

Review

Type 2 Diabetes and Alzheimer's Disease: Molecular Mechanisms and Therapeutic Insights with a Focus on Anthocyanin

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Abstract

Type 2 Diabetes Mellitus (T2DM) is a recognized risk factor for Alzheimer's Disease (AD), as epidemiological research indicates that those with T2DM have a markedly increased risk of experiencing cognitive decline and dementia. Chronic hyperglycemia and insulin resistance in T2DM hinder cerebral glucose metabolism, reducing the primary energy source for neurons and compromising synaptic function. Insulin resistance impairs signaling pathways crucial for neuronal survival and plasticity, while high insulin levels compete with amyloid- β (A β) for breakdown by insulin-degrading enzyme, promoting A β buildup. Additionally, vascular issues linked to T2DM impair blood-brain barrier functionality, decrease cerebral blood flow, and worsen neuroinflammation. Elevated oxidative stress and advanced glycation end-products (AGEs) in diabetes exacerbate tau hyperphosphorylation and mitochondrial dysfunction, worsening neurodegeneration. Collectively, these processes create a robust biological connection between T2DM and AD, emphasizing the significance of metabolic regulation as a possible treatment approach for preventing or reducing cognitive decline. Here, we review the relationship between T2DM and AD and discuss the roles insulin, hyperglycemia, and inflammation therapeutic strategies have in successful development of AD therapies. Additionally evaluated are recent therapeutic advances, especially involving the polyflavonoid anthocyanin, against T2DM-mediated AD pathology.

Keywords: type 2 diabetes mellitus (T2DM); Alzheimer disease (AD); oxidative stress; mitochondrial dysfunction; neuroinflammation; insulin resistance; hyperglycemia



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1. Introduction

Diabetes is a metabolic disease characterized by hyperglycemia secondary to insulin resistance or deficiency and progressive glucose intolerance. Insulin resistance/insensitivity is the body's inability to properly respond to insulin and glucose intolerance is a pathological process often secondary to insulin resistance characterized by the inability to maintain normal glucose levels. Type 1 Diabetes Mellitus is an autoimmune process affecting pancreatic beta cells, which produce insulin. Type 2 Diabetes Mellitus (T2DM) also has pancreatic beta cell dysfunction but is broadly considered an acquired insulin resistance whose risk factors include obesity, smoking, alcohol consumption, sedentary lifestyle, and high carbohydrate diets alongside processed foods [1–6]. T2DM contributes to Alzheimer's Disease

(AD) by promoting insulin resistance, impaired glucose metabolism, oxidative stress, and amyloid- β and tau pathology, thereby accelerating cognitive decline.

Diabetes is the seventh leading cause of mortality in the US and AD is sixth [7]. Both diseases have environmental and, to a lesser degree, genetic determinations associated. Common between them is insulin resistance, which promotes cognitive decline, memory deficits, and other characteristic symptoms displayed in AD. Another feature of T2DM is impaired insulin-like growth factor signaling, inflammation, oxidative stress, and the aforementioned glucose intolerance [7–10]. Recent studies suggest that impaired insulin-like growth factors promote amyloid beta aggregation and accumulation via different signaling pathways [11–13].

Inflammation is a protective mechanism of the body that promotes leukocyte activation, mobilization, resource sequestration, and local or generalized in-hospitality for presumed invading microbes.

Chronic low-grade inflammation adversely affects central and peripheral organs by promoting cell death and activating microglia and astrocytes, which release proinflammatory cytokines that exacerbate amyloid beta misprocessing and tau hyperphosphorylation. Excessive reactive oxygen species (ROS) production, coupled with compromised antioxidant defenses, induces oxidative stress, damaging cellular components and activating pathways that contribute to amyloid accumulation and neurofibrillary tangles [13–18].

Recent evidence indicates that glucose intolerance and blood glucose dyshomeostasis promote abnormal tau phosphorylation, memory impairments, and cognitive decline, contributing to AD pathology [19–21]. This study summarizes the risk factors for T2DM, elucidates the mechanisms by which T2DM induces AD pathology, and explores how T2DM therapeutic strategies may slow or potentially halt the progression of AD-related complications.

2. Methodological Approaches

This study is motivated by our previous studies on the role of anthocyanin against different neurodegenerative diseases (APP/PSEN-1 transgenic mice and LPS-treated mice).

APP/PS1 and LPS-treated mice represent two distinct approaches to modeling neurodegeneration. APP/PS1 mice are transgenic models carrying mutations in amyloid precursor protein (APP) and presenilin-1 (PS1), leading to progressive amyloid- β plaque accumulation, synaptic dysfunction, and cognitive decline, thus closely mimicking the genetic and pathological hallmarks of AD. In contrast, LPS-treated mice are generated by systemic or intracerebral administration of lipopolysaccharide (LPS), which induces robust neuroinflammation through microglial activation and cytokine release. While they do not develop amyloid plaques or tau pathology, they are widely used to study inflammation-driven neurodegeneration and its contribution to cognitive deficits.

Here, we searched for potential research articles focusing on obesity, diabetes, and AD. In addition, to identify studies on the role of anthocyanin in obesity, diabetes, and AD, we conducted searches using the keywords “anthocyanin,” “obesity,” and “diabetes” in all available and independent databases, e.g., PubMed (<https://pubmed.ncbi.nlm.nih.gov>, accessed on 31 May 2025), Google Scholar (<https://scholar.google.co.kr>, accessed on 31 May 2025), and Web of Science (<https://apps.webofknowledge.com>, accessed on 25 May 2025). For a clear understanding of these studies, the abstracts were fully studied and the main findings were recorded. For comparisons among the different groups, the anthocyanin-treated group was compared with the toxin treated/model group. The dose and route of administration of anthocyanin, duration of treatment, and toxic compounds used in these studies were not considered. All studies covering animal and cellular models were included.

