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Type 2 Diabetes (T2DM) and Parkinson's Disease (PD): a Mechanistic Approach

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Abstract

Growing evidence suggest that there is a connection between Parkinson's disease (PD) and insulin dysregulation in the brain, whilst the connection between PD and type 2 diabetes mellitus (T2DM) is still up for debate. Insulin is widely recognised to play a crucial role in neuronal survival and brain function; any changes in insulin metabolism and signalling in the central nervous system (CNS) can lead to the development of various brain disorders. There is accumulating evidence linking T2DM to PD and other neurodegenerative diseases. In fact, they have a lot in common patho-physiologically, including insulin dysregulation, oxidative stress resulting in mitochondrial dysfunction, microglial activation, and inflammation. As a result, initial research should focus on the role of insulin and its molecular mechanism in order to develop therapeutic outcomes. In this current review, we will look into the link between T2DM and PD, the function of insulin in the brain, and studies related to impact of insulin in causing T2DM and PD. Further, we have also highlighted the role of various insulin signalling pathway in both T2DM and PD. We have also suggested that T2DM-targeting pharmacological strategies as potential therapeutic approach for individuals with cognitive impairment, and we have demonstrated the effectiveness of T2DM-prescribed drugs through current PD treatment trials. In conclusion, this investigation would fill a research gap in T2DM-associated Parkinson's disease (PD) with a potential therapy option.

Keywords Parkinson's disease · Type 2 diabetes mellitus · Insulin · Pathophysiology · Therapeutics

Introduction

Parkinson's disease (PD) is a movement disorder depicted by dopaminergic (DA) neuron depletion in the basal ganglia region [1]. It is characterised by four cardinal symptoms of rigidity, postural imbalance, bradykinesia, and tremor [2]. The cause and severity of PD may be influenced by a variety of demographic and environmental factors [3, 4]. PD is multi-factorial, but ageing is considered to one of the prime causative agent amongst others [5, 6]; however, the pathophysiology of PD is still elusive [7]. People living with PD are more likely to develop several other diseases, including heart disease [8], cancer [9], gastrointestinal disorders [10], type 2 diabetes mellitus (T2DM) [11], vitamin D deficiency [12], peripheral neuropathy [13], and musculoskeletal diseases [14]. Amongst these associated diseases, T2DM has been the most commonly associated disease with PD. In an earlier study, it was stated that lysosomal disruption, mitochondrial dysfunction, aberrant protein build-up, and chronic inflammation are some of the common possible

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signalling pathways that may cause protein misfolding and insulin resistance, in both PD and T2DM [15]. Interestingly, there is also an evidence for cross-seeding between islet amyloid polypeptide (IAPP) and αSyn [16]. Also, metabolically in T2DM, insufficient insulin production causes disruptions in glucose metabolism and chronic inflammation, whereas similar metabolic downregulation is seen in early PD conditions [17]. As a result, insulin is now widely recognised to play an important role in neuronal survival and brain function. Insulin action is vital for neuronal synaptic plasticity and aids learning and memory. Therefore, alterations in insulin metabolism and signalling in the central nervous system (CNS) can contribute to the development of many brain disorders [18]. The pathogenesis of these brain diseases suggested to be significantly influenced by both insulin resistance and reduced insulin action through many mechanisms [19]. Therefore, understanding the role of insulin and its signalling pathway is essential to investigate, in T2DM and PD [20]. Hence, in this review, we have discussed the link between T2DM and PD, by focusing the function of insulin in the brain, and its clinical and pre-clinical evidences on T2DM and neurodegeneration. We have also reported the efficiency of common therapeutic compounds on T2DM and PD, thereby concluding the need of research on the signalling pathways correlating T2DM and PD with its effectiveness on the development of therapeutic strategies for both.

Accompaniment Between T2DM and PD

The specific protein known as amylin misfolds may contribute to T2DM pathogenesis due to the loss of pancreatic beta cells, which in turn results in insulin insufficiency and hyperglycaemia and speed up of disease progression [21, 22]. Additionally, this amylin has been linked to PD pathophysiology since it interacts with alpha-synuclein (αSyn), which has been reported in an in vitro study[23]. This αSyn is also produced in pancreatic islets which plays a crucial role in glucose regulation [24]. Whereas in T2DM, IAPP aggregation takes place in the pancreatic cells [25]. As a result, it is important to maintain the balance of the protein levels between production, release, and clearance. Note that there may be an imbalance in the proportion of amylin or αSyn, which could encourage the formation of toxic aggregates in the brain and modulate pancreatic beta cells [26]. Ultimately, there is a possibility that these two proteins will interact indirectly or directly and result in T2DM and PD when their levels are altered [27]. Few reports have shown that oxidative stress, protein aggregation, neuroinflammation, insulin resistance, and mitochondrial dysfunction are involved in the aetiology of T2DM and PD. Almost all of the biomolecules in a cell can be damaged by oxidative stress, which can result in dysfunction and cell death. In T2DM and PD, oxidative stress damages pancreatic beta-cells as well as dopaminergic cells [28]. Another mechanism is insulin resistance, which inhibits insulin signal transduction which contributes to T2DM pathogenesis, also an imbalance in insulin inside the brain could also promote PD progression by impairing mitochondrial function [29] through an increase in reactive oxygen species (ROS) generation [30] [31]. Another important mechanism is neuroinflammation, where the microglia plays a crucial role in PD [32], whereas its activation plays a key role in the dysregulation of energy homeostasis, promotes excessive glucose levels, and has an influence on the occurrence of T2DM [33]. In this review, we have incorporated and depicted an overview of studies with epidemiological evidences supporting the association between T2DM and PD in Table 1.

T2DM and Neurodegeneration: the Role of Insulin

The pancreatic beta-cells secrete insulin, a polypeptide hormone with a molecular weight of approximately 6000 Da [47]. The protein insulin is made up of two chains—an A chain, which has 21 amino acids, and a B chain, which has 30 amino acids—joined by sulphur atoms. Proinsulin, a prohormone molecule with 74 amino acids, is the precursor of insulin. Only a small amount of proinsulin is secreted normally since it is a relatively inert protein. The proinsulin molecule is split into two parts in the endoplasmic reticulum of beta cells, resulting in the A and B chains of insulin and an intervening, biologically inactive C peptide [48, 49]. Insulin enters the brain after being secreted by pancreatic b-cells, and this process is tightly controlled and may be altered by conditions like obesity, diabetes mellitus, fasting, and neurodegenerative diseases [50]. In fact, the brain has historically been assumed to be insensitive to insulin since it does not increase glucose absorption or metabolism in the brain. However, in the last two decades, studies in this domain have uncovered specific insulin effects in the brain, and there are growing evidences that reveals insulin to act in both central and peripheral brain regions and serves several functions [51, 52]. The development of the nervous system is found to be highly influenced by insulin action in the brain, which controls proliferation, specialisation, and nerve growth [18, 53]. Additionally, brain insulin functions as a neuroprotector by inhibiting the effects of apoptosis, β-amyloid toxicity, oxidative stress, and ischemia [31, 54, 55]. If the brain insulin metabolism is impaired, the protective effects of insulin may be reduced [56], which leads to cognitive impairment and depression as well as the lack of insulin action in the brain, and may increase the risk of neurodegenerative disorders [30, 57]. Insulin disturbances

Table 1 Concomitance between T2DM and PD

Study design	Study area	Objective	Sample size	Method	Result	Conclusion	References
Case–control	Italian population	Glucose metabolism abnormalities	110 patients	• Oral-glucose-tolerance-test	PD patients with dementia • ↑ disease duration • ↑ motor disability	Insulin resistance • ↑PD with dementia • ↑PD without dementia	[34]
Inter-group comparative analysis	South Korea	Effect of DM on PD patients	671 patients	• Neuroimaging analyses • DAT • Assessment of longitudinal changes in LED	• ↓baseline DAT availability • ↓working memory • ↓frontal/executive function • ↑longitudinal changes in LED	DM patients with PD • ↓baseline striatal dopamine • ↓cognitive function • ↓brain structural alterations	[35]
Retrospective, case–control	Italy	Clinical features of patients with idiopathic PD (IPD)	PD ($n=89$); control ($n=89$)	• UPDRS	• Higher UPDRS motor score • Severe Hoehn and Yahr staging	The onset of DM before the onset of PD • ↑extreme PD symptoms	[36]
Meta-analysis	Italy	Relationship between pre-existing DM and PD	Nine studies/1,947 citations	• Data obtained from electronic databases	Onset of DM before the onset of PD • ↑risk for future PD	• DM is a risk factor for PD	[37]
Cohort study	America	Association between T2DM and PD	21,841 participants	Questionnaire	• ↑DM had an PD risk	No conclusive evidences, so more studies remain to be established	[38]
Cross-sectional study	Spain	Association between PD and DM	79 PD and 4919 controls	NEDICES	• No association between prevalence of PD and DM	The risk of PD in DM might be limited to longer disease duration	[39]
Retrospective, cohort study	Spain	Association between T2DM and subsequent PD	81,90,323 participants	Linked English national Hospital Episode Statistics and mortality data	• The relative increase was greater in those with complicated T2DM and when comparing younger individuals	↑rate of subsequent PD following T2DM	[40]
Prospective	Northeast America	Obesity and DM are related to the risk of PD	656 PD	Medical history and anthropometric variables	DM was not significantly associated with PD risk	No evidence between baseline DM and PD	[41]
Prospective	Singapore	Impact of DM in PD patients	PD, DM ($n=12$); control ($n=65$)	MRI imaging and neuropsychological assessments	• ↓routine cognitive screening tests (MMSE and MOCA) • ↑atrophy in the cortical White matter	DM in PD • ↑cognitive decline	[42]
Retrospective, cohort study	Taiwan	Age-sex-specific incidence, relative risk of PD	DM ($n=603,416$); control ($n=472,188$)	Incidence rate and relative risk of PD evaluation	• DM elevated risk of PD patients especially in women and younger patients	A stronger link between DM and young-onset PD deserves further investigation	[43]

