded state of PPAR, the binding of corepressor proteins, *viz*. SMRT (NCoR/silencing mediator of retinoid and thyroid receptors), can block the transcription through the histone deacetylases (HDACs). During ligand binding, PPAR could induce the dissociation of NcoR/SMRT and HDACs that allows the recruitment of transcriptional coactivators, *viz*. PGC1-a or SRC-1 along with histone acetyltransferases that allow chromatin opening for the RNA polymerase II activity in neurons. Thus, the modulation of ligand binding efficacy of PPAR may benefit the development of novel therapeutic modalities, thus inducing neuronal cell survival.

6.3. PPAR and Neurotransmission

GLT-1 transporter has been reported to be altered through the Aβ42 induced lipid peroxidation product, *i.e*., 4-hydroxy-2-nonenal in AD brain [110], which indicates that the altered expression of APP in AD conditions may invoke GLT-1 downregulation.

For instance, the co-localization of PPAR-α occurs during the injection of lipopolysaccharide in mice models, which triggers neuroinflammatory responses across the specific regions of the brain [111]. Furthermore, the co-localization of PPAR-γ in microglia is comparatively lesser than PPAR-α [111]. The co-localization of PPAR-α in the hippocampus, CA1, CA2, CA3, and dentate gyrus was substantially observed in mouse models, and the PPAR-α could control the calcium influx and several hippocampal genes involved in synaptic plasticity [65]. Furthermore, PPAR-α is also involved in modulating the expression of NMDA receptor subunits, such as NR2A and NR2B [112], and AMPA-receptor associated GluR1 subunit [113, 114] involved in synaptic plasticity. PPAR-α agonists could be beneficial to enhance the synaptic activity through the modulation of the above receptor isoform expression during neurodegeneration. Signaling pertaining to the PPAR-α may lead to the changes in gene expression encoding for enzymes involved in the endogenous antagonists of GluR and foster the GLT-1 transporter endocytosis in astrocytes [115]. These cells can confer glutamate homeostasis in the brain by co-ordinating with GLAST and EAAT1 [116]. Changes in this transporter expression could be conducive to the imbalance in GLT-1 function in AD patients [117]. For instance, the downregulation of PPAR-α is more significantly observed in the AD brain, which may link to the alteration in GLT-1 function that consequently disturbs glutamate homeostasis in AD. PPAR-α agonists, such as GW7647 and WY14, 643, can modulate the GLT-1 expression in astrocytes [115]. Table **1** presents previous therapeutic strategies that have been proven effective in several experimental models against AD.

Table 1. Various FDA approved drugs and other drugs that can be repurposed as a therapeutic regimen against neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease, Parkinson's disease, and Amyotrophic lateral sclerosis (ALS).

Alzheimer's Disease (AD)				
Target	**Agent**	**Mechanism of Action**	**Experimental Model**	**References**
Glutamate excitotoxicity	NMDA glutamatergic receptor antagonist	Helps reinstate brain metabolic functions.	Hippocampal slices of aged (23-25-month-old) rats	[118]
Cholinergic deficiency	Acetylcholinesterase inhibitor	Possibly stimulates the production of trophic factors, *e.g.*, IGF-1; activates PI3K-Akt, protects against glutamate neurotoxicity; promotes neuronal survival.	Mouse	[119]
Aβ-42 accumulation and fibrillization	Gamma secretase inhibitor drugs; BACE1 inhibitors to reduce cleavage and production of toxic peptides	Enhances PI3K-Akt signaling; reduces insulin resistance; reduces GSK-3β activity, resulting in decreased tau phosphorylation.	8 SH-SY-5Y cells (*in vitro*)	[120]
Tau hyperphosphorylation	GSK-3β and protein phosphatase 2A inhibitors	Helps to restore insulin responsiveness; reduces oxidative stress.	Four- to six-week-old female Sprague–Dawley (SD) rats	[121]
Insulin deficiency	Insulin therapy-intranasal Incretins, *e.g.*, GLP-1 to stimulate insulin	Maintains survival and function of cells, requiring insulin stimulation; supports glucose uptake, brain metabolism and neuronal plasticity; enhances cognition; decreases APP burden and tau hyperphosphorylation.	Mouse	[122]
Hyperglycemia	Antihyperglycemic agents-biguanides	Enhances glucose uptake and insulin receptor sensitization.	Albino rats	[123]
Insulin resistance	Insulin receptor sensitizers, *e.g.*, PPAR-$_{\gamma}$ agonists	Enhances cellular glucose uptake and insulin receptor sensitization; anti-inflammatory and anti-oxidant properties.	Mouse	[124]
Neuroinflammation and Oxidative stress	Anti-oxidants Radical scavengers Anti-inflammatory agents	Transition metal chelators help reinstate insulin sensitivity and glucose utilization; decrease A42 deposition; decrease A42 and tau fibrillization; support microvascular function and cerebral perfusion; decrease cytokine activation-mediated injury.	Mouse	[125]
Neuroprotective effects	DSP-8658	Microglial Aβ phagocytosis gets enhanced.	Mouse	[126, 127]
Neuroprotective effects	Rosiglitazone	Decrease the accumulation of the Aβ proteins in the cortex and hippocampal regions inside neurons.	Mouse	[126, 127]
Neuroprotective effects	Pioglitazone	Enhancement in the hippocampus-dependent cognition, learning and memory performance.	Mouse	[126, 127]
Parkinson's Disease (PD)				
Neuroprotective effects	GSK0660	Provide protection in case of MPP+ induced toxicity.	Human neuroblastoma cells, SH-SY5Y cells	[128]
Neuroprotective effects	Intrastriatal infusion of GW0742	Increased protection in the case of MPTP-induced dopaminergic neuron damage.	Mice Rats	[128, 129]
Motor and non-motor symptoms	Palmitoylethanolamide	Increased protection in the case of MPTP-induced dopaminergic neurons damage, TH^{+} neurons of substantia nigra, microglial activation, GFAP positive astrocytes and over-expression of S100β.	Mice PPAR-α KO mice	[130]
Restoring adult neurogenesis	Indomethacin	Increased protection in the case of MPTP; protects against MPTP-induced neurotoxicity, microglial activation and infiltration of lymphocytes.	Mouse	[131]
Neuroprotective effects	Ibuprofen, Aspirin Acetaminophen	Increased protection in the case of glutamate, 6-OHDA and MPP+ induced dopaminergic neuronal damage.	Mesencephalic culture	[132]