3. Common Risk Factors for Type 2 Diabetes Mellitus (T2DM)

3.1. Obesity

Obesity is a chronic metabolic disorder characterized by excessive accumulation of body fat that reduces overall health and increases the risk of cardiovascular disease, T2DM, and neurodegeneration. Elevated circulating free fatty acids induce chronic low-grade inflammation in peripheral and central tissues, promote lipotoxicity, and impair insulin secretion, contributing to insulin resistance. The global rise in obesity, driven by sedentary lifestyles and diets high in calories and fat but low in fiber, is a major risk factor for T2DM reported in recent studies, sharing common pathways of chronic inflammation and insulin resistance [1,22–25] (Figure 1).

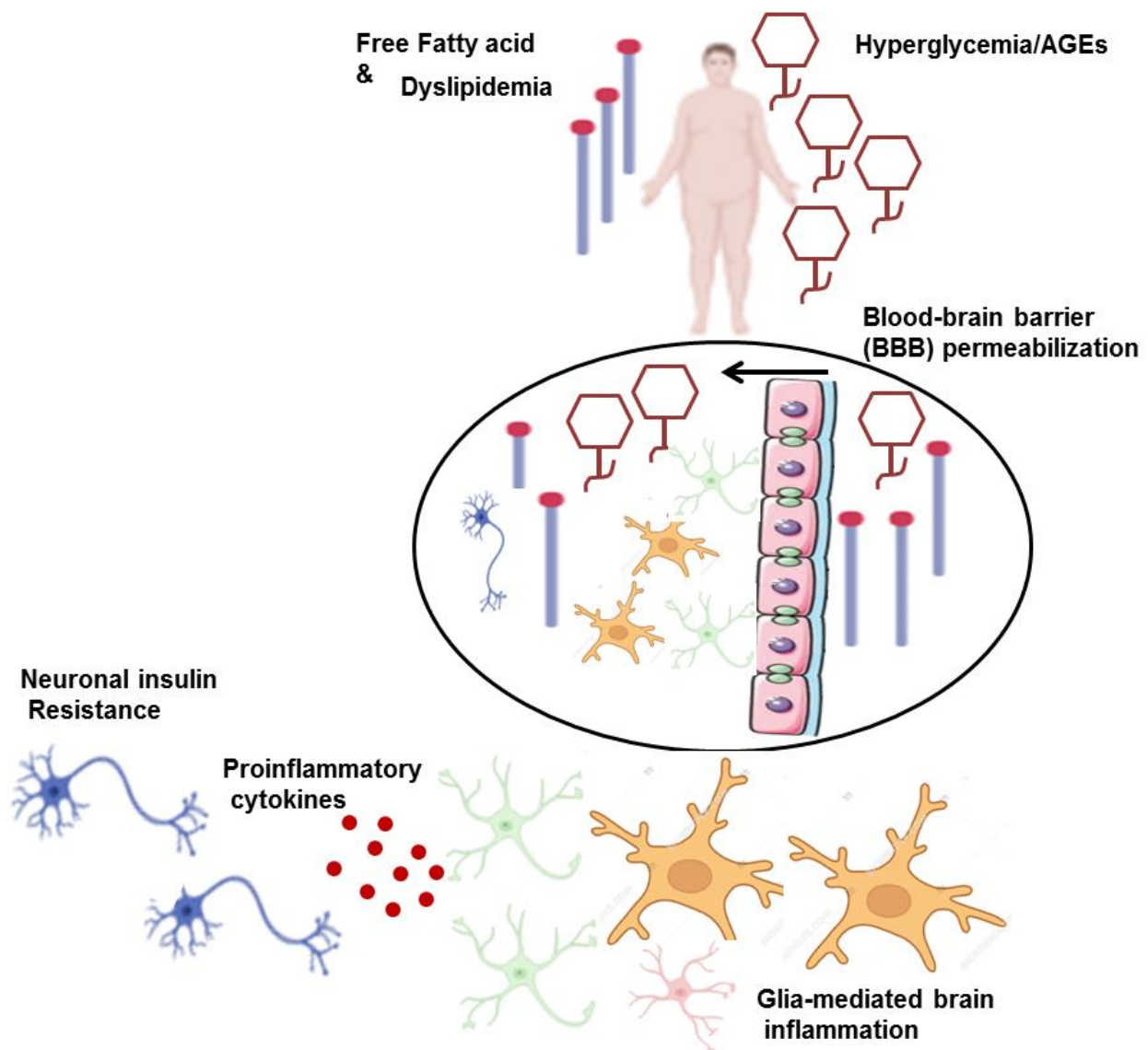


Figure 1. Figure indicates how obesity induces insulin resistance. Both chronic and acute free fatty acid induces lipotoxicity and compensates insulin insensitivity. Obesity is also involved in prostaglandins release and chronic low-grade inflammation which later on mediates insulin resistance.

3.2. Smoking, Alcohol Consumption, Sedentary Life Style/Lack of Exercise, Chronic Stress or Depression, Gut Microbiota Imbalance

Smoking is a well-established lifestyle hazard that negatively affects nearly every organ system due to both the primary addictive component, nicotine, and a myriad of carcinogens

and irritants used in the manufacture and presentation of these tobacco products. Nicotine is a powerful brain stimulator, creating dependency by altering neurotransmitter release and reinforcing compulsive use. Beyond addiction, the continuous inhalation of toxins in cigarette smoke, including tar, carbon monoxide, and thousands of free radicals—directly damages the lungs, leading to chronic inflammation, tissue remodeling, and a heightened risk of chronic obstructive pulmonary disease (COPD) and lung cancer. Smoking also compromises the immune system by altering the structure and activity of immune proteins, reducing the efficiency of frontline immune cells such as macrophages and neutrophils, and diminishing the production and effectiveness of protective antibodies. As a result, smokers are more vulnerable to respiratory infections, delayed wound healing, and systemic diseases linked to immune dysregulation. The combined effects of addiction, cellular injury, and immune suppression make smoking a critical public health concern with far-reaching consequences for both individual health and societal burden.