Table 1 (continued)

Study design	Study area	Objective	Sample size	Method	Result	Conclusion	References
Cohort study meta-analysis	China	Associations between DM and the risk of PD	1,761,632 individuals from 7 population	Data obtained from electronic databases (PubMed, Embase, and Scopus)	↑DM associated with PD risk 38%	More large-scale prospective studies are warranted to further clarify this association and its mechanism	[44]
Case–control meta-analysis	China	Association between DM and the risk of PD	PD patients ($n = 21,395$); control ($n = 84,579$)	Data obtained from databases	↓DM association with future PD	DM individuals may have a decreased incidence of PD despite significant heterogeneity	[45]
Cohort study	USA	Relationship between DM and future risk of PD	288,662 with and without PD	Questionnaire	PD risk was higher amongst diabetic patients	↑ PD with DM ~40%	[46]

PD, Parkinson's disease; *T2DM*, type 2 DM mellitus; *DM*, DM mellitus; *DAT*, dopamine transporter; *LED*, levodopa-equivalent dose; *UPDRS*, Unified Parkinson's Disease Rating Scale; *NEDICES*, Neurological Disorders in Central Spain study; *HR*, hazard ratio; *CI*, confidence interval; *MMSE*, Mini-Mental State Examination; *MOCA*, Montreal Cognitive Assessment

associated with the diabetic phenotype (hyperglycemia, hyperinsulinemia, and hypercholesterolemia) have been linked to brain atrophy and PD pathological features [58]. It is still unclear whether insulin resistance is a cause or a result of PD; however, insulin action has been shown to play an important role in PD pathogenesis. Emerging data highlights the significance of insulin dysregulation that may lead to neuropathophysiological conditions, given the fact that the role and processes behind insulin action in the human CNS still raise many issues and are far from being fully understood (Fig. 1).

Insulin Signalling in Brain

In the brain, insulin will bind to its receptors causing the phosphorylation of substrates, Shc, and insulin receptor substrate (IRS) where IRS is responsible for the PI3K (Phosphatidylinositol-3-kinase)-Akt (also known as PKB (Protein kinase B) cascade and Shc for Ras-MAPK (mitogen-activated protein kinase) that functions in food behaviour, learning, memory, and neuromodulation [59]. For the activation of PI3K-AKT, initially, insulin binds to the α-subunit of the insulin receptor, leading to the formation of dimers and autophosphorylation of β-subunits [60]. PI3K first transforms the minor phospholipid from phosphatidylinositol (3,4)-bisphosphate (PIP_2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP_3), and this conversion is important for engaging PKB or AKT to the membrane of the cell [61]. AKT is responsible for the regulation of several other proteins in the insulin signalling cascade, including mTORC1 and FOXO1 [62]. It is also an active participant in several different signalling pathways of cell proliferation, cell growth, and metabolism [63]. Insulin binding also activates another series of cascades leading to MAPK pathway [62]. Small G-protein Ras is activated by the phosphorylation of guanosine triphosphate which further results in the MAPK-ERK cascade signalling [64]. MAPK is the pathway through which insulin can affect both learning and memory [65]. It is also responsible for the initiation of synaptic plasticity and cell differentiation through the transcription of various genes [66]. From these studies, it is evident that the insulin plays a major role in the brain and the deviation in their levels do have an impact on the metabolic and cognitive functions (Fig. 2).

Impact of Methylglyoxal in T2DM and PD

Methylglyoxal and T2DM

Certain conditions such as hyperglycaemia and glycation, a random event that typically takes place under biological circumstances, are generally aggravated in T2DM [67]. The key

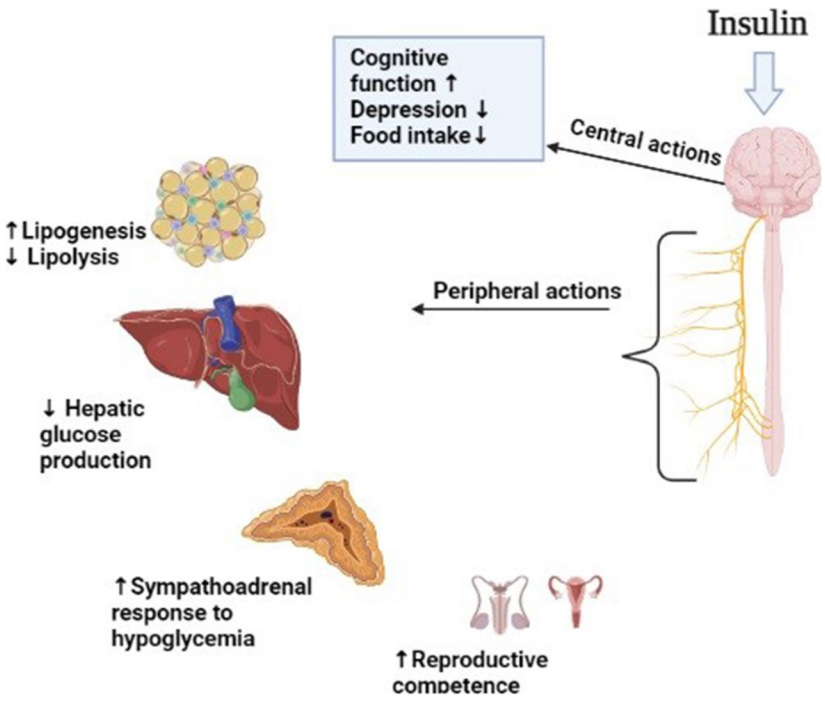

Fig. 1 Function of insulin in the brain. Insulin controls peripheral activities in the brain by autonomic nervous system (ANS) and the hypothalamic-pituitary axis (HPA). Insulin specifically acts in the hippocampus and prefrontal cortex to enhance cognitive function and lessen depression symptoms. Insulin reduces food intake and helps people lose weight by acting in the hypothalamic nuclei. Insulin functions in the brain to reduce hepatic glucose synthesis, enhance lipogenesis, reduce lipolysis, and boost the sympathoadrenal response to hypoglycemia via the efferent ANS to target organs. The hypothalamic-pituitary–gonadal axis is the pathway via which insulin improves reproductive competence

factor thought to be responsible for diabetes complications is hyperglycaemia, which occurs when there is an overwhelming quantity of glucose in the blood [68]. Methylglyoxal (MGO) is the main hazardous oxoaldehyde that is formed during hyperglycaemia in diabetes mellitus. In reality, the healthy levels of MGO in human plasma are about 150 nM, whilst T2DM individuals have been shown to have two to six times elevated levels [69, 70]. Prevailing thought is that methylglyoxal (MG), a reactive metabolite generated from glucose, and its breakdown by the glyoxalase pathway play a significant role in metabolic dysfunction, which connects hyperglycaemia to the onset of vascular problems in diabetes [71]. With a

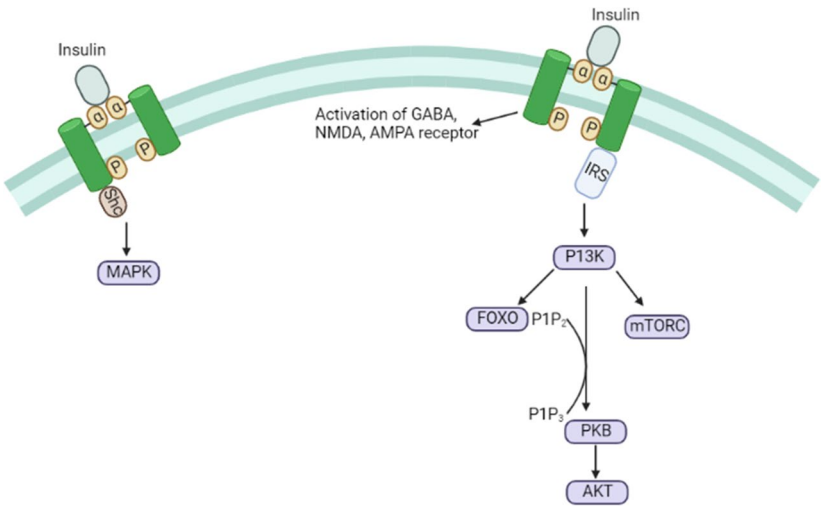

Fig. 2 Signalling pathways involved in insulin signals in the brain. When insulin ligand binds to its receptor, the receptor substrates IRS and Shc were phosphorylated. IRS activates PI3K-Akt pathway and insulin signalling cascade such as mTORC and FOXO1. PI3K first converts PIP_2 to PIP_3 that helps in engaging the Akt to the cell membrane. Shc activates MAPK pathway by activating the Ras protein through phosphorylation. Insulin binding also helps in the expression and recruitment of other receptors like GABA, NMDA, and AMPA. IRS, insulin receptor substrate; mTORC, mammalian target of rapamycin complex; FOXO1, Forkhead box protein O1; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol-3-kinase; PIP2, phosphatidylinositol (3,4)-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

