PROMISING EFFECT OF REPURPOSED ANTI-HYPERGLYCEMIC DRUGS IN THE TREATMENT OF ALZHEIMER'S DISEASE

A DISSERTATION

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IN
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Submitted by:

VANSHIKA ARORA

2K19/MSCBIO/29

Under the supervision of

PROF. PRAVIR KUMAR

DEPARTMENT OF BIOTECHNOLOGY
DELHI TECHNOLOGICAL UNIVERSITY
(Formerly Delhi College of Engineering)
Bawana Road, Delhi-110042

MAY, 2021

DELHI TECHNOLOGICAL UNIVERSITY
(Formerly Delhi College of Engineering)
Bawana Road, Delhi – 110042

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I, **Vanshika Arora** (2K19/MSCBIO/29) hereby certify that the work which is presented in major work entitled "**Promising Effect of repurposed anti-hyperglycemic drugs in the treatment of Alzheimer's Disease**" in fulfilment of the requirement for the reward of the degree of Masters of Science in Biotechnology and submitted to the Department of Biotechnology, Delhi Technological University, Delhi is an authentic record of my own, carried out during a period of January to May 2021, under the supervision of **Prof. Pravir Kumar.**

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DEPARTMENT OF BIOTECHNOLOGY
DELHI TECHNOLOGICAL UNIVERSITY
(Formerly Delhi College of Engineering)
Bawana Road, Delhi – 110042

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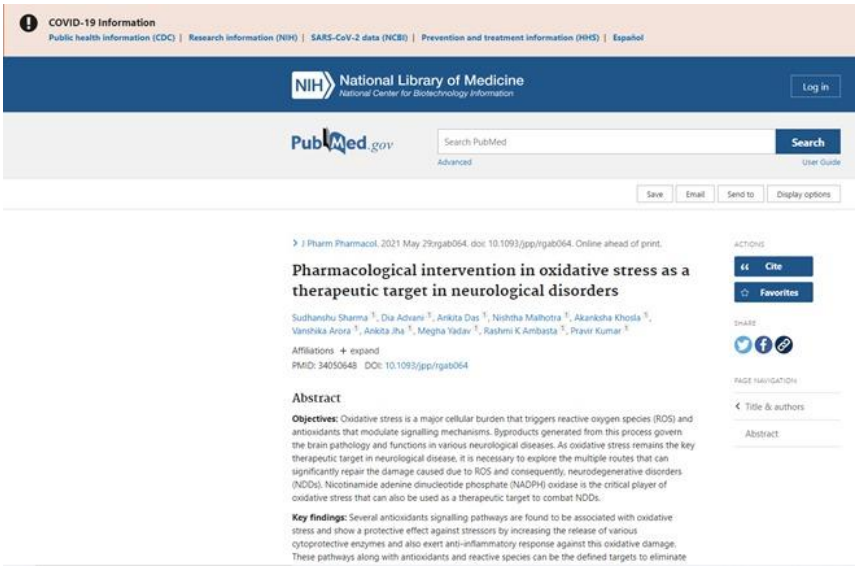

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Pharmacological intervention in oxidative stress as a therapeutic target in neurological disorders

Sudhanshu Sharma [1], Dia Advani [1], Ankita Das [1], Nishtha Malhotra [1], Akanksha Khosla [1], Vanshika Arora [1], Ankita Jha [1], Megha Yadav [1], Rashmi K Ambasta [1], Pravir Kumar [1]

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Abstract

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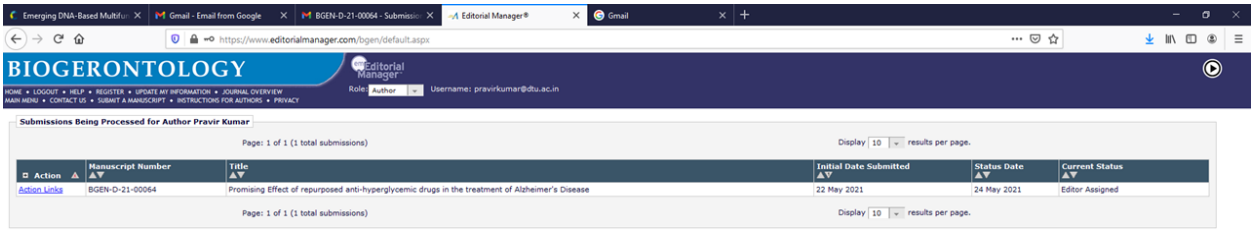
Objectives: Oxidative stress is a major cellular burden that triggers reactive oxygen species (ROS) and antioxidants that modulate signalling mechanisms. Byproducts generated from this process govern the brain pathology and functions in various neurological diseases. As oxidative stress remains the key therapeutic target in neurological disease, it is necessary to explore the multiple routes that can significantly repair the damage caused due to ROS and consequently, neurodegenerative disorders (NDDs). Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is the critical player of oxidative stress that can also be used as a therapeutic target to combat NDDs.

Key findings: Several antioxidants signalling pathways are found to be associated with oxidative stress and show a protective effect against stressors by increasing the release of various cytoprotective enzymes and also exert anti-inflammatory response against this oxidative damage. These pathways along with antioxidants and reactive species can be the defined targets to eliminate



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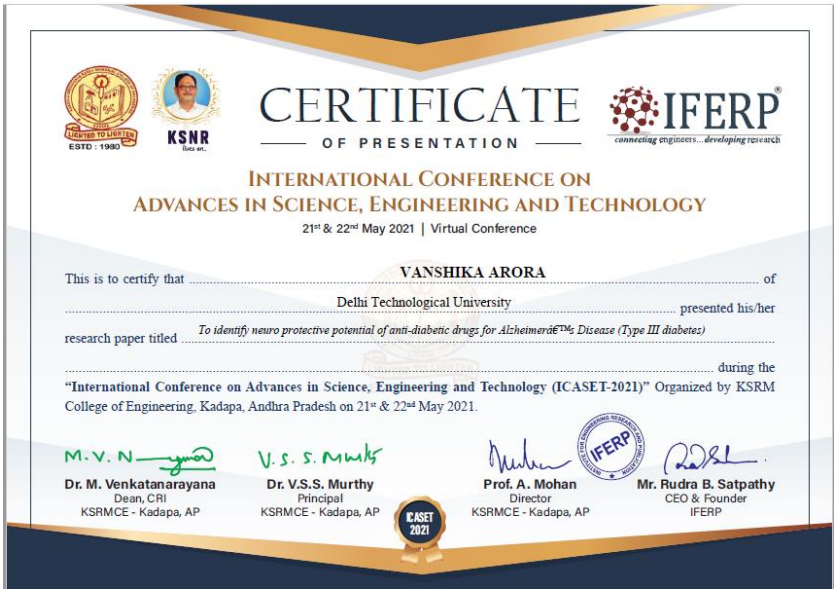

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(VANSHIKA ARORA 2K19/MSCBIO/29)