Chronic tobacco use, including cigarette smoking, is associated with elevated COVID-19 mortality rates and contributes to metabolic disorders such as T2DM by promoting systemic inflammation and insulin resistance. Also harming to health, prolonged alcohol consumption damages liver and other organ tissues, disrupts beneficial gut microbiota leading to dysbiosis, and alters brain neurotransmitter levels potentially causing neuropsychiatric disorders like depression and anxiety, which further exacerbate metabolic syndrome, cardiovascular dysfunction, and immune system impairment [26–36].

Regular exercise, such as intense walking, promotes endorphin release to alleviate anxiety, depression, and pain, while mitigating metabolic disorders like insulin resistance and beta-cell dysfunction, which are linked to T2DM and AD pathology through mechanisms involving toxic ceramides and inflammatory cytokines [37–40].

Additionally, gut dysbiosis, exacerbated by stress, sedentary lifestyles, aging (particularly over 45 years), and certain medications like antipsychotics and corticosteroids, fosters leaky gut and systemic toxin release, further driving blood glucose dyshomeostasis, insulin resistance, and metabolic syndrome, which contribute to metabolic disorders [41–43] (Figure 2).

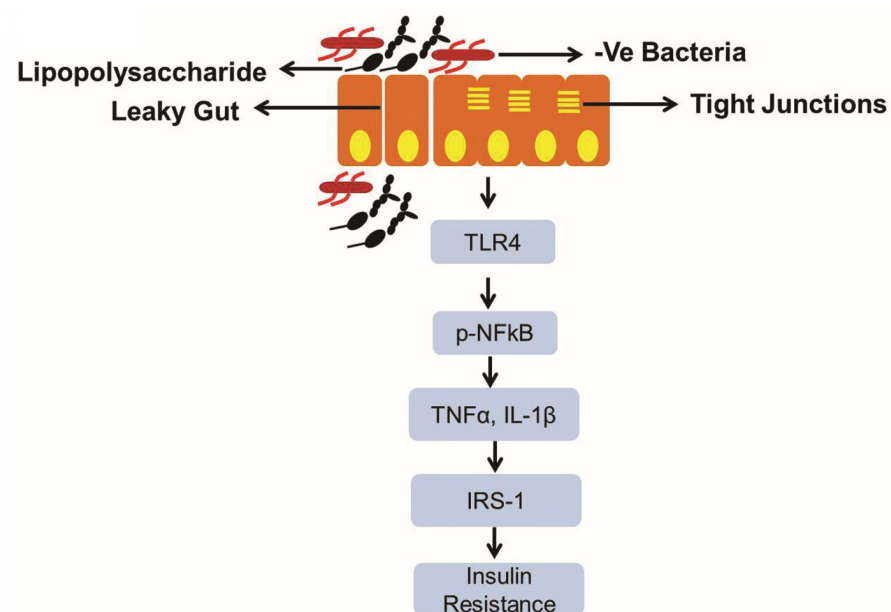


Figure 2. Figure represents how gut dysbiosis induces insulin resistance. It first activates toll like receptors which further activates transcription factor NFkB and inflammatory cytokines leading to insulin resistance.

3.3. Shared Links Between Type 2 Diabetes Mellitus (T2DM) and Alzheimer Diseases Pathology

There are several signaling pathways that potentially elaborate the mechanisms which are involved in T2DM mediated AD pathology alongside evidence that therapeutic approaches for T2DM could slow down the progressive nature of AD. Farris et al. demonstrated in a rat model that mutant insulin-degrading enzyme (IDE) leads to glucose intolerance, hyperinsulinemia, and brain insulin resistance, indicating that IDE hypofunction contributes to T2DM by impairing the degradation of amyloid- β (A β), amyloid precursor protein (APP) intracellular domain, and insulin. This complex interplay between insulin signaling, A β metabolism, and IDE dysfunction suggests that disruptions in this balance may reduce A β clearance, impair neuronal insulin responsiveness, and promote progressive cognitive decline associated with AD [44–49].

Under fresh and recent debate is the idea that neurodegeneration can occur in the setting of brain insulin resistance through the inability to stimulate the clearance of A β , resulting in its accumulation inside neuronal cells [40,44,50–53]. Recent evidence indicates that impaired brain insulin signaling—often accompanied by neuroinflammation and oxidative stress—can promote A β accumulation, but the mechanisms are complex and context-dependent. Experimentally, insulin is known to accelerate APP/A β egress from the trans-Golgi network to the plasma membrane, which in some models reduces intraneuronal A β and increases extracellular A β secretion (i.e., promoting trafficking/secretion rather than intracellular build-up). Insulin signaling influences APP processing and secretase function, meaning that interference with insulin receptor pathways can alter APP cleavage towards more amyloidogenic results. IDE is a legitimate A β -degrading protease found in brain tissue and its activity can be influenced by insulin signaling, although this connection is complex. While insulin can enhance IDE in certain situations, persistent hyperinsulinemia or insulin resistance may hinder IDE-driven A β clearance (partially due to insulin and A β vying for IDE as substrates and potential changes in IDE expression/activity in diseases). Ultimately, oxidative stress and inflammation—frequent partners of metabolic dysfunction—adversely impact various A β clearance mechanisms (such as proteolytic degradation, receptor-mediated transport, autophagy, and microglial phagocytosis), resulting in insulin signaling disruption generally leading to diminished clearance and heightened amyloid accumulation in vivo [47,54–56]. Besides insulin signaling, various other receptors are crucial in modulating tau phosphorylation and expression. Among these, the peroxisome proliferator-activated receptor gamma (PPAR γ) affects neuronal survival and glucose metabolism, and its activation has demonstrated a reduction in abnormal tau phosphorylation by regulating inflammatory and oxidative stress pathways. Likewise, insulin-like growth factor 1 (IGF-1) signaling promotes neuronal development and synaptic plasticity, while also offering protective effects against tau hyperphosphorylation via the PI3K/Akt and MAPK pathways. Dysregulation of these receptors disrupts the metabolic and inflammatory balance within the brain and plays a role in tau pathology, thereby connecting metabolic dysfunction to the advancement of AD [40,44,50,51,56–60] (Figure 3).