molecular weight of 72 Da, MGO is a-oxoaldehyde metabolite that is primarily produced as a by-product of glycolysis after the spontaneous breakdown of the triose phosphate intermediates glyceraldehyde-3-phosphate (G3P) and dihydroxyacetone phosphate (DHAP) [72]. Other minor sources of MGO production include the breakdown of glycated proteins [73], the threonine catabolism [74], and the metabolic activity of ketone bodies, where MGO is produced from the further oxidation of hydroxyacetone, which is generated from acetone hydroxylation [75, 76]. Nucleotides, lipids, and proteins undergo spontaneous chemical change as a result of MGO activity. It alters DNA primarily by forming the imidazopurinone adduct 3-(2'-deoxyribosyl)-6,7-dihydro-6,7-dihydroxy-6/7-methylimidazo-[2,3-b]purine-9(8)one (MGdG) by interacting with deoxyguanosine (dG) [77]. In addition, it can alter amino acids in proteins by forming advanced glycation end products (AGEs) by interacting with arginine, cysteine, and lysine residues in proteins [78]. The primary pathway for MGO detoxification in normoglycemic circumstances is the glyoxalase system, which also protects cells from MGO toxicity. During physiologic conditions, glyoxalases 1 and 2 (Glo-1 and Glo-2) are primarily responsible for the metabolism of MG, which results in the synthesis of D-lactate through a process that employs glutathione as a coenzyme. When reduced glutathione (GSH) is present, these enzymes react with MGO to create lactate [79]. In diabetic individuals, MGO plays a critical role in endothelial dysfunction that results in insulin resistance, hypertension, and nephropathy. In glycation processes, it is noticeably more sensitive than glucose. Additionally, AGEs are well-established, scientifically proven risk factors for the development of diabetes and associated consequences [78]. MG-modified proteins and MG-modified amino acids, also known as protein-bound AGEs and AGE-free adducts, correspondingly, are present in tissues and bodily fluids [80]. According to Stitt (2010), there were comparable increases in MG-H1 and CEL protein-bound and free adducts in plasma, suggesting that clinical translation may make MG-derived AGEs evaluated in plasma or serum biomarkers or risk indicators for vascular consequences in diabetes. These pieces of evidences show that AGEs and MGO produced from MG may be the best diagnostic biomarkers for the disease.

Methylglyoxal and PD

Researches have suggested that PD and T2DM may also be related [36, 81]. Here, it is hypothesised that PD and T2DM share a same fundamental causative mechanism that entails elevated levels of MG. One of the key characteristics of PD is a rapid decline in cellular reduced glutathione (GSH) levels in the initial phases of the disease. This leads to a reduction in the activity of the glyoxalase system, the primary catabolic pathway of the most significant glycation agent, MG [82]. The AGE levels rise as a result of the carbonyl stress, which eventually causes oxidative stress and further AGE formation. The loss of dopaminergic neurons and an increase in oxidative stress in the brain may both be caused by this harmful loop. According to Lee et al. [83], it was found that MGO could cause a-syn to oligomerize and also reduce the ability of glycated a-syn to bind to membrane in PD. Since PD is well recognised to be closely linked to the build-up and aggregation of α-synuclein. Additionally, beta-synuclein is highly glycation-susceptible, and beta-synuclein "knockout" animals had higher levels of MG, glycation stress, and glyoxalase activity [84]. Parkin affects energy metabolism, as well as a cell-based investigation has shown this [85]. Its over-expression was discovered to inhibit glucose uptake, reduce glycolytic rate, and promote oxygen consumption [86]. The generation of MG as a result of triosephosphate accumulation due to diminished NAD + accessibility or impaired glyceraldehyde-3-phosphate dehydrogenase activity is one effect of excessive glycolysis, as mentioned above. It is intriguing to learn that PD is linked to mitochondrial malfunction, which may impede NADH from being oxidised back to NAD + (through the malate or glycerol-phosphate shuttles) and enhance oxidative stress to glyceraldehyde-3-phosphate dehydrogenase in the cerebral cortex [87]. Therefore, these findings suggest that enhanced or inadequate glycolysis due to over production of MG leads to the PD phenotypes (Fig. 3).

Common Problems Observed in Both T2DM and PD

An association between T2DM and PD was first reported by Sandyk in 1993, where it was noted that PD patients with co-existent T2DM had worse motor symptoms and reduced response to treatment [88]. Also, a high prevalence of impaired glucose tolerance has been reported amongst PD patients (50–80%); however, a more recent estimate suggests that overtly impaired glucose metabolism occurs in only around 20% [89]. So there has to be a commonality between the characteristic features of the both the disease conditions in a similar pattern which has been explained below elaborately.

Insulin Dysregulation in PD

A peptide hormone called insulin is released into the bloodstream by pancreatic beta cells in response to postprandial hyperglycemia. Insulin receptors are expressed in the basal ganglia [90] and in the substantia nigra [91], which are the areas of the brain that are mostly affected in PD. Since a long time ago, it has been discovered that the hypothalamus, olfactory bulb, and midbrain all contain detectable levels of insulin [92]. According to experimental data, adult neuronal cells coming from the hippocampus and olfactory bulb as well as pyramidal neurons in the cortex produce insulin [93]. It has

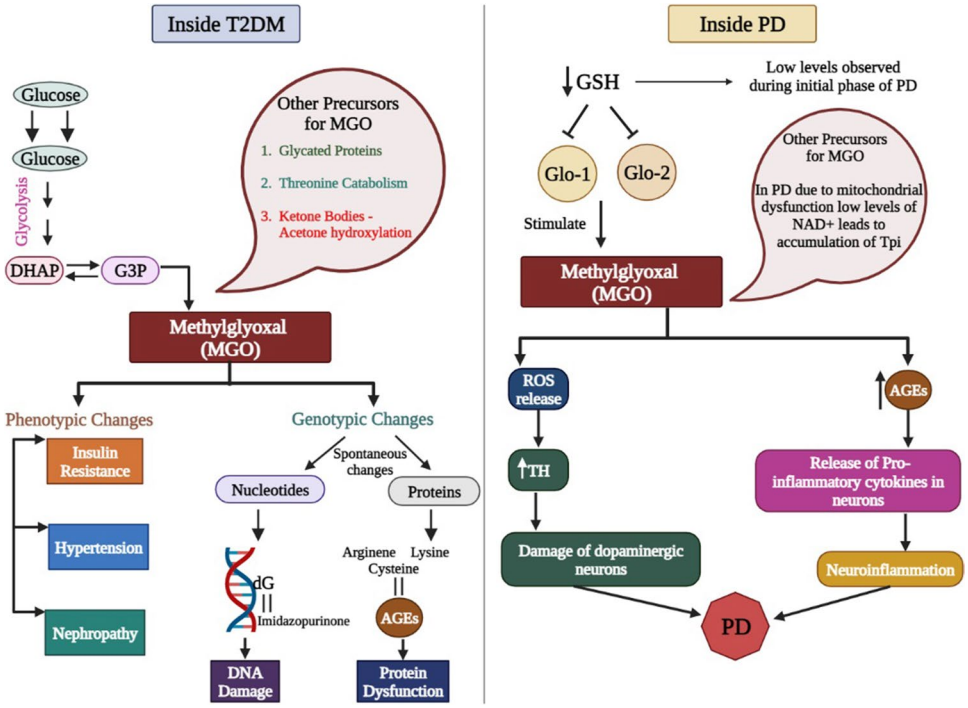

Fig. 3 Correlating the influence of methylglyoxal on T2DM and PD. This image depicts the possible influence of methylglyoxal on causing the T2DM and PD pathogenesis. In T2DM, glycolysis is the major factor for the release of MGO, whereas in PD in gets released due to low levels of GSH. Further in T2DM, it has a role in causing both phenotypic as well as genotypic changes. In PD, it impacts in two ways: (1) by increasing oxidative stress and (2) neuroinflammation in the cells

been discovered that there is a reduction in insulin signalling as a result of physiological changes brought on by ageing, particularly in PD patients. According to studies, patients with PD had much more insulin resistance and less insulin receptor mRNA in their substantia nigra pars compacta (SNpc) than age-matched controls [94, 95]. The loss of IGF-1 in the frontal cortex is substantially greater than that of insulin and IGF-1 signalling, and these changes are linked to higher levels of oxidative stress indicators and αSyn build-up in PD [96]. The suppression of IR-IRS-1-PI3K/AKT pathway in the hippocampus region of the brain, which in turn boosts the levels of phosphorylated IRS-1 at serine residues 636 and 616, would be the most likely molecular route by which insulin would be reduced in PD. Also, the phosphorylation of IRS-1 on serine residues, a crucial element of functional insulin signalling, prevents insulin/IGF-1 from binding to the IR and subsequent activation of downstream effectors. Further IR stimulates the aggregation of αSyn in PD [29]. Insulin resistance is linked to a more severe phenotype, a faster pace of disease progression, and a higher likelihood of cognitive deterioration in PD patients. These findings demonstrate that insulin dysregulation is a significant issue in both PD and T2DM. Figure 4a provides a brief explanation of the insulin dysregulation mechanisms between PD.