(Table 1) contd….

Parkinson's Disease (PD)				
Target	**Agent**	**Mechanism of Action**	**Experimental Model**	**References**
Master regulator of mitochondrial biogenesis	PGC-1α	Increased protection in the case of MPTP-induced dopaminergic neurons damage, oxidative stress and ROS generation; master regulator of mitochondrial biogenesis.	PGC-1α knockout mice	[133]
Neuroprotective effects	L-165041 and GW501516 (i.c.v infusion)	Increased protection in the case of MPP+ and staurosporine-induced cell toxicity; depletion of dopaminergic neurons and metabolites levels in the brain.	SH-SY5Y cells Mouse	[71]
Short-term neuroprotective effects	Fenofibrate	Increased protection in the case of MPTP-induced dopamine cell loss in the substantia nigra.	Wistar rats Mice	[71, 134]
Huntington's Disease (HD)				
Neuroprotective effects	Rosiglitazone	Increased protection in the case of HTT-induced toxicity in cells of the striatum and increased Sirt6 protein levels.	Mouse	[135-137]
Increase in the number of mitochondria and improvement in mitochondrial ultrastructure	Thiazolidinedione (TZD)	Decreased cellular stress induced by thapsigargin and H_2O_2.	Mouse	[134]
Short term neuroprotective effects	Bezafibrate (an PAN-PPAR)	Escalated mitochondrial biogenesis.	Mouse	[138]
Amyotrophic Lateral Sclerosis (ALS)				
Neuroprotective effects	Pioglitazone	Decreased microglial activation; increases expression of COX-2 and iNOS.	Mouse	[139]
Regulation of mitochondrial biogenesis.	PPAR-γ	Upregulated lipoprotein lipase and glutathione-S-transferase and aid in the scavenging o f lipid peroxidation by-products. Increased neuroprotection by enhancing the PPAR-γ transcriptional activity.	Transgenic Mouse	[140]
Mitochondrial dysfunction	PGC-1α	Regulated mitochondrial biogenesis; ameliorated muscle function.	Transgenic mice Human tissue	[141-143]

Abbreviations: BACE1=beta site AβPP cleaving enzyme 1; GLP-1=glucagon-like peptide-1; NMDA= N-methyl-D-aspartate; PPAR= peroxisome proliferator-activated receptor; PI3K= phosphatidylinositol 3 kinase; GSK-3β = glycogen synthase kinase 3β; AβPP= amyloid-β - precursor protein; Aβ 42=amyloid beta peptide-42 amino acids 1-42 cleavage product; IGF=insulin-like growth factor.