There have been many recent studies that implicate glucose deregulation and chronic hyperglycemia inducing oxidative stress in brain cells. It is well established that oxidative stress accelerates microgliosis, astrogliosis, and activates some stress kinases such as c-Jun N-terminal kinase (JNK). The activation of stress kinase JNK signal activates transcription factors such as NF κ B which in turn activates the release of proinflammatory cytokines such as TNF α , IL-1 β . NF κ B is also involved in the deregulation of BACE1 which abnormally cleaved the APP and induces A β accumulation. However, inflammatory cytokines accelerate the aggregation of A β inside neuronal cells and thus induces neurodegeneration and AD like pathology (Figure 4) [1,41,61,62].

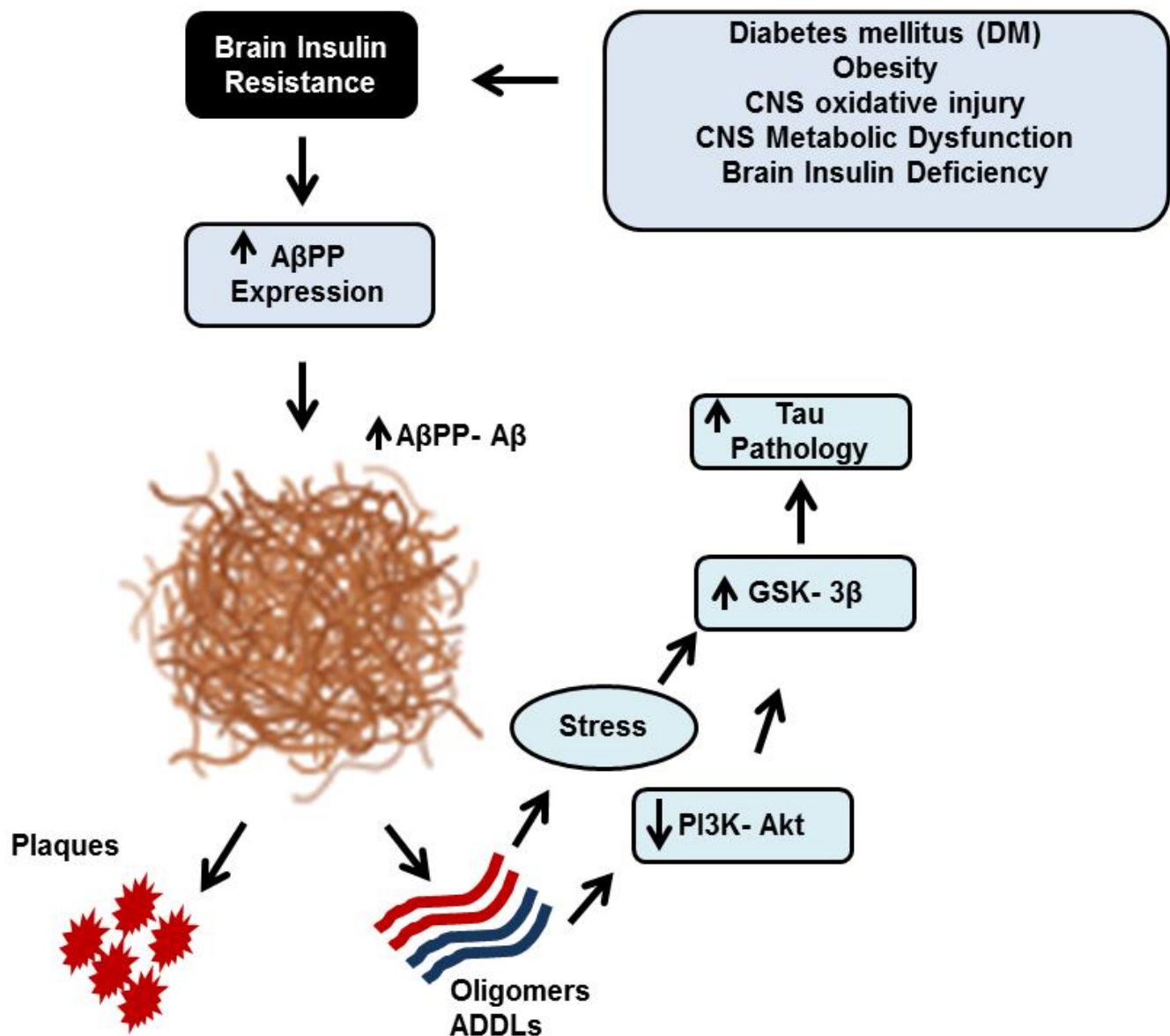


Figure 3. Figure illustrates insulin resistance in the brain and the accumulation and harmful effects of APP-A. Insulin resistance in the brain, resulting from peripheral insulin resistance conditions or primary toxic and neurodegenerative brain processes, fosters neuroinflammation and heightened APP expression. Through the activity of Beta and Gamma secretases, AbPP is cut to produce an overabundance of 40–42 kD APP-A peptides that cluster and create insoluble fibrils and plaques, or oligomers and diffusible ligands derived from APP-A (ADDLs), which are harmful to neurons. APP-A oligomers and ADDLs induce oxidative stress and heightened activation of kinases that result in Tau hyperphosphorylation, followed by its ubiquitination, misfolding, and aggregation. APP-A oligomers and ADDLs might hinder insulin receptor activity and lead to insulin resistance. Individuals with the ApoE e4 allele or Presenilin mutations are at risk for heightened and atypical APP cleavage, leading to APP-A accumulation, aggregation, and fibril development, which is associated with elevated rates and familial instances of AD.