Oxidative Stress and Mitochondrial Dysfunction

An imbalance in the levels of ROS and difficulty of the body to outrage its toxic reactive intermediates leading to cellular damages are known as oxidative stress. A hyperglycaemic state can lead to an increase in the levels of oxidative stress-induced DNA damage markers such as 8-hydroxy-2′-deoxyguanosine (8-OHdG) and 8-oxo-7, 8-dihydro-2′-deoxyguanosine; lipid-peroxidation products measured as thiobarbituric acid-reactive substances (TBARS); protein oxidation products such as nitrotyrosine and carbonyl levels and also lower the activity of antioxidant enzymes. Exposure of β-cell line and isolated pancreatic islet cells to oxidative stress has been shown to inhibit the promoter activity and mRNA expression of the insulin gene therefore, decreasing insulin gene expression [97]. Oxidative stress is also strongly suspected to be involved in chronic hyperglycaemia-induced insulin resistance [98]. Increased ROS production in T2DM patients is thought to activate many detrimental pathways including hexosamine pathways, advanced glycation end-products (AGEs) formation, and PKCβ1/2 [99]. Hyperglycemia condition can induce oxidative stress by several mechanisms such as glucose autoxidation, polyol pathway, AGE formation, and PKCβ1/2 kinase. Elevated free fatty acids, leptin, and other circulating factors in T2DM patients may also contribute to cause ROS overproduction. Similarly, even in PD brains, the loss of dopaminergic neurons occurs mainly due to ROS levels which result from dopamine metabolism, low glutathione (GSH), and high levels of iron and calcium in the SNpc [100]. Additionally, the brain contains high concentrations of

polyunsaturated fatty acids, which under oxidative stress conditions result in lipid peroxidation and the generation of toxic products [101]. Therefore, it is evident that excessive free radical generation, known to promote oxidative stress and cytokine production, appears to be the main trigger factors for cellular dysfunction including impaired insulin signalling and mitochondrial dysfunction resulting into T2DM and PD. In Fig. 4b, we have depicted the possible mechanism of oxidative stress in T2DM and PD in a comparable manner.

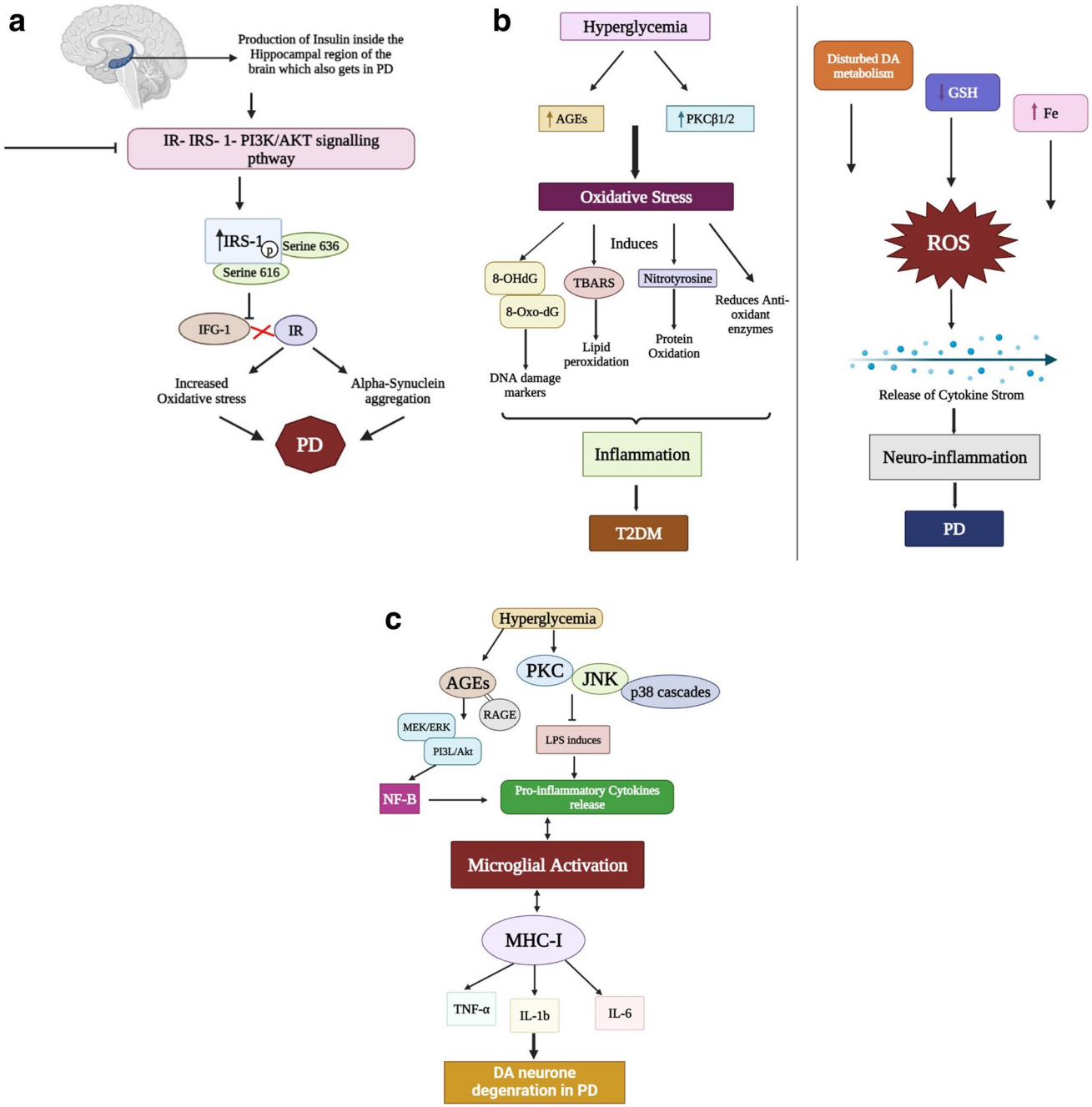

Fig. 4 (a) Dysregulation of Insulin in PD pathogenesis. In PD, the production of insulin is hindered which directly or indirectly inhibits the IR-IRS-1-PI3K/AKT signalling pathway of insulin production. This results into consecutive production of either oxidative stress or aggregation of a-syn which is mostly observed in PD. (b) Impact of oxidative stress on T2DM and PD. This image lets us to easily compare the similarities and differences amongst the impact of oxidative stress on T2DM and PD. In both the cases, inflammation is the major role of disease pathogenesis. (c) Importance of microglia in T2DM and PD. Generally, the activation of microglia causes morphological as well as functional changes which results into disease conditions. This image enables us to understand the role of microglia activation in both T2DM and PD and how it triggers inflammation more easily

Microglial Activation and Inflammation

Microglial activation is a process of morphological and functional change that can be triggered by inflammation and vascular injury. Microglial stimulation and the consequent production of inflammatory mediators, which ultimately cause injury to brain tissue, are the principal manifestations of neuroinflammation. Microglial activation and inflammatory responses are modulated by signalling molecules, such as MAPKs and triggering receptor expressed on myeloid cells 2 (TREM-2) [102, 103]. The three main MAPKs are extracellular signal-regulated kinases 1 and 2 (ERK1/2), p38 MAPK, and c-Jun N-terminal kinases (JNK), which control a variety of cellular processes and are crucial in controlling the expression of pro-inflammatory cytokines like tumour necrosis factor-alpha (TNF-alpha) and interleukin-1 alpha (IL-1 alpha) [104]. According to a recent study, chronic cerebral hypoperfusion CCH-induced stimulation of microglia encourages the production of pro-inflammatory substances, which further contribute to cognitive dysfunction and long-term potentiation (LTP) impairment [105]. Additionally, in humans and rats with T2DM, microglial activation and an inflammation are also involved [106, 107]. Inflammation can be exacerbated by mitochondrial ROS brought on by hyperglycemia by activating the PKC, JNK, and p38 cascades [108]. JNK inhibition lessens the lipopolysaccharide (LPS)-induced activity of inflammatory cytokines in microglia, as activation of p38 is crucial for cytokine production and release [109]. In an in vitro model using microglial cell line, AGEs in diabetes trigger the MEK/ERK, PI3K/Akt, and NF-B pathways via RAGE, which causes the activation of pro-inflammatory cytokines [110]. These studies suggest that the JNK cascade is the most important mechanism contributing to oxidative/inflammatory stress and microglial activation during acute glucose fluctuations by evaluating the efficacy of all signalling pathway inhibitors especially in T2DM. In an effort to pinpoint a putative mechanism that might contribute to neuroinflammation and possibly underlying the aetiology of PD, the intricacy of microglial stimulation signals came under great scrutiny. In particular, areas of the SN and striatum in PD patients were found to have MHC-II immunoreactive microglia [111, 112]. M1 pro-inflammatory microglial cell activation encourages the production of substances that damage DA neurons in the brain. Followed which nuclear factor-kB is the primary initiator of inflammation and the first signal to do so. Other pro-inflammatory cytokines, such as tumour necrosis factor-alpha, interleukin 1b, and IL-6, are then released into the body [4]. Therefore, these results demonstrate that there is a tight relationship between microglia activation and inflammation in both T2DM and PD, which requires further study (Fig. 4c).

Drugs Available for T2DM

People with T2DM are probable to develop many health complications such as heart problems, retinal issues, and brain strokes. The finest kind of medication will depend on a number of factors, including the severity of diabetes, age, and whether with additional health issues. Here, we describe the drugs developed to treat T2DM, which has lack of scientific findings with convincing results (Table 2). As previously mentioned, T2DM and PD share several common characteristics, and it has been suggested that there is a list of drugs that have influenced the signalling pathways in both T2DM and PD, and are listed in detail in (Table 3).