ABSTRACT

Diabetes mellitus (DM) and Alzheimer's illness (AD) are both profoundly common circumstances in the older populace and significant general wellbeing trouble. Alzheimer's disease (AD) has trademark neuropathological anomalies, including localized degenerations of neurons, amyloid beta aggregation in brain tissue and neurofibrillary tangles, activating the genes that are pro-apoptotic, and leads to oxidative stress. Here the brain capacities keep on disintegrating, there is a decreasing face-to-face intellectual capacity, memory, artlessness, and socializing conduct. A system that successively interlinks every one of these wonders under one occasion is inadequate. Aggregating proof has demonstrated the vital functioning of insulin deficit and insulin obstruction as arbiters of Alzheimer’s degeneration of neurons. Thus, the inspection of the proof coming from the improvement of diabetes specialist prompted AD model organism. This phase appears to advance with AD to such an extent that, in the terminal stages, it declines and gets worldwide. APP-Aβ deposition, oxidative stress, impeded glucose and tau hyperphosphorylation and energy digestion all have been connected to annoyance in insulin/IGF flagging. We close that AD could also be alluded to as "type III diabetes". Also, inferable from normal pathophysiology with diabetes normal remedial system could be compelling for AD patients. The review will share detailed insights into pathological features and mechanisms of action of anti-diabetic drugs for the treatment of AD.

CONTENTS

Cover page	i
Candidate's declaration	ii
Certificate	iv
Acknowledgement	vi
Abstract	vii
Contents	viii
List of figures	x
List of tables	x
List of abbreviations, symbol	xi
CHAPTER 1 INTRODUCTION	1
CHAPTER 2 ALZHEIMER'S AND DIABETES OVERLAPPING PATHOLOGIES	3
CHAPTER 3 ALZHEIMER'S PROGRESSION ON ACCOUNT OF DIABETES	7
3.1 Brain Insulin Resistance	7
3.2 Amyloidogenesis	8
CHAPTER 4 LINKING AD AND DIABETES; ROLE OF SIGNALING PATHWAY	9
CHAPTER 5 ANIMAL MODEL OF ALZHEIMER'S DISEASE AND DIABETES	10
CHAPTER 6 ANTI-DIABETIC DRUGS—A PROMISING SOLUTION FOR AD PATIENTS	10
CHAPTER 7 LINK BETWEEN INSULIN AND AD (TYPE III DIABETES)	12
7.1 Role of Insulin in brain	13
7.2 Insulin-mediated AD pathology	14
7.3 Evidence of insulin resistance in AD	15
CHAPTER 8 ANTI-DIABETIC DRUGS CLASSIFICATION AND ITS NEUROPROTECTIVE POTENTIAL FOR TREATMENTS OF ALZHEIMER'S DISEASE	15
8.1 Metformin	15

8.2 Thiazolidinediones	15
8.3 Glucagon-Like Peptide Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors	16
8.4 Amylin Analog	16
CHAPTER 9 METHODOLOGY	16
CHAPTER 10 RESULTS, DISCUSSION AND CONCLUSION	17
10.1 Results	17
10.2 Discussion	17
10.3 Conclusion	18
REFERENCES	19
LIST OF PUBLICATIONS	29

LIST OF TABLES

Table 1: List of anti-diabetic drugs and their mechanism of action

Table 2: Insulin affecting major cell types of brain

LIST OF FIGURES

Figure 1: Cognitive functions affected by type 1 and type 2 diabetes.

Figure 2: Relationship between Type 2 diabetes and AD

Figure 3: Role of Signaling cascade in AD and DM

Figure 4: Involvement of Insulin Receptor in pathogenesis of AD

Figure 5: Docking Results

LIST OF SYMBOLS, ABBREVIATIONS AND NOMENCLATURE

AD	Alzheimer's Disease
ADDLs	Amyloid beta-derived diffusible ligands
AGEs	Advanced Glycation End products
Aβ	Amyloid Beta
CNS	Central Nervous System
DM	Diabetes Mellitus
DPPI	Dipeptidyl Peptidase-4 Inhibitors
GLP-1	Glucagon-like peptide-1
GLUT	Glucose transporter
GSK	glycogen synthase kinase
IDE	Insulin Degrading Enzymes
MAPK	mitogen-activated protein kinase
NFT	Neurofibrillary tangles
PI3K	phosphoinositide-3 kinase
PPARγ	proliferator-activated receptor-gamma
STZ	Streptozotocin
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TNF-α	Tumor necrosis factor-α
VEDF	vascular endothelial development factor

CHAPTER-1 INTRODUCTION

Diabetes mellitus (DM) addresses significant general wellbeing trouble and a developing predominant constant abnormality. Hence, realized DM is spread amongst vast majority of population which may be over 300 million, and it is assessed that the quantity of DM subjects is relied upon to ascend to more than 600 million by two decades more. Alzheimer's illness (AD) is the fundamental driver of cognitive infestation, influencing more than 20 million individuals worldwide, and its predominance keeps on expanding. Both are age related pathological disorders, and in the few years, an attention seeking connection is emerged from the two pathological conditions ; thus, the terminology given "type 3 diabetes" has been planned to express insulin resistance-induced AD. Numerous epidemiologic confirmations demonstrated a nearly multiplied danger for AD in diabetic patients, contrasted and the subjects not suffering from DM; the Rotterdam study displayed a double increment of AD in DM and an even magnified hazard related to insulin treatment. The identification of major characteristic points leads to explain the connection between two pathological conditions are: insulin resistance and inflammatory signaling pathways.

The connection between DM and its pathological conditions is well understood, though central nervous system is greatly affected —mainly concerning cognitive disorder—is still not that clear for the scientists. The association has, nonetheless, got expanding consideration over the previous decade. The seriousness of intellectual brokenness suffered by people with DM is influenced by the beginning of diabetes, level of blood glucose level control, and period of DM. Moreover, type 2 diabetes (T2D) demonstrates more communal significant proofs and related highlights, such as insulin obstruction, are related to expanded danger for dementia. Subsequently, there has likewise been much interest in deciding how much anti-diabetic medicines may either secure against dementia or be utilized as novel drugs for neuronal disorders. (Figure 1).