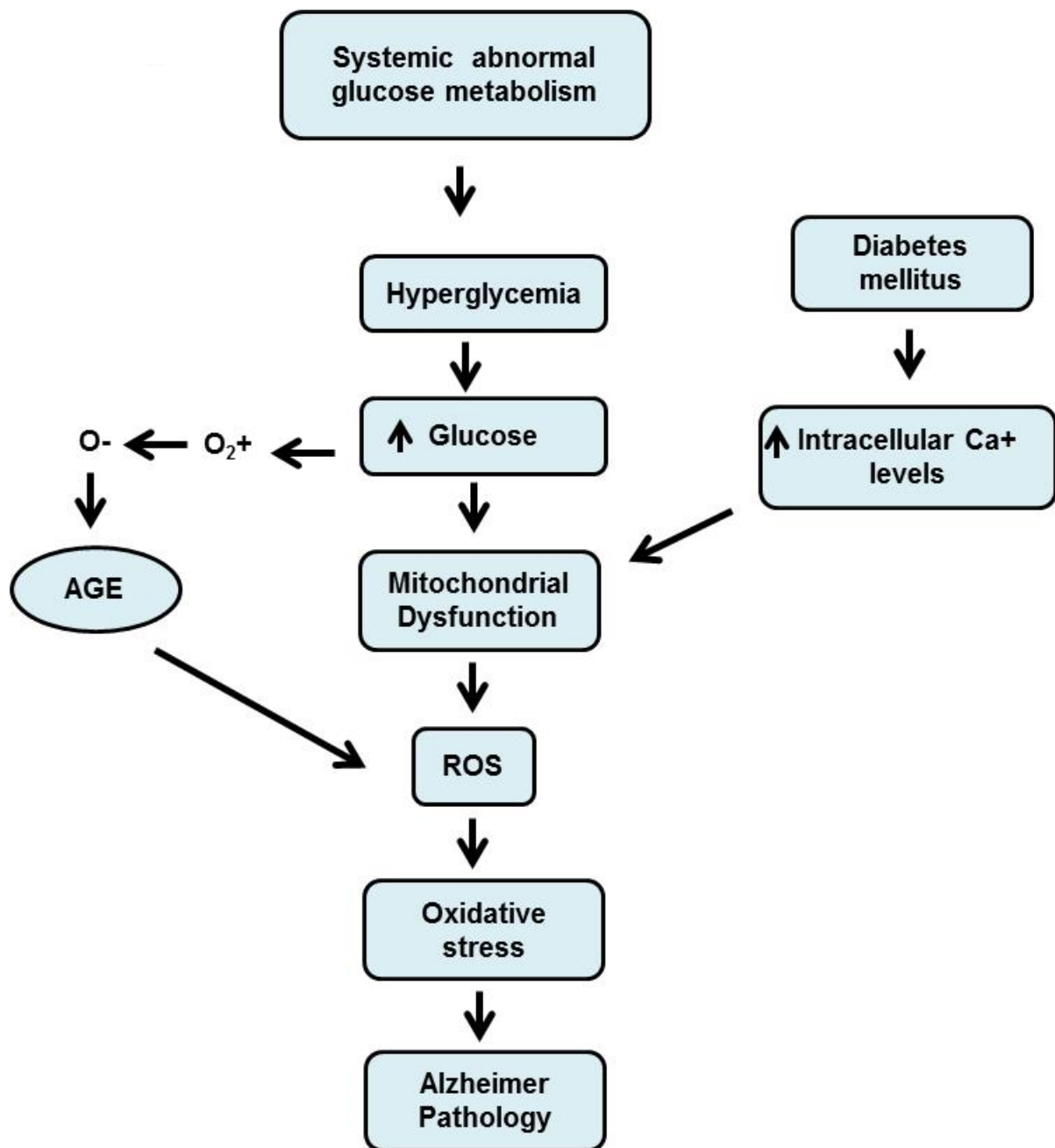


Figure 4. Figure illustrates how hyperglycemia induces AD like pathology through mitochondrial dysfunction, oxidative stress, calcium overload. Oxidative stress will then lead to Alzheimer's Disease pathology.

The mitogen-activated protein kinase (MAPK) pathway is a highly conserved signaling network that processes extracellular signals like growth factors, cytokines, oxidative stress, and metabolic changes into intracellular responses that control cell survival, proliferation, differentiation, and immune function. Among the three primary MAPK families—extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinases (JNKs), and p38 MAPKs—p38 and JNK are notably responsive to stress signals and inflammatory substances. In hyperglycemia, prolonged increases in glucose levels lead to an overproduction of ROS, such as hydrogen peroxide (H_2O_2), which serve as secondary messengers to stimulate both protein kinase C (PKC) and upstream kinases like the MAPK kinase (MKK) family. Phosphorylation events that depend on PKC enhance MAPK signaling, resulting in the activation of p38 MAPK and JNK, which subsequently adjust transcription factors such

as NF- κ B and AP-1, facilitating the expression of pro-inflammatory cytokines (e.g., TNF- α , IL-1 β , IL-6) and adhesion molecules that worsen vascular and neuronal inflammation. Moreover, hyperglycemia increases the expression of Src homology region 2 domain-containing phosphatase-1 (SHP-1), which is a negative regulator of receptor tyrosine kinase signaling. Uncontrolled SHP-1 removes phosphate groups from the platelet-derived growth factor receptor- β (PDGFR- β), hindering downstream survival mechanisms like PI3K/Akt and leading to apoptosis in endothelial and neuronal cells. At the same time, the buildup of advanced glycation end products (AGEs) enhances oxidative stress and MAPK activation by interacting with the receptor for AGEs (RAGE), establishing a detrimental cycle of ROS generation, kinase activation, and neuroinflammatory signaling. Together, these mechanisms connect metabolic imbalance in diabetes to neuronal damage, synaptic impairment, and the advancement of neurodegenerative diseases like Alzheimer's [63–67]. Adiponectin, a protein hormone secreted by white adipocytes, regulates insulin sensitivity, fatty acid oxidation, and glucose homeostasis while exerting anti-inflammatory effects. It acts through AdipoR1 and AdipoR2 receptors, activating AMPK and other signaling pathways to enhance glucose uptake, improve insulin sensitivity, and maintain metabolic and energy homeostasis [68–70].