Mechanism of Action of Metformin in T2DM

Since a decade, metformin has been prescribed as a common drug to treat T2DM [174]. Metformin acts as an inhibitor of mitochondrial complex I, which ultimately results in the decrease in ATP synthesis and an increase in AMP levels activating the AMPK pathway [175]. AMPK regulates glucose metabolic pathway and energy balance [176]. As an AMPK activator, metformin regulates all the major metabolic pathways for glucose uptake, carbohydrate metabolism, and lipid metabolism [176]; and it was thought to be a key therapeutic target for obesity, T2DM, ageing, and neurodegeneration [215]. It functions by lowering the insulin-mediated hepatic glucose synthesis levels and by improving insulin sensitivity in T2DM patients [216], it is neuroprotective in human neural stem cells against amyloid-beta-induced mitochondrial dysfunction mediated through the PI3K/Akt pathway [217], and long-term treatment with metformin seems to decrease the risk of cognitive decline in diabetic patients [218] and improve depressive and cognitive performance, changing the glucose metabolism in depressed patients [164]. The inhibition of insulin and insulin growth factor receptor signalling by metformin results in alterations in metabolic balance. Metformin's antidiabetic actions are primarily brought by the AMPK pathway [177] but it can also occur in an AMPK-independent mechanism [178]. Genes coding for the enzymes involved in glucogenesis are reduced by AMPK through phosphorylation of CREB binding protein (CBP) [179]. Activation of AMPK results in decreased adenosine monophosphate which inhibit fructose-1,6-bisphosphatase-1, a major enzyme in gluconeogenesis [180]. Similarly, metformin causes AMPK activation which involves in reduction of PD pathogenesis [181]. When AMPK deficiency is detected in *Drosophila*, the characteristics of PD was observed [182]. From the data, a possible mechanism of metformin for its neuroprotective role has also been revealed and it is reported to be a hotspot in linking PD and T2DM. Metformin functions similarly in PD too by inhibiting complex I which then activates the AMPK pathway. Complex I

Table 2 List of drugs used in T2DM

S. no	Plant/drug	Extract/compound	Mechanism of action	Organ function	Findings	Recommended/not recommended	Reference
1	*Moringa oleifera*	Moringa seeds	Lessening the expression of iNOS, IL-1β, NO, TNF-α	Liver	↓plasma glucose levels, HbA1c	Recommended	[113]
2	*Garcinia macrophylla*	5,7,4′,5″,7″,3‴,4‴-heptahydroxyflavanone [3–6″] flavones	Antibacterial, antioxidant, and anti-T2DM	-	↓ glucose level	Recommended	[114]
3	Albendazole lansoprazole	-	Activation of AMPK and PPAR pathways and incretin-like effect	-	↑ glucose, HbA1c, triglyceride, LDL, leptin ↓insulin and HOMA-β	Recommended	[115]
4	Remogliflozin etabonate (100 mg and 250 mg)	-	SGLT2 inhibition improves urinary glucose excretion thereby decreases blood glucose levels		↓ glucose levels	Recommended	[116]
5	Metformin hydrochloride	-	Lessens intestinal glucose absorption, declines hepatic glucose production, increases insulin sensitivity	Liver	↓HbA1c levels, FBG, and weight loss	Recommended	[117]
6	Remogliflozin metformin teneligliptin	-	-	-	↓glucose levels, weight	Recommended	[118]
7	*Rhizoma coptidis*	Berberine and polyphenols	Improves β cell dysfunction	Liver adipose tissues	↓IL-6, TNFα ↑islet cell viability	Recommended	[119]
8		Alkaline and flavone category compounds	MAPK1, STAT3, INSR, and 38 signalling pathways	-	Insulin resistance	Recommended	[120]
9	*Morus alba*	Chlorogenic acid, isoquercitrin, and quercitrin	-	-	Glucose absorption, insulin secretion, antioxidant, anti-inflammatory, antihyperglycemic, and antihyperlipidemic activities, declined obesity	Recommended	[121]
10	*Zingiber officinale*	-	-	Heart	↑diastole function and blood pressure ↓ HbA1c, triglycerides	Recommended	[122]
11	Glargine/lixisenatide	-	GLP-1 RA, control postprandial glucose improved β-cell function	-	↓ HbA1c, weight gain ↓ glucose levels	Recommended	[123]
12	Gegen Qinlian decoction berberine	-	Proinflammatory cytokines Nfkb1, Stat1, and Ifnrg1	Pancreas	Enriched gut microflora ↓ glucose levels	-	[124]
13	Gegen Qinlian decoction (meta-analysis study)	-	-	Pancreas	↓ glucose levels ↑islet function ↓insulin resistance and sensitivity indexes	A need for clinical prognosis and islet function	[125]

Table 2 (continued)

S. no	Plant/drug	Extract/compound	Mechanism of action	Organ function	Findings	Recommended/not recommended	Reference
14	Huanglian Jiedu decoction	Decoction has Huanglian, Huangqin, Huangbo, and Zhizi mixture	Targets AKT1, IL-6, FOS, VEGFA, CASP3	Pancreas	↓ glucose levels, HbA1c	Recommended	[126]
15		-	Enhance GLUT4, INSR, MAPK1	-	Improve in fasting glucose level, lipid level, insulin sensitivity index	Recommended	[127]
16	*Nigella sativa* (meta-analysis study)	Thymol, thymohydroquinone, dithymoquinone, nigellone, alpha-hederin, flavonoids, and fatty acids	Antidiabetic, antioxidant, anticancer, hypolipidemic, and anti-inflammatory properties	-	↓ HbA1c, glucose level, insulin resistance	Recommended	[128]
17	Metformin with Chinese traditional medicine	-	-	-	Lessened the hyperglycemia, altered gut microflora, improved insulin resistance	Recommended	[129]
18	GLP-1RAs and oral antidiabetic drugs (meta-analysis)	-	-	Heart	Improvement in left ventricular diastolic function	Recommended	[130]
19	GLP-1 RA and SGLT-2i (meta-analysis)	-	-	Pancreas	5 studies—GLP-1 RA showed decreasing effect in cardiovascular complications, glucose reduction	Recommended	[131]
20	Metformin and DDP-4 inhibitors	-	AMPK pathway activation, NFK-β, and mTOR suppression	-	Adverse outcome from COVID-19	Not recommended	[132]
21	Statin, fibrates, and its combination	-	-	-	↓lipid levels	Recommended	[133]
22	Incretin, DDP-4 inhibitors, and GLP-1 RA	-	-	-	↓ HbA1c	Recommended	[134]
23	Anti-hyperglycaemic therapies (GLP-1 RA and SGLT2i)	-	-	-	No change in HbA1c levels	Recommended	[135]
24	Metformin (meta-analysis)	-	-	-	↓ HbA1c ↓ glucose levels	Recommended	[136]
25	Aspirin and statin	-	-	Heart	↓cardiovascular complications in T2DM	Recommended	[133]
26	Tofogliflozin with DDP-4 inhibitors	-	-	Pancreas	↓postprandial glucose	Recommended	[137]
27	*Momordica charantia*	-	-	Pancreas	↑insulin secretion ↓glucose uptake	Recommended	[138, 139]

Table 2 (continued)

S. no	Plant/drug	Extract/compound	Mechanism of action	Organ function	Findings	Recommended/not recommended	Reference
28	Metformin	-	-	Pancreas	↑epigenetic markers	Recommended for diagnosis	[140]
29	Chenpi	5-OH PMFs	Antidigestive and anti-inflammatory AMPK activation		↓hepatic steatosis ↓glucose levels	Recommended	[141]
30	Aloe vera	-	-	-	↓glucose levels	Recommended	[142]
31	Berberine	-	-	Pancreas	↓ HbA1c levels ↓ cholesterol and triglyceride ↑insulin secretion	Recommended	[143]
32	*Pueraria lobata* (meta-analysis)	-	-	Pancreas	Anti-diabetic activity	Recommended	[144]
33	SGLT-2i and GLP-1 RA	-	-	Heart	↓cardiorenal problems, stroke	Recommended	[145]
34		-	-	Heart kidney	↓renal risk No significance in cardio condition	Recommended	[146, 147]
35	Sulfonylureas, DPP-4 inhibitors, meglitinides	-	-	Heart	↑myocardium infection	Recommended	[148]
36	Acupuncture with Chinese herbal medicine (meta-analysis)	-			↓glucose levels ↑ insulin sensitivity and resistance	Recommended	[149]
37	Ipragliflozin (meta-analysis)	-	-	-	↑ genital infection No significance in glucose level	Not recommended	[150]
38	Ginseng supplementation	-	-	-	↑fasting glucose, postprandial insulin, and HOMA-IR Lipid levels were altered	Recommended	[151]
39	Shenqi Jiangtang Granules Baihu Jia Renshen Decoction Tianqi Jiangtang Capsule (meta-analysis)	-	-	Pancreas	↓hypoglycemia levels	Recommended	[152–154]
40	Chinese tradition medicine vs. Western medicine (meta-analysis)	-	-	Pancreas	Traditional medicine showed enhanced insulin sensitivity, decreasing body weight, protects from β cells	Recommended	[155]

Table 2 (continued)