Figure 1 Cognitive Functions Affected by Type I and Type II DM

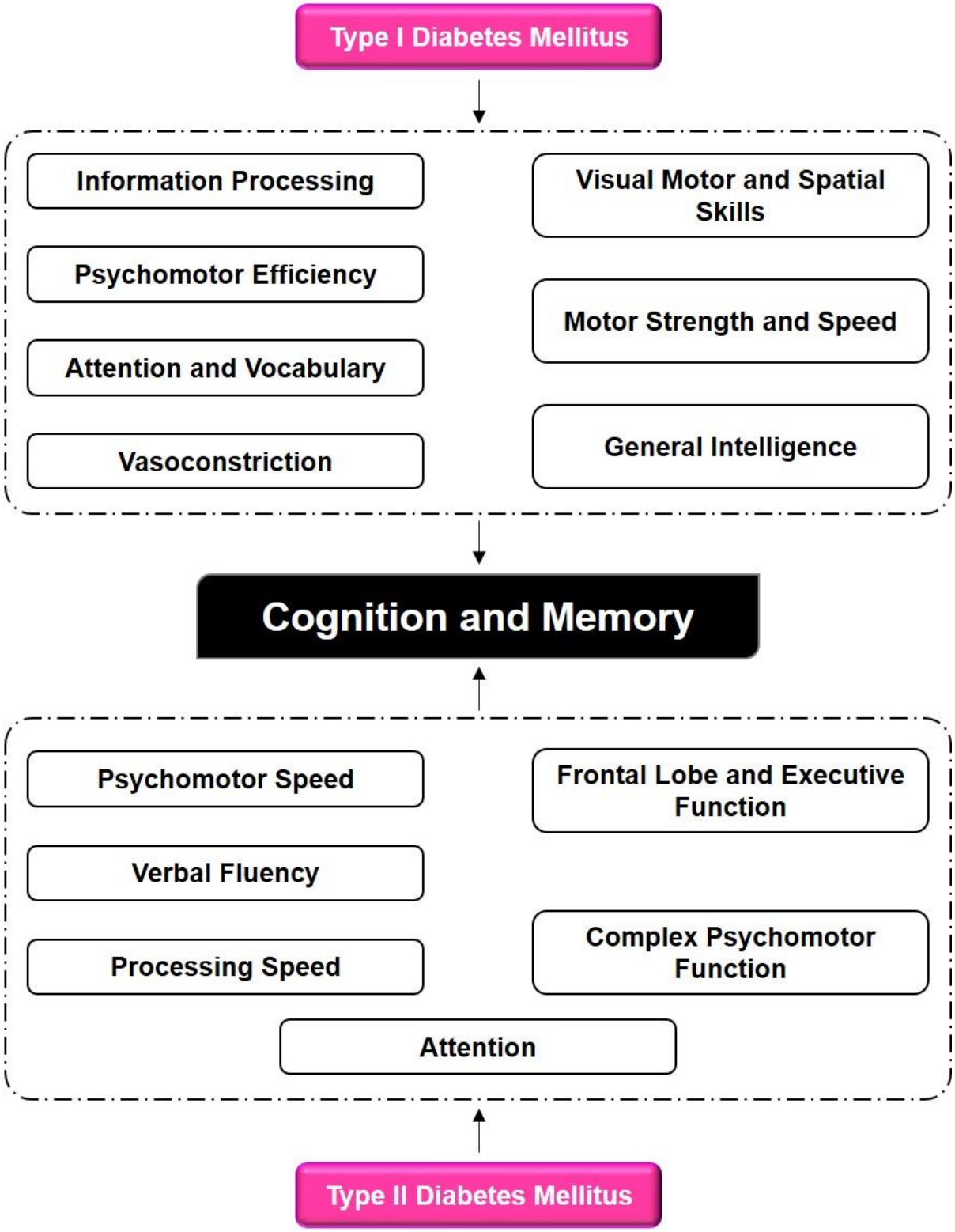

Figure 1: Different cognitive functions affected through Type I Diabetes, namely data processing, psychomotor efficiency, and vocabulary, vasoconstriction, visual and spatial skills. Similarly, cognitive functions affected

by type II diabetes include psychomotor speed, verbal fluency, processing speed, complex psychomotor function, which ultimately leads to memory impairment and dementia.

CHAPTER – 2 ALZHEIMER'S AND DIABETES OVERLAPPING PATHOLOGIES

2 major indications of type II DM (T2DM) include Hyperinsulinemia and Insulin resistance , has been demonstrated of significant danger issues for old dementia [1]. Undoubtedly, while an intense organization of Insulin shows positive response to memory spaces, dysfunctions result from the ongoing organization. Insulin-degrading enzyme (IDE) help to improve the glucose metabolism in brain to diminish its level [2]. amyloid-beta (Aβ) degradation and insulin; subsequently, hyperinsulinemia may decide a serious hindrance for IDE-dependent Aβ degradation, prompting Aβ aggregation. In addition, in Diabetes, the change of insulin flagging decides less IDE creation, bringing about a decrease of Aβ degradation; the cycle certainly prompts strange Aβ amassing inside of the brain. In this way, expanding insulin motioning in the brain may diminish Aβ amassing. Insulin has additionally been accounted for to improve Aβ removal from the cerebrum [3]. Add to insulin opposition in AD by altering neural connection conformity. This modified shape adaptation is answerable for the diminished proclivity of ligand and synaptic insulin receptor (figure 2).

Furthermore, strange portrays numerous neurodegenerative problems by protein processing. Specifically, the statement of extracellular Aβ plaques gives off an impression of being exacerbated by weakened insulin flagging capacity in AD; irregular Aβ prompts hyperphosphorylation of the tau protein is prompted by degradation of amyloid beta, [4]. These adjusted pathways include glycogen synthase kinase-3 (GSK-3), the protein that led to tau phosphorylation to make Alzheimer’s NFTs, which has been demonstrated as the beginning of downregulation in light of Insulin. Patho-physiology of AD is described by loss of neurotransmitters, while insulin receptor flagging increments synaptic density. Curiously, the hindrance of insulin flagging appears to go before Aβ aggregation in a model organism of transgenic mouse of AD [5]. The signaling pathway plays a critical role here[6].

Further, both T2DM and AD are to a great extent identified with inflammatory processes. Insulin resistance is related to raised degrees of proinflammatory cytokines. All of these cytokines are viewed as a roundabout indication of the immunologic dysfunction that prompts insulin resistance. In like manner, C-responsive protein and IL-6 are associated with Aβ plaque

accumulation and development, and on the opposite side, a decreased Alzheimer's frequency has been accounted for in subjects under ongoing nonsteroid anti-inflammatory treatment [7]. Another pertinent angle is addressed by the proinflammatory part of astrocytes and microglia encompassing Aβ plaques capable of irreversible neuronal damage as an outcome of supplement course initiation. Strangely, Insulin appears to have calming impacts straightforwardly smothering proinflammatory cytokines and inciting anti-inflammatory arbiters, as exhibited in both preclinical and clinical investigations.