In T2DM, gene mutations and transcription factors are crucial in making patients susceptible to AD by linking metabolic issues to neurodegenerative processes. Transcription factors like NF- κ B, FOXO, and CREB are dysfunctional in T2DM: NF- κ B remains continuously activated by high blood sugar and advanced glycation end products (AGEs), promoting proinflammatory gene expression and ongoing neuroinflammation; FOXO transcription factors, typically protective against oxidative stress, become inappropriately activated during insulin resistance, resulting in pro-apoptotic signaling; and CREB, vital for learning and memory, is hindered by defective insulin/PI3K/AKT signaling, leading to diminished synaptic plasticity. Other regulators such as PPAR γ and Nrf2, which typically mitigate oxidative stress and inflammation, are functionally compromised, intensifying neuronal susceptibility. At the same time, gene mutations associated with familial or sporadic AD—including those in APP, PSEN1, and PSEN2 (which lead to abnormal amyloid precursor protein processing and increased A β plaque formation)—interact with metabolic stress from T2DM to worsen the pathology. Moreover, the APOE ϵ 4 allele, the most significant genetic risk factor for late-onset AD, exacerbates insulin resistance, hinders A β clearance, and hastens lipid dysregulation in individuals with diabetes. Variants in IDE are essential, as diminished IDE activity in T2DM obstructs insulin and A β degradation, resulting in their harmful buildup. Altered transcriptional regulation combined with mutations in susceptibility genes establishes a feedback loop of insulin resistance, inflammation, amyloid accumulation, and tau hyperphosphorylation, thus clarifying the increased risk and severity of Alzheimer's disease in patients with type 2 diabetes mellitus [71–79].

3.4. Potential Therapeutic Strategies and Approaches

Adipose tissue hormones, including leptin, adiponectin, and resistin, collectively known as adipokines, regulate body metabolism, and their dysregulation, particularly elevated leptin and resistin levels in obesity, promotes insulin resistance (IR) and contributes to T2DM. Hyperglycemia-induced ROS production, driven by oxidative stress, is a critical mechanism in T2DM pathogenesis, exacerbating disease progression, while insulin-sensitizing interventions may mitigate T2DM through multiple pathways [80,81]. The pathophysiology of diseases linked to diabetes mellitus is largely influenced by deregulation of the antioxidant defense system and an imbalance in the generation of reactive oxygen species. Therefore, controlling oxidative stress may help prevent diabetes mellitus and other neurodegenerative illnesses, either by increasing the body's natural antioxidant

system or by preventing oxidative stress. According to earlier research, administering anthocyanins derived from wild Chinese blueberries to pancreatic β -cells significantly decreased ROS and increased the body's natural antioxidant defense system, which in turn controlled the glucolipotoxicity brought on by hyperglycemia. In streptozotocin-induced diabetic rats, anthocyanins were shown to reduce oxidative stress by lowering malondialdehyde levels and restoring the activities of key antioxidant enzymes such as superoxide dismutase and catalase [82–88]. Rat studies revealed that anthocyanin-rich grape-bilberry juice could lower leptin and resistin levels. Furthermore, it was demonstrated that grape-bilberry juice increased the percentage of polyunsaturated fatty acids and decreased the amounts of SFAs in rat plasma. The anthocyanin rich fruits and vegetables are listed in Figure 5.



Figure 5. Natural dietary Anthocyanin sources. Various fruits and vegetables are rich sources of natural dietary anthocyanin. Horizontally from top left to bottom right: Grapes, Grapefruits, Blueberries, Strawberries, Cranberry, Watermelons, Eggplants, Peaches, Avocadoes.

Several studies indicated that anthocyanin could significantly prevent metabolic disorders including IR and T2DM. Since beneficial bacteria in the gut ferment complex carbohydrates produce short-chain fatty acids (SCFAs) and contribute to the synthesis of various vitamins and amino acids, increasing the number of beneficial bacteria and controlling gut dysbiosis is another strategy that may address T2DM-associated complications. It is widely reported that anthocyanins can raise the concentrations of gut-microbiome supportive bacteria like *Lactobacillus-Enterococcus* and *Bifidobacterium*. Emerging evidence indicates that hyperglycemia, glucose intolerance, and insulin resistance are defining features of T2DM, where persistent hyperglycemia promotes neuroinflammation and oxidative stress, thereby triggering neuronal apoptotic pathways and contributing to neurodegeneration; both oxidative stress and neuroinflammation are also central to the pathogenesis of AD (Tables 1 and 2).

Table 1. Comparative table of therapeutic strategies.

Therapeutic Strategy	Mechanism of Action	Key Benefits	Challenges/Limitations	Examples
Insulin-based (e.g., intranasal insulin, insulin sensitizers)	Enhances central insulin signaling, restores PI3K/AKT pathway, improves glucose utilization, reduces tau phosphorylation	Improves memory, synaptic plasticity, and energy metabolism; bypasses peripheral resistance with intranasal delivery	Variable efficacy in clinical trials; risk of hypoglycemia (systemic); requires frequent dosing	Intranasal insulin, metformin, pioglitazone
Anti-inflammatory drugs	Inhibit NF-κB activation, reduce microglial/astrocytic activation, suppress cytokine release (IL-1β, TNF-α)	Decrease neuroinflammation, protect synapses, may slow progression of neurodegeneration	Limited long-term efficacy; side effects (GI bleeding, immune suppression); mixed clinical trial results	NSAIDs (ibuprofen, naproxen), TNF-α inhibitors, minocycline
Antioxidants	Neutralize ROS, enhance mitochondrial function, activate Nrf2/ARE signaling	Reduce oxidative stress, prevent mitochondrial damage, improve neuronal survival	Limited BBB penetration for many antioxidants; inconsistent clinical outcomes	Vitamin E, coenzyme Q10, resveratrol
Anthocyanins (polyphenolic antioxidants)	Multifunctional: antioxidant, anti-inflammatory, insulin-sensitizing; modulate PI3K/AKT, inhibit Aβ aggregation and tau phosphorylation	Broad action on metabolism and neuroprotection; improve insulin sensitivity, glucose homeostasis, cognition; natural and safe	Low bioavailability, rapid metabolism, lack of standardized dosing; need for large-scale clinical trials	Blueberry anthocyanins, blackcurrant extract, purple corn anthocyanins

Table 2. The benefits and challenges of anthocyanins versus FDA-approved drugs for Alzheimer’s Disease (AD).