S. no	Plant/drug	Extract/compound	Mechanism of action	Organ function	Findings	Recommended/not recommended	Reference
41	Cotadutide (meta-analysis)	-	-	Pancreas	↓glucose levels, HbA1c and body weight	Recommended	[156]
42	SGD	-	Influences PI3K-Akt, AMPK, and PPAR	Pancreas	↓ glucose levels and lipid levels ↓	Recommended	[157]
43	Sancai powder	-	-	Pancreas	↓glucose levels, HbA1c, lipid levels	Recommended	[117]
44	Zhimu-Huangbai herb pair	-	-	Pancreas	↓glucose levels	Recommended	[158]
45	Naoxintong capsule	-	Arachidonic acid metabolism, fatty acid β-oxidation, and glycerophospholipid metabolism	Pancreas	↓hyperlipidemia, hyperglycemia, myocardial infarction, insulin resistance	Recommended	[159, p. 20]
46	Pioglitazone and canagliflozin	-	-	-	↓ glucose levels, lipid levels, HbA1c	Recommended	[160]
47	Canagliflozin	-	-	Kidney	↑ renal oxygen in T2DM	Recommended	[161]
48	Pine bark extract	-	-	Pancreas	↓ HbA1c, VCAM-1, cholesterol levels, UACR	Recommended	[162]
49	Jinlida granules	-	-	Pancreas	↓ HbA1c and glucose levels	Recommended	[163]

iNOS, inducible nitric oxide synthase; *IL-1β*, interleukin-1 beta; *NO*, nitric oxide; *TNF-α*, tumour necrosis factor alpha; *HbA1c*, glycated haemoglobin; *T2DM*, type 2 diabetes mellitus; *LDL*, low density cholesterol; *HOMA-β*, homeostasis model assessment of β-cell function; *AMPK*, adenosine 5′ -monophosphate activated protein kinase; *PPAR*, peroxisome proliferator-activated receptor; *SGLT-2*, sodium glucose co-transporter-2; *SGLT-2i*, sodium-glucose cotransporter-2 inhibitors; *FBG*, fasting blood glucose; *GLP-1 RA*, glucagon-like peptide 1 receptor agonists; *DDP-4*, dipeptidyl peptidase-4 inhibitors; *NFK-β*, nuclear factor kappa B; *mTOR*, mammalian target of rapamycin; *COVID-19*, coronavirus disease-19; *5-OH PMFs*, 5-demethylated poly methoxy flavones; *HOMA-IR*, homeostatic model assessment of insulin resistance; *SGD*, Shengmai-Yin and Ganmai dazao decoction; *VCAM-1*, vascular cell adhesion molecule 1; *UACR*, urinary albumin-to-creatinine ratio; *PPAR*, peroxisome proliferator-activated receptors; *P13K-Akt*, phosphatidylinositol 3-kinase-protein kinase B; *GLUT4*, glucose transporter type 4; *INSR*, insulin receptor; *MAPK1*, mitogen-activated protein kinase 1; *IL-6*, interleukin-6; *FOS*, Fos proto-oncogene; *AP-1*, transcription factor subunit; *VEGFA*, vascular endothelial growth factor A; *CASP3*, caspase 3; *Stat1*, signal transducer and activator of transcription 1; *Ifngr1*, interferon gamma receptor 1; *STAT3*, signal transducer and activator of transcription 3

Table 3 Therapeutics targeting signalling pathways common in both T2DM and PD

Therapeutic drug	Mechanism	Model	Dosage	Methods	Result	Conclusion	References
Metformin	Amyloid aggregation	Healthy human blood	200 mmol/L	• Spectrophotometry • In vitro assays	• ↑anti-AChE • ↑anti-Aβ aggregation	Metformin may be regarded as an effective adjuvant to donepezil	[233]
	Oxidative stress and mitochondrial dysfunction	ASCs	25 µmol/L	• Western blot • Immunoblot • SDS-PAGE	• ↓oxidative stress • ↓mitochondrial dysfunction • ↑adipogenicity • ↑insulin sensitivity	Metformin may improve impaired adipogenesis and insulin sensitivity	[234]
	Microglial activation and chronic inflammation	BV-2 and bEnd3 cells	50 mg/kg	• Western blot • Immunohistochemistry • PCR	• ↓p38 MAPK phosphorylation • ↓pro-inflammatory cytokines • ↓TLR-4 mRNA expression • ↓IL-6 • ↓TNF-α mRNA expression	Metformin suppresses microglial activation by increasing AMPK phosphorylation	[235]
GLP1R agonists/ GIP receptor	Amyloid aggregation	Clonal mouse insulin-secreting cell line (min6)	25 mM	• RT-PCR • ELISA • Western blotting	• ↓hIAPP-induced LC3II/I ratio • ↓hIAPP-induced cleaved caspase-3 • ↓p62 expression	Exendin-4's has the potential in the treatment of diabetic ß-cell failure	[236]
	Microglial activation and chronic inflammation	Mice	5.0 mg/ml	• Immunofluorescence • Western blotting • Immunofluorescence staining	• ↓Iba-1 • ↓IL-1β • ↓TNF-α release • ↓TNC microglial number • ↑allodynia • ↓CGRP and c-fos in the TNC	GLP-1R agonist liraglutide might represent a new therapeutic approach for treating chronic migraine	[237]
	Impaired synaptic plasticity	Mice	_	• Open field assessment • Object recognition task • Water maze task	$Glp1r^{-/-}$ mice • ↓motor activity • Normal exploratory activity and anxiety levels	GLP-1R is crucial for some forms of memory formation and synaptic plasticity	[238, p. 20]
	Microglial activation and chronic inflammation	Mice	25 nmol/kg	Rotarod and grip strength assessment	• ↓increased levels of activated microglia and astrocytes ••••↑ GDNF	GLP-1/GIP dual agonist has the potential to exhibit superior neuroprotective effects	[239]
	Impaired synaptic plasticity	Mice	10 nmol/kg	• Western blotting • Water maze • Probe test	• ↓memory loss • ↑synaptic plasticity • ↓amyloid plaques • ↓pro-inflammatory cytokine levels	GLP-1/GIP dual receptor agonist was more effective at reversing memory loss	[240]
Insulin	Oxidative stress	Cultured cortical neurons	10 M	• MTT assay • SDS-PAGE • UV-spectrophotometry	• ↓oxidative stress • ↓necrotic and apoptotic cell death • ↓ascorbate/Fe2 + -mediated lipid and protein oxidation	Insulin may help reduce the damage caused by oxidative stress that develops in several neurodegenerative diseases	[31]

Table 3 (continued)

Therapeutic drug	Mechanism	Model	Dosage	Methods	Result	Conclusion	References
	Impaired synaptic plasticity	Mice	20 µl	• Immunohistochemistry and image analysis • Western blotting	• ↓rapamycin complex 1 (mTORC1)	Intranasal insulin prevents general anaesthesia-induced apoptosis of hippocampal cells and deficits in synaptic plasticity and memory	[241]
	Microglial activation and chronic inflammation	Microglial cell line	125 ng/ml	• Western blot • Immunocytochemistry • Phagocytosis assay	• ↑ phagocytic activity • ↓NO • ↓TNF production • ↓ROS	Insulin has beneficial effects on CNS injury or neurodegenerative conditions	[242]

PI3K, phosphatidylinositol 3-kinase; *Akt*, protein kinase B; *GSK-3 beta*, glycogen synthase kinase-3 beta; *FOXO1*, Forkhead box protein O1; *NF-κB*, nuclear factor kappa-light-chain-enhancer of activated B cells; *mTOR*, mammalian target of rapamycin; *DA4-JC*, dual GLP-1/GIP receptor agonist; *ASCs*, adipose-derived stromal cells; *HIAPP*, human islet amyloid polypeptide; *TNC*, trigeminal nucleus caudalis; *CM*, chronic migraine; *AMPK*, 5′ AMP-activated protein kinase; *NO*, nitric oxide; *TNF*, tumour necrosis factor; *ROS*, reactive oxygen species; *iNOS*, inducible NO synthase; *AChE*, human acetylcholinesterase; *Aβ*, amyloid beta; *bEnd3*, endothelial cells; *TLR-4*, Toll-like receptor-4; *TNF-α*, tumour necrosis factor-α; *GDNF*, glial derived neurotrophic factor

is one of the primary sources of ROS where metformin reduces the ROS generation through reverse electron transfer but will not boost their production [183]. Metformin therapy drastically reduced the amount of cytochrome C released from mitochondria into the cytosol, especially in the aged brain [35]. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated PD mice model, metformin exhibits neuroprotective benefits where it enhances mobility and muscular activity [184]. Another way through which ROS is reduced is by NAD(P)H inhibition and activation of AMPK [185]. Experimentally gathered data shows that ROS is the major factor in the death of dopaminergic neurons in PD patients [186]. A drop in ROS levels will result in a significant attenuation of DNA damage [187]. The incidence of cognitive decline in people with T2DM was considerably lowered by metformin therapy [188]. Metformin reduces neuroinflammation by an increase in the antiapoptotic protein Bcl-2 [189]. In addition, metformin mediated activation of AMPK also increases serine/threonine *PP2A* (protein phosphatase 2A) that dephosphorylates and reduce αSyn levels [190]. As a result, there are numerous molecular processes explaining metformin's multiple beneficial effects, but there are limited studies conducted on therapeutic potential in PD; hence, more studies need to be elucidated in PD pathogenesis. Hence, from the studies, it is probable that AMPK targeted therapy might lessen the neurodegeneration, in PD where more research is required on therapeutics effects of metformin to confirm its neuroprotective role. The probable mechanism is depicted in Fig. 5.