7. EXISTING CLINICAL AND PRE-CLINICAL REPORTS IN THE CONTEXT OF AD

Currently, several lead molecules are in the preclinical and clinical trials for the treatment of AD. For instance, resveratrol is an antioxidant molecule that has effectively completed phase II clinical trial, and it has the capability to cross the blood-brain barrier in the treatment of AD [144]. Etanercept is another drug molecule that exerts protective effects against AD, and it can impair TNF-α activity; however, it is still in phase II clinical study for its safety and tolerability [145]. Simvastatin is a cholesterol-lowering drug, which could be used as a drug-repurposing strategy, but no significant clinical efficacy has been observed against AD models in clinical studies [146]. Neflamapimod is another selective blocker of p38-MAPK-alpha isoform and could have a significant ameliorative effect against AD in transgenic mice [147]. Phase II clinical studies of neflamapimod can enhance episodic memory in AD patients [148]. Other clinical trials pertaining to azeliragon (TTP488) could block the receptors for advanced glycation end products (RAGEs) and enhance cognition in AD patients [149], but their clinical efficacy has not delivered fruitful outcomes in clinical trials; hence, phase III trials have been terminated. Pioglitazone is a PPAR-γ agonist which delivered significant clinical outcomes against AD, but the phase III trials were discontinued due to lack of efficacy [150-152].

Furthermore, the development of novel inhibitors of γ-Secretase is another significant strategy to mitigate Aβ-generation. Semagacestat is a γ-Secretase blocker to mitigate Aβ production. However, the phase III clinical trials for this molecule have been discontinued due to the adverse events induced in terms of dose-dependent cognitive and functional defects [143]. Avagacestat is a γ-secretase that has been reported to block the Aβ production *in vitro* and mice models, but its clinical trials have also been terminated due to the lack of efficacy [153-156].

Table 2. Various FDA-approved drugs and other drugs having PPAR-α agonist activity that can be repurposed as a therapeutic regimen against neurodegenerative diseases and bipolar disorder.

PPAR-α Agonists Repurposed for the Treatment of Neurodegenerative Disorders				
Repurposed Drug Molecule	**Neurodegenerative Disorder**	**Elucidated Pharmacological Action from Experimental Models**	**Elucidated Pharmacological Action from Clinical Trials**	**References**
Gemfibrozil	Alzheimer's disease	(1) Stimulates ADAM10 (2) Reduces Aβ synthesis and leads to deposition of Aβ plaque (3) Enhances learning and memory	Downregulates the expression of BACE1	NCT0204505 [180]
Fenofibrate	Parkinson's disease	(1) Protective effect in the case of MPTP-induced toxicity (2) Decreases inflammation	**NA**	[181, 182]
	Drug-resistant Nocturnal frontal lobe epilepsy	-	A decrease in seizure frequency Having effects on motor-behavioral seizures	[183]
WY-14643	-	(1) Decreases tau protein and inflammation markers (2) Improves results in the Morris water test	**NA**	[184]
GW7647	Neuroprotection	(1) Regulates APP amyloidogenic processing (2) Decreases the expression of sAPPβ and BACE1 (3) Reduces Aβ release and Aβ production	**NA**	[62]
Bezafibrate	Bipolar disorder	Reverses some of the mitochondrial and cellular abnormalities	Positive change in Montgomery-Åsberg Depression Rating Scale	NCT02481245 [185]
Other Drugs Repurposed for the Treatment of Neurodegenerative Diseases				
Exenatide	Parkinson's disease	Neuronal protective effects and hypoglycemia.	Not yet reported	NCT01174810 [186]
Pioglitazone	Parkinson's disease	Blocks conversion of MPTP to its active toxic metabolite MPP+ via inhibition of MAO-B.	Unable to modify progression in early Parkinson's disease.	NCT01280123 [187]
Isradipine	Parkinson's disease	Protects striatal dopaminergic terminals and SNc dopaminergic cell bodies.	Prevents excess calcium influx by blocking calcium channels and decreasing metabolic stress, thus resulting in neuroprotection.	[188]
Deferiprone	Parkinson's disease	Scavenges both aqueous iron and iron that is loosely bound to dopamine with the entrapment of iron in Fe-DFP complexed form. This drug critically halts the iron-catalyzed degradation of dopamine and associated generation of toxic metabolites.	Chelates iron from various brain regions and improves PD symptomology	NCT01539837 [189]
Inosine	-	Effects mediated through its metabolite urate.	Has been found to be effective in raising serum and cerebrospinal fluid urate levels in early PD	NCT00833690 [190]

NA: Not available.

Several aggregation inhibitors were developed against AD to target amyloidogenic pathways. For example, PBT2 trials in phase II/III were terminated due to the lack of efficacy, although it could be a metal protein-attenuating compound to impair Aβ aggregation [153, 157]. Scyllo-inositol can act as a blocker of Aβ aggregation, and the phase II clinical trials have reported good clinical outcomes in AD patients [158, 159]. Tramiprosate is abundant in seaweed and can exhibit neuroprotective effects for AD patients by blocking beta-sheet formation, and consequently, impairing the Aβ aggregation [160]. This drug molecule can foster the long-term potentiation induced through Aβ toxicity, subsequently conferring to the mitigation of soluble and insoluble Aβ aggregation in mice models [161, 162]. However, clinical statistical analysis has not delivered good outcomes, although the drug has provided beneficial effects in AD patients [163-167]. A prodrug of Tramiprosate, ALZ-801, in a combinatorial regimen with graphene quantum dots (GQDs), delivered significantly promising clinical outcomes in AD patients [168-170]. Another drug, Sodium oligo-mannurarate (GV-971), has been reported to impair Aβ aggregation [171].