Category	Anthocyanins (Natural Compounds)	FDA-Approved AD Drugs (Donepezil, Rivastigmine, Galantamine, Memantine, Lecanemab, Aducanumab)
Primary Mechanism	Antioxidant, anti-inflammatory, insulin-sensitizing, modulation of PI3K/AKT, inhibition of Aβ aggregation and tau hyperphosphorylation	Symptomatic cholinesterase inhibition (donepezil, rivastigmine, galantamine); NMDA receptor antagonism (memantine); Aβ clearance via monoclonal antibodies (lecanemab, aducanumab)
Target Pathology	Broad: oxidative stress, neuroinflammation, insulin resistance, mitochondrial dysfunction, Aβ/tau pathology	Narrow: cholinergic deficits, glutamate excitotoxicity, or amyloid deposition
Evidence (Preclinical vs. Clinical)	Strong preclinical evidence (in vitro, in vivo models of T2DM-AD); limited but growing human data	Extensive clinical trial evidence leading to FDA approval, though effects are modest (except newer anti-amyloid therapies with mixed results)

Table 2. Cont.

Category	Anthocyanins (Natural Compounds)	FDA-Approved AD Drugs (Donepezil, Rivastigmine, Galantamine, Memantine, Lecanemab, Aducanumab)
Cognitive Benefits	Improves memory and learning in animal models; some human trials show better cognition and glucose metabolism	Provides modest symptomatic cognitive improvement (cholinesterase inhibitors, memantine); amyloid antibodies slow cognitive decline slightly
Metabolic Effects	Improves insulin sensitivity, glucose homeostasis, and mitochondrial function (highly relevant for T2DM-AD)	No direct metabolic benefit
Safety Profile	Generally safe, dietary origin, few side effects	Can cause nausea, bradycardia (cholinesterase inhibitors), dizziness, GI issues, infusion reactions, brain swelling/bleeding (antibodies)
Accessibility	Widely available in diet and supplements; cost-effective	Prescription only; antibody therapies are extremely expensive
Challenges	Low bioavailability, variable absorption, lack of standardized dosing, limited large-scale clinical trials	Modest efficacy in slowing disease progression; some drugs controversial; high cost and safety risks (especially with biologics)
Translational Potential	Promising as adjunct therapy or preventive strategy, especially in diabetes-mediated AD	Established for symptom management; newer drugs aim at disease modification but remain debated

Vitamins with antioxidant properties, such as B complex, C, and K, and anthocyanins regulate glucose metabolism, reduce hyperglycemia, and lower the risk of T2DM in prediabetic individuals while mitigating AD pathogenesis and diabetes-induced neuroinflammation [89–98]. Additionally, anthocyanins enhance insulin sensitivity, improve pancreatic β -cell function, and inhibit insulin resistance-driven dysregulation of insulin-degrading enzyme (IDE), which impairs A β clearance and exacerbates AD-related neurodegeneration [99–115].

Anthocyanins mitigate AD pathology by acting as potent antioxidants, scavenging reactive oxygen species (ROS), enhancing endogenous antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione peroxidase), and suppressing neuroinflammation through inhibition of microglial activation and pro-inflammatory cytokine production via NF- κ B and MAPK pathway modulation. They also reduce A β accumulation by inhibiting β -secretase (BACE1) activity, promoting clearance via IDE and neprilysin, attenuating tau hyperphosphorylation through kinase regulation (e.g., GSK-3 β , CDK5), and preserving mitochondrial function, synaptic plasticity, neurotrophic signaling (e.g., BDNF/TrkB), cerebral blood flow, and insulin sensitivity to mitigate cognitive decline [116–118].

The pharmacokinetics of anthocyanin metabolites are central to understanding their therapeutic potential in AD and T2DM. After oral ingestion, anthocyanins are rapidly absorbed in the stomach and small intestine, though their parent forms show poor bioavailability (<1% of intake detected in plasma). Instead, the majority undergo extensive metabolism by intestinal enzymes, phase II conjugation (methylation, glucuronidation, sulfation), and colonic microbiota degradation into smaller phenolic acids (e.g., protocatechuic acid,

ferulic acid, vanillic acid). These metabolites, instead of the whole anthocyanins, primarily explain their systemic biological effects. Pharmacokinetic research indicates that intact anthocyanins reach peak plasma concentrations within 1–2 h, while microbial metabolites emerge later and last longer, providing continuous bioactivity. Significantly, various metabolites derived from anthocyanins have the ability to penetrate the blood–brain barrier, where they influence PI3K/AKT signaling, decrease amyloid- β aggregation, and inhibit neuroinflammation associated with AD. Simultaneously, peripheral metabolites enhance insulin sensitivity, block α -glucosidase, promote GLUT4 translocation, and decrease oxidative stress, which are vital for managing DM. Nonetheless, variation in absorption, swift metabolism, and unique differences in gut microbiota makeup present significant obstacles for uniform pharmacological effects. Approaches like nanoparticle transport, combined use with stabilizers, and dietary enhancement are being investigated to boost anthocyanin bioavailability, thus increasing their practical potential for addressing AD and DM [118–122].