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonist

The GLP-1 receptor agonists are primarily known to be a group of anti-diabetic medications, and this GLP-1 has an intestinal peptide known as incretin that promotes glucose-dependent insulin secretion whilst inhibiting glucagon release to maintain blood sugar levels [191] and also GLP-1 exhibits potent and strictly glucose-dependent insulinotropic activity through unique GLP-1 receptors in the plasma membrane of pancreatic cells [192]. This inhibits glucagon secretion, which may be as clinically relevant as GLP-1's insulinotropic action [193]. Furthermore, GLP-1 decreases food intake (most likely by activating GLP-1 receptors in the central nervous system and slows stomach voidance, resulting in lower postprandial glucose excursions and food intake) [192]. Few studies have also discovered that as one progresses from normal glucose tolerance to insulin resistance, plasma GLP-1 concentrations decreases [194, 195]. Also, GLP-1 is expressed in all regions of the brain, including the frontal cortex, hypothalamus, thalamus, hippocampus, cerebellum, and substantia nigra and has a key role in neuronal metabolism and neuroprotective effect in the brain through crossing the blood brain barrier (BBB) [196]. Additionally, GLP-1 exhibits regulatory effects that includes stimulation of cell

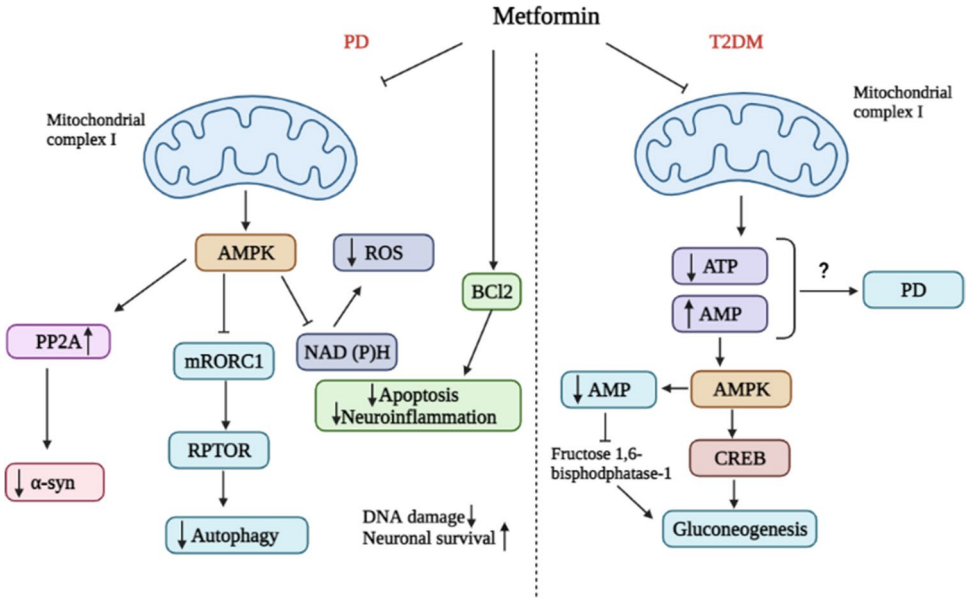

Fig. 5 Metformin: anti-diabetic and neuroprotective role. Metformin has a neuroprotective role through the AMPK pathway which is also their anti-diabetic pathway. AMPK is activated through inhibition of mitochondrial complex I and it drastically reduces the ROS levels causing neuronal survival. Metformin enhances autophagy by inhibiting mTORC1 which was phosphorylated by AMPK, anti-apoptosis by increasing anti-apoptotic protein Bcl-2, reduces DNA damage, and neuroinflammation hence accounting for neuronal protection. Metformin reduces the αSyn aggregates by increasing PP2A. AMPK, AMP-activated protein kinase; ROS, reactive oxygen species; mTORC1, mammalian target of rapamycin complex 1; Bcl-2, B-cell lymphoma 2; PP2A, protein phosphatase 2

neogenesis, growth, and differentiation; prevention of cell apoptosis; and boosting cell survival [197]. There are several GLP-1 analogues, particularly exenatide, liraglutide, and lixisenatide, which regulates cellular pathways that protect the neurons, maintain mitochondrial function, prevent apoptosis, and respond to oxidative stress in addition to their effects on glucose homeostasis [198, 199]. GLP-1 receptor agonists exhibits neuroprotective and neurorestorative characteristics in various PD experimental models. Exenatide-treated animal models can halt 6-hydroxydopamine (6-OHDA), MPTP, and LPS-induced dopaminergic degeneration and restore DA imbalance in PD, resulting in significant improvements in behaviour and motor function [200–202]. Longer-acting GLP-1 analogues (liraglutide and lixisenatide) have also shown protective benefits and enhanced motor function in MPTP induced PD mouse model [198]. Taken together, GLP-1 receptor agonists are already a proven fundamentally anti-diabetic medication, and also there is strong evidence that GLP-1 activity has a positive impact on the treatment of PD pathogenesis, as shown in numerous PD models.

Dipeptidyl Peptidase-4 Inhibitors (DPP-4i)

The anti-diabetic medication DPP-4i (gliptins) inhibits DPP-4, a proteolytic enzyme that has shown neuroprotective effects in the brain [203], and in T2DM, the inactivation of GLP-1 in the peripheral circulation is prevented by DPP-4 inhibitors by reducing DPP-4 activity in peripheral plasma thereby prevents T2DM condition and improves glucose metabolism [73]. DPP-4 inhibitors on elderly people with T2DM and mild cognitive impairment enhances glucose control, prevents deterioration of cognitive abilities, and also decreases β-amyloid toxicity and tau hyperphosphorylation in human neural cells [204]. DPP-4 inhibitors might improve synaptic function, lessen the loss of dopaminergic cells, and/or assist the regenerative process in PD by either increasing endogenous levels of GLP-1 and GIP both systemically and in the brain, or by acting directly on them [205]. Data from DPP-4 inhibitors in PD experimental models are inconsistent. In a rotarod test, rats were given saxagliptin before the induction of rotenone, which showed increased striatal DA production and decreased dopaminergic neuronal loss, resulting in improved motor performance and coordination [206]. However, rats given supramaximal doses of sitagliptin (a DPP-4 inhibitor with a significantly longer half-life than saxagliptin) were not protected against MPTP-induced striatal dopaminergic degeneration [207]. Thus, DPP-4 may be useful for T2DM with PD patients in terms of their initial dopamine degradation and in long-term effects it may also play a potential role in non-diabetic PD patients.

Insulin

Insulin is found to be beneficial in treating both T2DM and PD conditions. In general, insulin interacts with the brain in several ways, likely through the complex insulin/IR signalling pathway, including effects on cognition, memory, learning, and synaptic plasticity [208]; and importantly exogenous insulin can be administered nasally to prevent effects on peripheral glucose levels, and it may have benefits for PD patients [57]. At clinically significant levels, insulin enters the brain by passing the BBB, preventing neuronal death by activating protein kinase B, and regulating tau phosphorylation, beta-amyloid precursor protein metabolism, and beta-amyloid clearance in in vivo [209] [210]. Intranasal insulin administration increases mood and memory whilst preserving the volume of brain regions damaged by neuropathology, and it also improves cerebral glucose metabolism which is mediated through PI3K/Akt pathway [211]. Insulin reduced α-synuclein levels in MPP-positive C6 glial cells [212]. Insulin contributes in directing the autophagic process to protect the neurons by enhancing the autophagy of harmful proteins, by suppressing mTORC1 activity, activating Akt survival molecule, and increasing mTORC2 activity [213]. Injection of intranasal insulin was conducted in PD patients which revealed that the insulin-treated patients showed improvements in verbal fluency and motor severity compared to baseline scores at the end of the exposure period, and, more importantly, there were no reports of changes in serum glucose levels or hypoglycaemia [214]. Therefore, as we know that insulin is primarily known to regulate blood sugar levels, and with the evidence provided above, it is clear that insulin, through interactions with the complex insulin/IR signalling network, can help to treat multiple processes associated with the onset of PD.

Sulfonylureas

Sulfonylurea is primarily an antidiabetic drug and there are generations of drugs under the sulfonylurea class. The sulfonylurea glimepiride is linked to altered cell signalling and synaptic membranes and provides several protective advantages for neurons and is used to treat T2DM [220]. Gliclazide is a second-generation sulfonylurea hypoglycaemic medication. It reduces the free radical synthesis or increases their scavenging by lowering oxidative stress, protecting against DNA damage, and boosting antioxidant status, and may also help to regulate the physiological diseases that underlie both T2DM and ageing [221]. Glibenclamide is another generation of sulfonylurea, it is a KATP channel inhibitor where it decreases the amyloid-induced behavioural impairments and anxiety in a rat model, and it may be used as a therapeutic target for neurodegenerative diseases which is mediated through PI3K/Akt pathway [222]. In a rodent PD model, glibenclamide protected dopaminergic neurons by inhibiting inflammasome activation, microglial polarisation, and oxidative stress [223]. In both BV2 microglial cells and mouse PD models, glibenclamide was able to limit microglial activation and reduce excessive neuroinflammation. Furthermore, glibenclamide's anti-neuroinflammation actions may be caused through mechanisms that regulate the c-Jun N-terminal kinase (JNK) and NF-B signalling pathways [224]. Together, these data suggest a possible role of sulfonylureas in treating both PD and T2DM.

Thiazolidinediones

Thiazolidinediones (TZDs), such as pioglitazone and rosiglitazone, are useful to improve insulin sensitivity in muscle, adipose, and hepatic tissue and reduce systemic insulin resistance. This includes the transfer of extra fatty acids to peripheral fat, and this improves insulin sensitivity by lowering the availability of fatty acids in the liver, muscles, and circulation to treat the T2DM condition [225]. Pioglitazone, the only commercially available TZD, can enter the brain, decrease glial activation, lessen neurodegenerative-related diseases [226], lessen spatial learning impairment, and prevent tau hyperphosphorylation by improving Akt signalling [227]. Various toxin induced PD models, including MPTP [228], LPS [229], 6-OHDA [230], and rotenone [231] showed that the pioglitazone and rosiglitazone have neuroprotective effects that improve behavioural and motor responses. The suppression of pro-inflammatory pathways, as well as the modification of mitochondrial activity and oxidative stress responses, is suggested to be the causes of these effects [232]. Considered together, there is evidence that TZD action has a beneficial impact on the treatment of both T2DM and the aetiology of PD.