Central obesity, characterized as both elevated weight list and mean midriff perimeter, addresses a notable danger factor for improving insulin obstruction through an expanded fiery reaction that adjusts insulin receptor flagging pathway. This may bring about metabolic condition, an issue likewise portrayed by dyslipidemia and hypertension, as often as possible antecedent of T2DM. The part of corpulence in advancing AD has been investigated in numerous examinations, and albeit the fundamental instruments of this cooperation aren't yet known, AD hazard has corresponded with insulin resistance, advanced glycation end (AGEs) products and oxidative stress, and hyperglycemia. Besides, some proof proposes that leptin could be utilized as a biomarker to improve the comprehension of AD danger and progression. Epidemiological information proposes that insulin opposition is related to the expanded danger of intellectual hindrance. Further, PET examinations have shown that more noteworthy insulin restriction is related to an AD-like example of diminished cerebral glucose metabolic rate in frontal, parietotemporal, and cingulate areas in adults with T2DM. In this manner, it isn't astonishing that Insulin could be a viable treatment for AD by expanding neuronal glucose take-up and cell ATP levels [8]

AGEs are varied mixtures getting form from nonenzymatic responses which are amino acid based with the protein amino gatherings, nucleotides, and lipids. This interaction that typically happens during maturing is quickened in diabetic patients because of the expanded arrangement of responsive oxygen species. In this respect, Sasaki and teammates have depicted an upgraded AGE immunoreactivity likewise in AD subjects, especially in Aβ plaques and NFTs of hippocampal neurons [11].

The previously mentioned overrun of ROS which reactive oxygen species and the overall expansion in oxidative pressure are qualities of DM. proteins that are oxidized start gathering has likewise been shown in the hippocampus, frontal and transient projections of gentle intellectual

hindrance patients, proposing an early effect of oxidative harm in AD advancement [12]. Mitochondria appear to assume a vital part in this interaction, as proposed by Moreira and partners, who have distinguished an association of mitochondrial brokenness in the advancement of neural degeneration and uncontrolled digestion in a rodent model of type 2 DM [13].

Figure 2 Relationship Between T2DM and AD

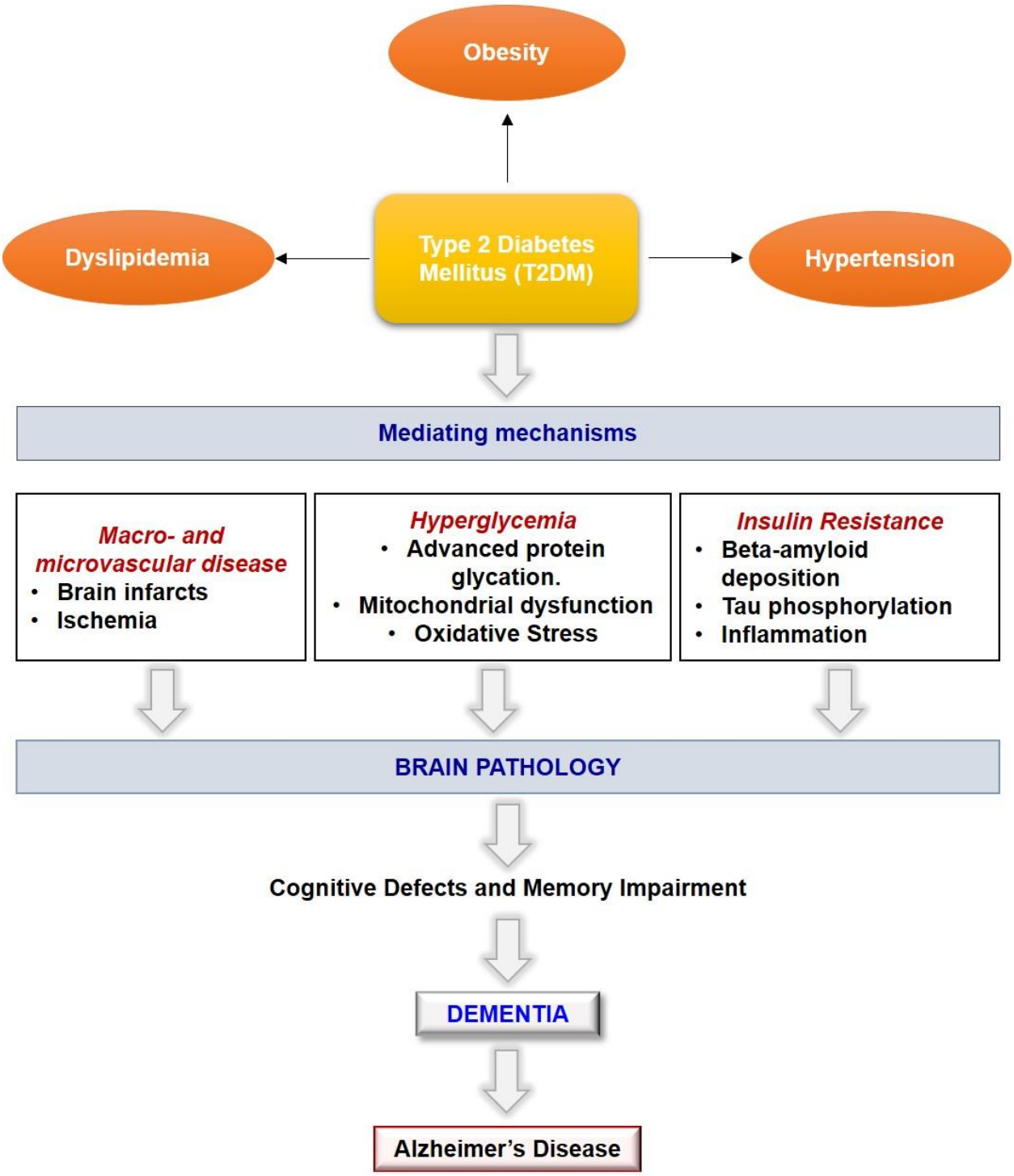

Figure 2: Pathological mechanism associated with Diabetes that might cause AD. Mechanisms are connecting Diabetes (Type 2 Diabetes Mellitus (T2DM)) furthermore, dementia. T2DM, just as obesity, hypelipidaemia and hypertension, are related to and expanded danger of macro and microvascular changes, hyperglycemia, and insulin resistance are giving ascend to dementia.

CHAPTER 3 ALZHEIMER'S PROGRESSION ON ACCOUNT OF DIABETES

The etiology of DM and AD is very intricate. Danger criteria for the two sicknesses fairly will, in general, cover. Instances of covering mechanisms of both intricate pathophysiological conditions, DM and AD are an aggravation, mitochondrial dysfunction and oxidative stress. Because of past scientific studies, sum up the possible component's basic increase in blood glucose level- prompted defective memory and spatial capacity. Midst proposed systems, brain IR and amyloid genesis are fundamental for hyperglycemia-instigated disability of psychological capacity. brain insulin resistance is mainly exaggerated inflammation of neurons, mitochondrial dysfunction and increase in oxidative stress and Aβ aggregation in brain sore. Delayed experience of increase in blood glucose level just as undeniable degrees of Aβ in the cerebrum can prompt decay of neuronal construction and capacity, bringing about poor cognitive execution.

3.1 Brain Insulin Resistance (IR)

A polypeptide insulin is a chemical to keep up homeostasis of glucose by bringing expanded glucose level of blood down back ordinary reach [14]. Mice with neuron-explicit deletion of insulin receptor had weakened glycemic reaction to hypoglycemia by hindering hypothalamic counter-administrative reaction to low degrees of blood glucose. This exhibits that Insulin can go about as a glucose sensor in the nerve center, including brain glucose homeostasis [15].