7.1. Vaccines

Nowadays, the development of vaccines against Aβ has been gaining medical importance as immunotherapies against AD. For instance, the AN-1792 is a first-generation vaccine implicated against AD, but its clinical trial has been terminated due to the associated adverse effects, viz. cerebral inflammation [172]. Later, the follow-up study also failed to deliver clinical outcomes in terms of mitigating symptoms of dementia. Other vaccines, CAD 106 and ACC-001, have been reported to deliver promising results in phase II clinical trials against AD; nevertheless, phase III trials are ongoing [173].

7.2. Aβ Antibodies

Another therapeutic modality, the application of Aβ antibodies, could be used as passive immunotherapy for AD treatment. For instance, bapineuzumab and solanezumab are significant monoclonal antibodies implicated for impairing the development of Aβ (1–6) and Aβ (12–28), respectively [174, 175]. However, the phase III clinical trial was stopped due to observance of no significant cognitive enhancement, even though there was a decline in senile plaques and tau protein [154]. Ponezumab could prove to be effective in blocking the Aβ40 formation in the hippocampus of mice models of AD [176], but its phase II trials were terminated due to the lack of efficacy in mitigating brain Aβ load and cognitive enhancement [177-179]. Although GSK933776 and LY2599666 administration proved effective in preclinical studies of AD, their clinical efficacy in Phase I trials of AD patients was not found to be effective.

Weiping Qin *et al.* explored the mechanisms through which the altered PGC-1α expression may influence AD-amyloid neuropathology, and to test the hypothesis that the promotion of PGC-1α expression in neurons might be developed as a novel therapeutic strategy in AD. Therapeutic preservation of neuronal PGC-1α expression may promote the non-amyloidogenic processing of APP, precluding the generation of amyloidogenic Aβ peptides [76]. Kai Lun Chang *et al.*, from the National University of Singapore, reported DSP8658, a novel selective PPAR α/γ modulator, to complete the Phase I clinical stage; it is considered a preferred drug candidate for the treatment of AD. DSP-8658 enhances the microglial uptake of Aβ, which is a proposed trigger for the onset of AD and also improves cognitive function in APP/PS1 transgenic mice [77]. Talwar *et al.* reported the abundance of Apolipoprotein E (APoE) levels in the cerebrospinal fluid of patients with AD. They reported the possible association between ApoE levels in the cerebrospinal fluid (CSF) and AD [78]. Datusalia *et al.* elucidated the molecular mechanisms and evaluated the pharmacological interventions in CNS diseases, like stroke (middle cerebral artery occlusion induced focal cerebral ischemia), global cerebral ischemia (BCO model), epilepsy (seizure models), Parkinson's (MPTP model), memory impairment (Beta-amyloid model), *etc*. They worked extensively on the amelioration of diabetes-induced cognitive deficits by GSK-3β inhibition, modulating the neurotransmitters and neuroinflammation [79].

CONCLUSION

PPARs are nuclear receptors that can facilitate the development of novel therapeutic modalities against several neurodegenerative diseases, such as PD, AD, and HD. PPARs exhibit a promising role in modulating the mitochondrial and proteasomal dysfunction, ROS-mediated oxidative stress, and neuroinflammation involved in the pathophysiology of neurodegenerative diseases. Agonists of PPARs could modulate the mitochondrial dynamics, as reported in *in vitro* and *in vivo* models, and offer neuroprotection by modulating the protein expressions involved in neurodegeneration. Furthermore, the PPARs are also involved in modulating neurotransmission and long-term potentiation during AD conditions. Although several drugs, like Aβ aggregate inhibitors, vaccines, and natural antioxidants, are at different levels of clinical phase trials, their efficacy is very limited and constrained by adverse effects [191,192]. Hence, it is crucial to develop already existing drugs (*e.g.*, glitazones) as drug repurposed novel PPAR agonists and determine their efficacy in preclinical and clinical AD models.

AUTHORS' CONTRIBUTIONS

Priya Durai (PD), Narasimha M. Beeraka (NMB), Hemanth Vikram P.R (HVPR), Prakash Krishnan (PK), and Prashantha Kumar B.R (PKBR) conceptualized and designed the study. NMB, PD, PKBR and HVPR performed literature analysis and wrote the original manuscript draft. PKBR, NMB revised, edited, and extended the final draft.

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CONFLICT OF INTEREST

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

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