Traditional Indian Medicinal Plants to Treat T2DM and PD

Traditionally, moringa seeds containing isothiocyanates reported to delay T2DM rat models [113]. Similarly, biflavonoid compound isolated from *Garcinia macrophylla* plant suggested to decline blood sugar level in diabetic rats [114]. Anti-diabetic activity by benzimidazole derivatives, albendazole, and lansoprazole in rats showed effective treatment strategy in curing T2DM [115]. In T2DM patients, remogliflozin etabonate reported to be an effective therapeutic option in lowering glucose levels [116]. In a comparative study using metformin sustainable-release tablet and original metformin tablet, metformin sustainable-release had significantly showed the therapeutic efficiency in T2DM than original tablet [164]. In participants with insulin glargine along with oral hypoglycemic therapy received

remogliflozin which showed an alternative approach with drastic reduction of T2DM [118]. By using network pharmacology and docking analysis, mechanistic insights of *Rhizoma coptidis* were explored against T2DM which suggested to show anti-inflammatory effects thus proving to be competent in antidiabetic research [119, 120]. In a systemic review, *Morus alba* reported to be a potential therapeutic target for T2DM though it lacks more studies on synergistic effects [121]. Apart from drugs, exercise was recommended for glucose management and T2DM control [165]. In a clinical trial using *Zingiber officinale* as an add-on therapy in T2DM showed improved blood pressure, proper function of diastole, and maintenance of lipid profile [122]. In a 26-week treatment with insulin glargine/lixisenatide in Japanese T2DM patients inadequately controlled over oral antidiabetic drugs [123]. In a rat model, Gegen Qinlian Decoction and berberine showed the decline of blood glucose levels and alteration of gut microbiota [124]. Likewise, Ren et al. (2021) evaluated the effect of Gegen Qinlian Decoction on clinical prognosis and islet function in T2DM. The berberine effects in reducing glucose levels and maintenance of intestinal flora has revealed to be beneficial in T2DM [166]. Similarly, *Huanglian Jiedu* Decoction and its active compounds showed effective against T2DM [126, 127]. Studies have reviewed on beneficial aspects of curcumin and cinnamon on T2DM [167, 168]. Similarly, *Nigella sativa* and *Taraxacum officinale* revealed to show anti-diabetic properties on T2DM [128, 169]. In an open label clinical trial, metformin with Chinese traditional medicines alleviated T2DM along with alterations in gut microbiome [129]. Also, the Chinese traditional medicines effect on gut microflora reduced T2DM [124]. In a meta-analysis study, oral antidiabetic drugs and glucagon-like peptide-1 receptor agonists were assessed in heart failure occurring in T2DM, were the drug liraglutide showed a promising effect in preventing heart failure [130]. In a review, a placebo-controlled outcomes on lessening the glucose levels by glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, and dipeptidyl peptidase-4 inhibitors were deliberated by Elbelt. (2018) and González-González et al. [132]. Recently, T2DM patients confirmed with COVID-19 infection showed that the usage of metformin and dipeptidyl peptidase-4 inhibitors had minimal contrary outcomes when compared to non-users. In T2DM patients receiving statin, fibrates and its combination showed decrease in lipid levels which shows the necessity in treating diabetes [170]. Therapeutic approaches using incretin and sodium-glucose cotransporter-2 inhibitors have made beneficial effect in renal function in T2DM [134]. Anti-hyperglycaemic drugs showed no significant change in haemoglobin A levels in glycaemic patients [135, p. 202]. In a meta-analysis study, the efficiency of metformin decreased the plasma glucose levels in T2DM patients [136]. The use of statins in T2DM patients has increased drastically since it has reduced the cardiovascular complications and mortality [133]. The add-on therapy using tofogliflozin to dipeptidyl peptidase-4 inhibitors has shown a reduced glucose level in T2DM [137]. In a review, *Momordica charantia* (bitter gourd) has been recommended as an anti-diabetic drug and more studies on its preparation, dosage, and duration were suggested to prove its efficiency in T2DM [138]. *Momordica charantia* has shown drastic reduction in glycaemic levels in T2DM patients [139]. Tolerance and intolerance of metformin was investigated in T2DM patients by measuring the epigenetic markers in blood which showed the effectiveness of epigenetics as a diagnostic tool in diabetes [170]. The extract of chenpi, 5-demethylated polymethoxyflavones (5-OH PMFs) reduced the T2DM as well as obesity with an enhancement in lipid profile [141]. In a meta-analysis study, aloe vera was reported to show an effective therapy in glycaemic control in T2DM and in pre-diabetic condition [142]. In diabetic rats, the effects of berberine were investigated to show a reduced lipid and glucose levels with an activation of adenosine 5′-monophosphate-activated protein kinase pathway [143]. In a meta-analysis, the root of *Pueraria lobata* has evidently showed that T2DM can be treated by increasing insulin levels and reducing glucose absorption [144]. By the use of sodium-glucose cotransporter-2 inhibitors in Japanese T2DM patients, the risk of heart failure and kidney related outcomes was reduced [145]. A comparison study was carried out using sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists in T2DM patients were the sodium-glucose cotransporter-2 inhibitors showed improvement on renal function with or without albuminuria [146]. Similar comparison study showed controlled effects on cardiorenal function in T2DM [147]. In a monotherapy study, metformin was compared with sulfonylureas and meglitinides showed increased risk to cardiovascular complications in T2DM [148]. In a meta-analysis study, acupuncture combined with Chinese herbal treatment showed positive therapeutic openings in T2DM [149]. The treatment using ipragliflozin has shown adverse effects causing genital infections in T2DM patients [150]. In a clinical trial, ginseng showed an efficient action on glucose levels with contradiction in lipid metabolites in T2DM [151]. The Chinese medicines, Shenqi Jiangtang Granules, Baihu Jia Renshen Decoction, and Tianqi Jiangtang Capsule reported as a safe therapy for T2DM [152–154]. In a Bayesian network meta-analysis study, the effective role of Chinese tradition medicine against T2DM was deliberated comparing with western medicines [152]. The cotadutide drug has been a potent drug in treating T2DM which has been effective in decreasing glucose levels, haemoglobin A, and body weight [156]. The Chinese medicine Astragali Radix-Coptis Rhizoma and *Allium sativum L.* was used to treat T2DM were its mechanistic action using network pharmacology was explained in

Table 4 Ongoing clinical trials on anti-diabetic drugs for PD

S. no	Study	Drug	Status	Organisation
1	Exenatide once weekly over 2 years as a potential disease modifying treatment for Parkinson's disease (exenatide-PD3)	Exenatide	Active, not recruiting	University College, London
2	Effects of exenatide on motor function and the brain	Exenatide	Active, not recruiting	University of Florida
3	A clinical study of NLY01 in patients with early Parkinson's disease	NLY01	Active, not recruiting	Neuraly, Inc
4	SR-exenatide (PT320) to evaluate efficacy and safety in patients with early Parkinson's disease	PT320	Active, not recruiting	Peptron, Inc
5	Safety and efficacy of liraglutide in Parkinson's disease	Liraglutide	Active, not recruiting	Cedars-Sinai Medical Centre
6	GLP1R in Parkinson's disease (GIPD)	Semaglutide	Not yet recruiting	Oslo University Hospital
7	Study to evaluate the effect of lixisenatide in patients with Parkinson's disease (LixiPark)	Lixisenatide	Active, not recruiting	University Hospital, Toulouse

a study [171, 172]. The combined effect of Shengmai-Yin and Ganmaidazao decoction (SGD) in T2DM showed declined insulin resistance [157]. In a review, the therapeutic effect of *Cyclocarya paliurus* was explained with mechanistic outcome in treating T2DM [173]. In a randomised clinical study, the Sancai powder showed effective results in T2DM patients in 12 weeks when compared with metformin [141]. In T2DM rats, Zhimu-Huangbai herb pair metabolites and ingredients reported with clinical efficacy in T2DM [158]. In T2DM rats treated with Naoxintong Capsule showed anti-diabetic activity with effective mechanistic strategy [159]. The blend of pioglitazone and canagliflozin treatment showed an improvement from T2DM and metabolites levels [160]. Canagliflozin improved the renal function in T2DM diagnosed patients [161]. The supplementation of pine bark extract was given to T2DM and has control on glycaemic levels and obesity [162]. The effect of Jinlida granules on glycemic levels was reported with a need in improvement in T2DM treatment [163]. From the studies discussed, it is well-known that ground-breaking discoveries have been coming up in treating T2DM. However, the mechanistic insights on previous drugs should be investigated for deliberating clinical assistance to the patients. Previously, it is known that many reviews, systemic reviews, and meta-analysis have been published on T2DM drugs; here, we have deliberated the commonly used western and traditional drugs involved in T2DM with recent outputs in Table 2.

Ongoing Clinical Trials About the Use of T2DM Drugs for PD

The relationship between PD and T2DM is supported by both epidemiological and experimental data. Both diseases are becoming more common worldwide and are strongly linked to ageing. At present, many clinical trials have been applied to repurpose prevailing drugs as well as to address the need for the development of vaccines and drugs against T2DM associated PD. Currently, the established T2DM drugs undergoing clinical trials has the probability to treat PD (Table 4). Additional research is needed to explore the efficiency of T2DM drugs on PD cure.

Future Perspective and Conclusion

It is now understood that insulin can have a significant impact on how the brain functions. The regulation of neuropathological characteristics of neurodegenerative diseases, such as PD, can be influenced by changes in insulin metabolism and signalling. Numerous in vivo and in vitro studies indicate the connection between T2DM and neurodegeneration and raise the possibility of therapeutic use of several anti-diabetics in the prevention or treatment of conditions like PD. The pathophysiological connections between T2DM and neurodegenerative diseases, as well as how anti-diabetics affect neurodegeneration, are not fully understood, and further studies are necessary to understand these connections and their therapeutic implications.

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Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication All authors provide consent for publication.

Conflicts of Interest The authors declare no competing interests.

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