Intense hyperinsulinemia in light of expansions in the blood where glucose levels are elevated in the subjects encourages transport of glucose across the BBB inside the brain [18]. The hippocampus is enriched with high levels of insulin receptors [19]. Receptors empowers Insulin to be associated with remembrance and intellectual capacity since the hippocampus is the central region that is liable for remembrance [20]. ICV that is intra-cerebral or intra-venous organization of Insulin can improve longitudinal or oral memory in rodents and patients suffering with AD [21]. Notwithstanding, persistent hyperinsulinemia in cerebrum insulin obstruction prompts weakened insulin flagging and cutoff points accessible insulin by lessening insulin carriers of a blood-mind hindrance [22]. Accordingly, disabled insulin flagging and restricted accessibility of Insulin by persistent hyperinsulinemia are related to the disability of psychological execution advancement of neuron degenerating disease [23]. Not permissible substances in ordinary conditions can

likewise enter inside of the cerebrum since blood-brain barrier carriers are upset under the state of ongoing brain insulin resistance [24].

3.2 Amyloidogenesis

Chief compulsive qualities of Alzheimer's is decrepit plaques and NFTs in the brain that cause neurodegeneration in AD [25].

Elevated glucose condition expands Aβ creation by restraining APP degradation, not by expanding APP combination in neurons like cells that are not really neurons[26]. Unusual insulin motioning in cerebrum insulin opposition builds Aβ collection and tau phosphorylation in rat models of type I and type II diabetes [27]. Streptozotocin (STZ)- instigated type I diabetes shows expanded degrees of APP, Aβ, and tau phosphorylation in the hippocampus of ageing quickened mice.in another study yet another transgenic mouse model organism was taken, STZ infusion instigated type I diabetes can exasperate Aβ aggregation in cerebrum joined by upregulation of beta-site APP severing protein I and the full-length APP [28]. Also, STZ-instigated diabetic rodents show the decay of hippocampus, Aβ total, neural connection loss in the brain, and weakened execution of remembrance and learning [29].

An elevated-fat diet routine prompted type II DM. A high-fat eating routine can likewise expand Aβ blend and tau phosphorylation and decrease synaptophysin immunoreactivity, bringing about hindered remembrance work in a model organism of Alzheimer's [30]. Elevated sugar admission is additional considerate nutritional aspect that can prompt insulin obstruction. Instance, 10% sucrose-improved water can bring about increase of body weight and insulin obstruction in model organism. This additionally shows highlights of glucose bigotry and hyperinsulinemia. Treatment of model organism of mice sucrose-improved water also presented extra Aβ storage in the brain with remembrance shortfalls [27].

CHAPTER 4 LINKING AD AND DIABETES; ROLE OF SIGNALING PATHWAY

Figure 3 **Role of Signaling Cascade in Linking AD and DM**

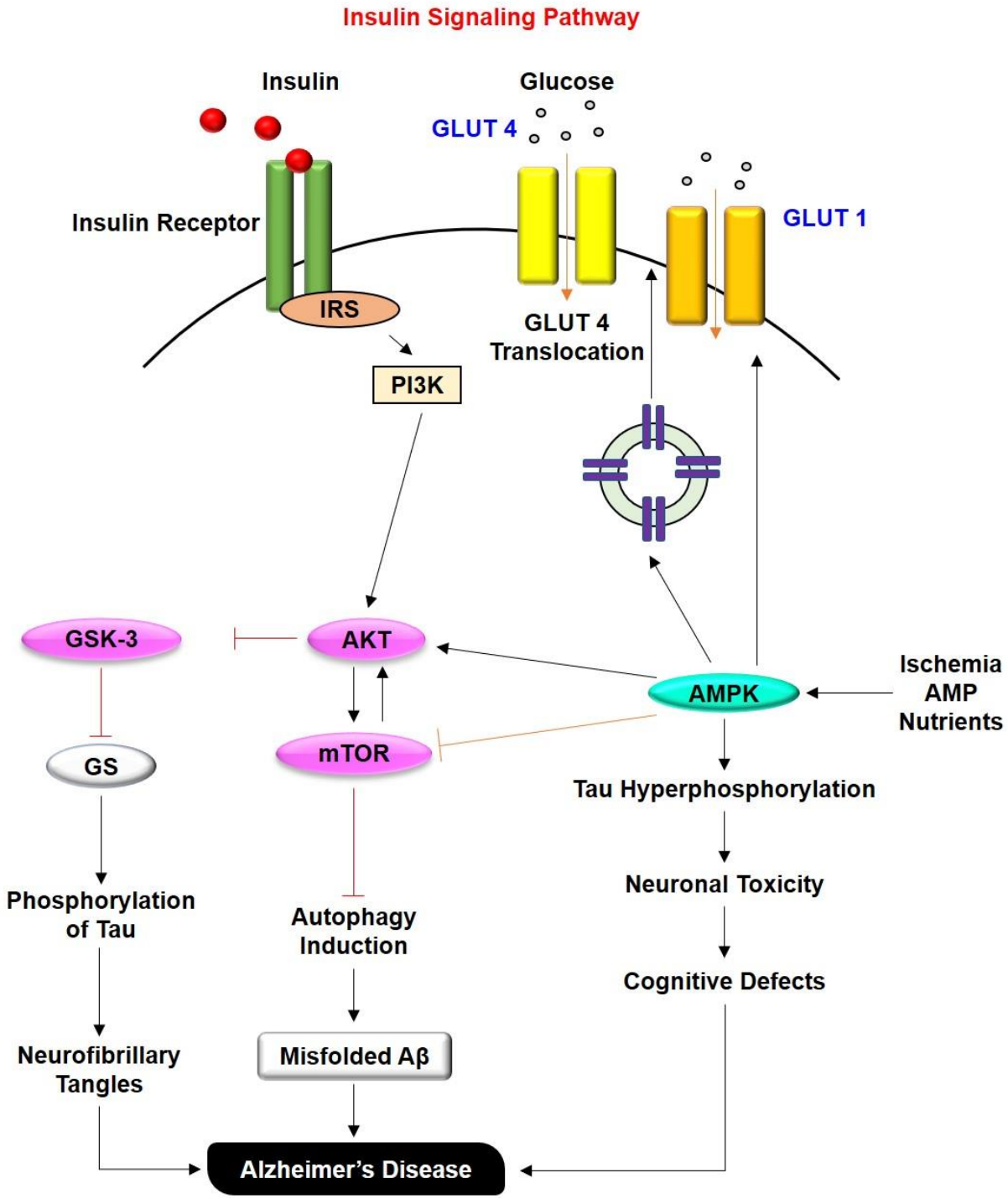

Figure 3: the interconnection among various signaling pathways and how tau hyperphosphorylation is responsible for neuronal dysfunction and death