Lipopolysaccharide (LPS) from Gram-negative bacteria during gut dysbiosis triggers systemic inflammation, pancreatic β -cell dysfunction, insulin resistance, and elevated cytokines, which cross the blood–brain barrier to promote A β pathology, neuroinflammation, and neuronal loss in AD. Daily anthocyanin consumption counteracts these effects by fostering beneficial gut microbiota, suppressing LPS-induced inflammation, enhancing insulin sensitivity via AMPK activation, and inhibiting AD pathogenesis by reducing β -secretase activity and tau hyperphosphorylation [123–135].

Anthocyanins have demonstrated considerable therapeutic promise in both in vitro and in vivo diabetes-mediated AD models, attributable to their noted antioxidant, anti-inflammatory, and neuroprotective characteristics. In vitro research involving neuronal and glial cultures subjected to elevated glucose or A β reveals that anthocyanins decrease oxidative stress, diminish NF- κ B-driven inflammatory signaling, and prevent tau hyperphosphorylation, thus maintaining synaptic integrity and cell survival. They further regulate insulin signaling pathways, recovering PI3K/AKT activity compromised by diabetic states. In vivo, anthocyanin supplementation in diabetic or transgenic AD animal models enhances cognitive function, decreases amyloid plaque accumulation, and hinders neuroinflammation by reducing microglial activation and cytokine production. Moreover, anthocyanins boost insulin sensitivity, support glucose regulation, and enhance mitochondrial performance, which together alleviate the metabolic and neurodegenerative issues connecting T2DM to AD pathology. These results emphasize anthocyanins as a versatile natural approach with possible applications for neurodegeneration linked to diabetes [136–138].

Anthocyanins exhibit comparatively low oral bioavailability due to their instability at physiological pH, swift metabolism in the intestine and liver, and additional degradation by gut microbiota; generally, less than 1% of the consumed parent compounds are present in plasma, with their conjugated and microbial metabolites constituting the majority of systemic activity. Nonetheless, both intact anthocyanins and their metabolites have been identified in the brain, suggesting a restricted yet meaningful potential to penetrate the blood–brain barrier (BBB), where they produce antioxidant, anti-inflammatory, and neuroprotective effects pertinent to AD. While effective dosage is still not standardized, animal studies frequently utilize 50–500 mg/kg/day, whereas human trials commonly use 300–600 mg/day of anthocyanin-rich extracts (such as those from blueberries or blackcurrants), which have demonstrated benefits in memory, glucose metabolism, and vascular function. Anthocyanins are regarded as safe and generally well accepted, with few documented adverse effects; mild stomach upset or diarrhea may happen at elevated supplemental amounts. The primary issues are their low bioavailability and individual

variability, which has led to investigations into nanoparticle formulations and combined dietary approaches to improve their clinical effectiveness [120,139,140].

Intranasal insulin, GLP-1 receptor agonists, and anti-inflammatory medications have arisen as potential treatment options for T2DM-related AD. Intranasal insulin transcends the blood–brain barrier and directly boosts central insulin signaling, enhancing synaptic plasticity, glucose usage, and memory performance while decreasing tau phosphorylation and A β accumulation. GLP-1 receptor agonists like liraglutide and exenatide improve insulin sensitivity in the periphery while also providing neuroprotective benefits by stimulating PI3K/AKT signaling, boosting neuronal survival, lowering oxidative stress, and aiding in amyloid clearance. Simultaneously, anti-inflammatory drugs—such as NSAIDs, TNF- α inhibitors, and new microglial modulators—address chronic neuroinflammation caused by insulin resistance related to T2DM and advanced glycation end products, consequently reducing NF- κ B activation, cytokine secretion, and synaptic damage. Collectively, these methods seek to address the metabolic, inflammatory, and signaling disruptions linking T2DM and AD, providing a comprehensive strategy to slow or avert neurodegeneration in individuals with diabetes [141–143].

Anthocyanins, pigmented flavonoids abundant in berries and grapes, are favored over other polyphenols for their potent antioxidant and anti-inflammatory properties, ability to cross the blood–brain barrier for neuroprotection, and broad metabolic benefits, including enhanced vascular function, glucose homeostasis, and mitochondrial health. Their accessibility in common dietary sources and roles as UV-protective and signaling molecules further enhance their therapeutic potential for cognitive health and metabolic disorders [144–146].

4. Conclusions

Prediabetes signifies a transitional phase between normal glucose processing and explicit Type 2 Diabetes Mellitus. During this stage, blood glucose levels can stay within the normal limits because of compensatory hyperinsulinemia, since pancreatic β -cells enhance insulin release to counteract insulin resistance in peripheral tissues like muscle, liver, and adipose tissue. Despite the maintenance of normoglycemia, the increased demand for insulin puts pressure on β -cells, ultimately resulting in their dysfunction and failure. With time, the failure of β -cells to maintain compensatory secretion leads to poor glucose tolerance and the advancement to clinical T2DM.

T2DM continues to be a significant worldwide health issue, strongly associated with inactive lifestyles, unhealthy eating patterns, and metabolic disorders that make individuals more susceptible to neurodegenerative problems like AD. Increasing data underscore the significance of gut microbiota and metabolites from nutrients in sustaining metabolic and neurological well-being, whereas dysbiosis and oxidative stress worsens disease progression. Among natural phytonutrients, anthocyanins have demonstrated notable potential owing to their capacity to lessen oxidative stress, regulate inflammatory pathways, improve endogenous antioxidant defenses, and promote metabolic equilibrium. Crucially, their neuroprotective effects could reduce the increased likelihood of dementia and AD in individuals with diabetes. Therefore, consistently consuming fruits and vegetables high in anthocyanins could serve as a safe and readily available preventive approach to combat metabolic and neurodegenerative diseases linked to diabetes. Ongoing research is vital to clarify the molecular processes driving these effects and to convert these discoveries into successful treatment strategies [87,147,148].

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