CHAPTER 5 ANIMAL MODEL OF ALZHEIMER'S DISEASE AND DIABETES

An investigation was directed to inspect whether changes normal for Alzheimer's infection happen in two rodent models with unconstrained beginning of T1DM and T2DM. 8-month-diabetic rats were taken as test models and the frontal cortices of inspected concerning neuronal). Neuronal misfortune happened in the two models, essentially more so in sort 2 diabetic BBZDR/Wor rodents contrasted and type 1 diabetic BB/Wor rodents and was related with a ninefold increment of dystrophic neurites. Application, β-secretase, β-amyloid, and CTF were essentially expanded in sort 2 diabetic rodents, as was phospho-Ţ. The insulin receptor articulation was diminished in sort 1 diabetes, while IGF-1 receptor was diminished in the two models, as were Akt and GSK-3β articulation. The information shows that β-amyloid and phospho-Ţ aggregation happen in trial diabetes and that this is related with neurite degeneration and neuronal misfortune. The progressions were more serious in the kind 2 diabetic model and have all the earmarks of being related with insulin obstruction and potentially hypercholesterolemia. The two models will give helpful devices to disentangle further robotic relationship among Diabetes and Alzheimer's infection [47].

CHAPTER 6 ANTI-DIABETIC DRUGS—A PROMISING SOLUTION FOR AD PATIENTS

Regardless of the blended discoveries of observational investigations, a huge group of writing and a few convincing speculations actually recommend that anti-diabetic treatments hold potential as medicines for dementia [6] (table 1) . Quite compelling, are perceptions that T2D and AD seem to share components in like manner, remembering irregularities for insulin signaling, mitochondrial dysfunction, unusual energy homeostasis, and neuroinflammation [48]. Many investigations have inspected the degree to which anti-diabetic prescriptions may affect cerebrum pathology—especially highlights of AD—with most of creature considers highlighting possible advantages on amyloid pathology, tau pathology, neurotransmitters, oxidative pressure, neurogenesis, neuroinflammation, and psychological capacity [49].

In any case, human clinical preliminaries—like observational examinations—show blended discoveries. Promising impacts of anti-diabetic meds have been seen in moderately more modest preliminaries. In a promising little preliminary, Luchsinger et al tried the impacts of metformin among 80 members with amnestic MCI and no determination of T2D and found a gainful impact of metformin on verbal memory [50]. A little fake treatment-controlled hybrid investigation randomized twenty nondiabetic members with MCI or mellow AD dementia to metformin followed by fake treatment or the other way around for about two months and found a critical constructive outcome of metformin on chief capacity, explicitly Trials B. Notwithstanding metformin, little preliminaries of TZDs have additionally shown useful impacts. A little pilot study which randomized patients with AD/amnestic MCI to oral rosiglitazone or placebo for a half year discovered better deferred review at both 4 and a half year, just as better particular consideration at 6 months. Pioglitazone was tried among 42 people with gentle AD and a going with determination of T2D and found an advantage of pioglitazone contrasted and control on MMSE and the Japanese variant of ADAS-Cog scores. Nonetheless, a proviso was the open label study plan [51].

Just few preliminaries have analyzed the effect of anti-diabetic prescriptions on likely indicators of AD pathology. The impact CSF biomarker of a drug class metformin of AD was assessed in a little preliminary, however consequences didn't demonstrate any impact. In a little preliminary did by the Craft bunch testing the effect of rosiglitazone on intellectual capacity, no change in plasma Aβ42 levels in the gathering getting rosiglitazone, however presented a decay amid subjects in the placebo group. Amyloid markers and tau pathology have additionally been assessed in cerebrospinal liquid as a feature of single focus and bigger multisite preliminaries of intranasal Insulin. Insulin was found to bring down ptau/Aβ42 in any event one examination, albeit another single site concentrate from this equivalent gathering didn't show an impact, and early outcomes from SNIFF didn't recommend a great impact on CSF biomarkers [52].

Table 1: List of anti-diabetic drugs and their mechanism of action

Drugs class	Mechanism of Action	Target organ	References
α – Glucosidase Inhibitors	Delay carbohydrate absorption from intestine	Small Intestine	[53,54]
Amylin analogue	Decrease glucagon secretion Slow gastric emptying Increase satiety	Pancreas	[55]
Biguanide	Decrease HGP Increase glucose uptake in muscle	Liver, Kidney and intestines	[56]
Bile acid sequestrant	Decrease HGP Increase incretin levels	Small intestine	[57]
DPP-4 inhibitors	Increase glucose-dependent insulin secretion Decrease glucagon secretion	Pancreas, adipose tissue, stomach, and brain	[58]
Dopamine-2 inhibitors	Activates dopaminergic inhibitors	pituitary gland	[59]
Glinides	Increase insulin secretion	Pancreas	[60]
GLP-1 receptor agonists	Increase glucose-dependent insulin secretion Decrease glucagon secretion Slow gastric emptying Increase satiety	pancreatic islet	[61]
SGLT2 inhibitors	Increase urinary excretion of glucose	proximal convoluted tubule and macula densa	[62]
Sulfonylureas	Increase insulin secretion	Pancreas	[60]
Thiazolidinediones	Increase glucose uptake in muscle and fat Decrease HGP	Adipocytes	[63]

CHAPTER 7 LINK BETWEEN INSULIN AND AD (TYPE III DIABETES)

Limits of the brain continue disintegrating, a reduction in person's memory related limits, memory, personality, suddenness, and blending conduct. A design that continuously interlinks all of these wonders under one event is insufficient. Consequently, this segment investigates the verification coming improvement of DM expert provoked AD model organism. Great proof has credited decrease in receptor of insulin in neurons to go previously go with starting period of AD. Progression with AD with the ultimate objective that, in the terminal stages, it decays and gets around the world. Hence it is referred to as type 3 DM. Likewise, standard pathophysiology with Diabetes ordinary accommodating framework is convincing for AD patients (figure 4).

Figure 4 Involvement of Insulin Receptor in the Pathogenesis of AD

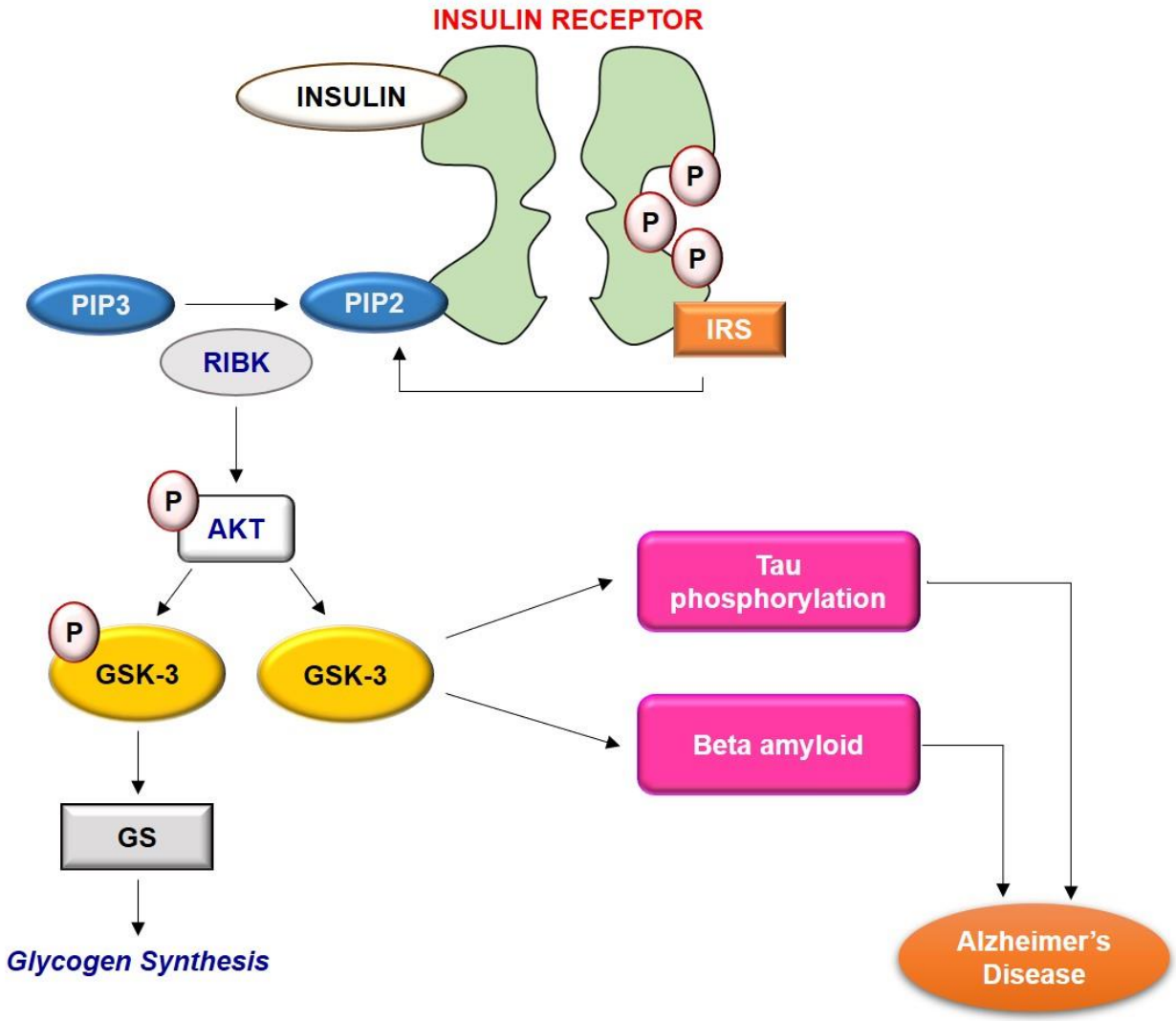

Figure 4: Insulin resistance role in AD development. The pathways interlinks and interconnects showing the pathology is related.

7.1 Insulin role in brain

Further, IR is by all accounts generally dispersed with a large portion focusing the neurotransmitter od neurons and astrocytes. Brain locales like hippocampus, amygdala, and septum have shown higher conveyance of insulin resistance. Inside the cell pathways, are supposedly enacted through IR and IGF-1 receptors incitement accordingly showing expansive effect of protein insulin motioning in the out the nerve center [68]. Hippocampus, with its plentiful insulin resistance substrate (IRS) proteins controls securing solidification of recollections accordingly recommending the part of Insulin in memory potentiation [69]. In sound grown-ups, fundamental mixture of Insulin yielded a critical progress in oral brain memory and particular

consideration [70]. It is well known to improve memory of person suffering from dementia [71] (table 2).

Table 2: Insulin affecting major cell types of brain

Cell types	Effects	References
Neuron	• IR (Insulin receptor) predominant isoform. • IR and IRS (Insulin Receptor Substrate)1 and IRS2 enriched in presynaptic and postsynaptic compartments. • Regulates expression and localization of ion channels, including GABA, NMDA and AMPA receptors. • Modulates catecholine release. • Regulates balance of LTP and LTD. • Facilitates GLUT3 and GLUT4 Trafficking. • Neurogenesis. • Inhibits apoptosis.	[74]
Microglia	• IR, IRS1 and IRS2 present. • Modulates inflammatory response, cytokine secretion.	[75]
Astrocytes	• IR- predominant isoform. • Signals via IRS1 and IRS2. • Promotes glycogen storage. • Enhances BBB glucose uptake. • Modulates inflammatory cytokine secretion.	[76]
Arterioles, capillaries and BBB	• IR-mediated transport of Insulin into brain across BBB. • Regulates BBB GLUT1 expression. • Promotes NO-mediated vasodilation, enhancing cerebral perfusion	[77]
Oligodendrocytes	• IR, IRS1 and IRS2 present. • Insulin effects not well studied.	[78]

7.2 AD pathology highly mediated by Insulin

Frolich and associates demonstrated IR for the first time [79]. The outcomes additionally reinforced when cerebrospinal liquid AD and mellow psychological debilitation subjects showed diminished degrees of protein Insulin. and receptor qualities have showed a connection connected to cutting edge phase AD. It was seen that AD minds introduced irritated Insulin and IGF-1-interceded neuronal turn of events and mitochondrial dysfunction [80]. Proof has recommended neurodegeneration of Insulin and IGF-1 receptor-bearing neurons to go before or go with starting phase of AD [81]. This insulin-interceded neurodegeneration advances with AD to such an extent that, in the later stages, it gets worldwide [80].

Defaulted insulin resistance accounts for most of the AD pathology and amyloid beta accumulation. Hence its degradation by insulin resistance enzymes are in great loss thus lead to AD progression [101].

7.3 Insulin resistance proof in AD

From the recent many years, proof is being accumulated by delivering diabetes specialist instigated exploratory AD creature models [102]. Notwithstanding a few elements known to trigger AD, overpowering proof recommends association of cerebral insulin/IGF obstruction in MCI, dementia, and AD. Cerebral Insulin, consented to be of pancreatic source, is known to tweak synaptic pliancy that controls learning and memory [103]. It has been appeared to prompt memory consolidation, recovery and eradication of contextual memory by means of phosphatidylinositol 3-kinase (PI3K) pathway. AD relationship with expanding brain insulin restriction without T2DM, shows essential weakened insulin signaling [104].

Cognitive impedance in rodents followed by ICV infusions of streptozotocin, with shortages in cognitive memory, IR and progressive dementia leads to solidified speculation of AD being a form of DM [105]. Other impacts of this drug-prompted impeded the protein Insulin and IGF motioning in the Central nervous system could be liable for this. A group of researchers recommended the reformist insulin obstruction, joined by diminished cerebral glucose digestion and inconspicuous cognitive disabilities at beginning AD organizes, and be filled as the marker of Alzheimer's disease in the MCI starting [106].

CHAPTER 8 ANTI-DIABETIC DRUGS CLASSIFICATION AND ITS NEUROPROTECTIVE POTENTIAL FOR TREATMENTS OF ALZHEIMER'S DISEASE

8.1 Metformin

This drug class is usually used for the diabetes therapy [110]. The receptors are commonly found in the small intestine, liver and kidney [111]. Later the drug was administered orally in the subjects and suggested the oral hyperglycemic are effective for AD patients in test population [114].

8.2 Thiazolidinediones

These classes of drugs are also repurposed for the treatment of both pathological conditions. First, pioglitazone is approved for the treatment of DM in positive response of insulin and controls the high cholesterol levels in the patients [115]. On the other hand, two drugs: Rosiglitazone and

Pioglitazone are used for the treatment of AD and are FDA approved. They enhance the expression of PPARγ in the AD brain temporal cortex part hence showing positive response [124].

8.3 Glucagon-Like Peptide Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors

A protein chemical Glucagon-like peptide-1 (GLP-1) a place with the incretin family, and it is discharged by the digestive tract because of food consumption [125]. The receptors are found on the pancreas in beta cells.[126]. When discharged, local GLP-1 is corrupted inside the space of notes by the chemical dipeptidyl peptidase-4 (DPP4); thusly, GLP-1 have certain analogs which are impervious to this DPP4 activity have been created for clinical use [127]. Few examples of GLP1-R agonists mentioned (liraglutide, lixisenatide and exendin-4) have been affirmed for diabetes therapy. In any case, GLP-1Rs are additionally found in the Central nervous system [128]. The receptors in CNS help to reduce the blood glucose level to great extent [132].

8.4 Amylin Analog

A small peptide amylin is a chemical which is co-emitted in response to glucose uptake along with insulin in light of supplement consumption [138]. In AD patients the level of the peptide in greatly reduced that the drug administration can improve their overall dementia condition [139].

CHAPTER 9 METHODOLOGY

1. Information extracted from freely available Drugbank databases.
2. Ligand and receptor name was extracted for each anti-diabetic drug class showing permeability towards blood brain barrier
3. These ligand and receptors now need to be docked
4. The pdb format files were downloaded from protein data bank.
5. The receptor and ligand .pdb files were now uploaded on Patchdock softwere and were submitted.
6. The results were mailed by the system.
7. Visualization of the results was done using Pymol tool.

CHAPTER 10 RESULTS, DISCUSSION AND CONCLUSION

10.1 RESULTS

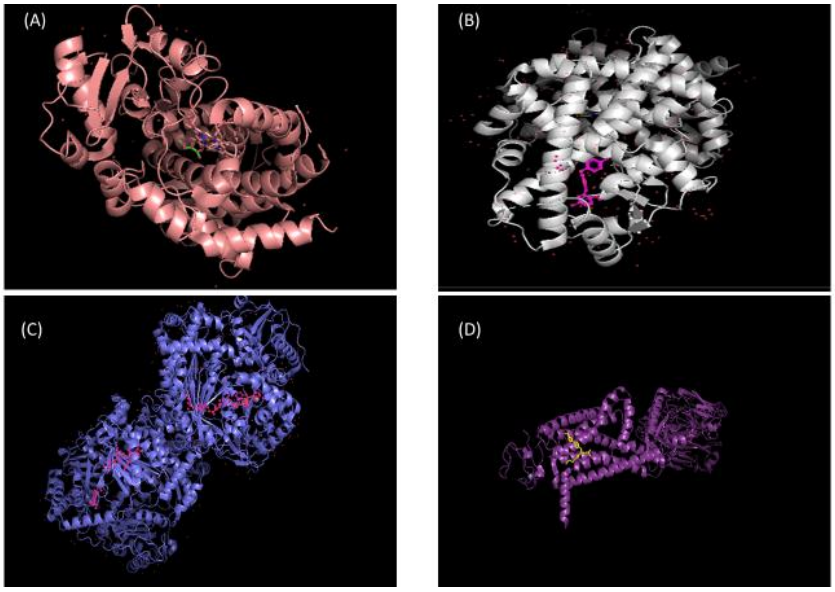

FIGURE 5: (A) Metformin as ligand and GABA receptors docking results, (B) TZD as Ligand and PPARγ receptor docking results, (C) GLP-1 receptors Agonist as ligand and GLP-1 receptor docking results, (D) Amylin Analog as Ligand and Amylin Analog receptor docking Results.

10.2 DISCUSSION

Screening is a reciprocal and elective strategy to docking for screening enormous substance library compounds against a given medication target. The pharmacophore highlights got from the protein-ligand complex uses the information on the potential associations that exist between the protein and the ligand, though the highlights that are gotten from the protein alone utilize dynamic site/problem area buildup data. The determined pharmacophore highlights can be utilized to screen DrugBank compounds for new signs.

10.3 CONCLUSION

We integrate information from various sources such as Protein-protein interaction network (PPI) with the available drug repositories for Diabetes. We then make use of various computational tools to rank the candidate drugs for their repurposing potential. The toxicity and pharmacokinetic studies will help us to identify the best anti-diabetic drug for AD treatment. To identify differentially expressed genes for Alzheimer's disease based on transcriptomics studies. To construct gene interaction network for Alzheimer's disease and Diabetes. To repurpose and validate anti-diabetic drugs for Alzheimer's disease. Determination of toxicity and pharmacokinetic properties of the identified repurposed drugs. Differentially expressed genes for Alzheimer's Disease will be identified that can be linked to Diabetes genes by PPI construction. Identification of common genes and signaling pathways involved in crosstalk between AD and Diabetes. Validation of identified drugs by virtual screening, molecular docking and network-based approaches. ADMET analysis and BBB permeability prediction of the identified drugs will validate the efficacy of the drugs with neuroprotective properties. Researching the repurposing of approved drugs intended to treat Alzheimer's Disease would help speed up the drug design process. The study will establish a therapeutic link between Alzheimer's disease and Diabetes. The study would help to elucidate neuroprotective properties of anti-diabetic drugs. The study would open up new possibilities for pharmaceutical groups and research workers engaged in drug development process. Hence docking will open new opportunities for validated targets verified from online available drug databanks and help the researchers to find new paths for in vitro and in vivo studies to commercialize the repurposed drugs

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LIST OF PUBLICATIONS

1. Sharma S, Advani D, Das A, Malhotra N, Khosla A, Arora V, Jha A, Yadav M, Ambasta RK, Kumar P. Pharmacological intervention in oxidative stress as a therapeutic target in neurological disorders. J Pharm Pharmacol. 2021 May 29:rgab064. doi: 10.1093/jpp/rgab064. Epub ahead of print. PMID: 34050648.