Journal of Population Therapeutics & Clinical Pharmacology

REVIEW ARTICLE
DOI: 10.53555/jptcp.v29i02.6486

NATURE'S REMEDY: PLANT-BASED THERAPIES FOR DIABETIC ALZHEIMER'S

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Abstract
Type 2 diabetes and Alzheimer's disease, when both conditions occur simultaneously, greatly worsen neurodegeneration and cognitive decline, making diabetic Alzheimer's disease a difficult healthcare issue to solve. Medicine derived from plants is gaining attention as a potential new treatment option due to its abundance of bioactive chemicals that have anti-diabetic and neuroprotective effects. This analysis focuses on the many ways in which chemicals found in plants have the potential to treat Alzheimer's disease in people with diabetes. Many chemicals found in plants have the potential to influence key pathways that are involved in the development of diabetes and Alzheimer's disease. Insulin signalling pathways, neuroinflammation, and amyloid-beta metabolism are all part of this category. Experts in the field may discover new ways to help diabetics slow down cognitive loss and neurodegeneration by using the wide variety of bioactive substances found in plants.

Keywords: Diabetes, Alzheimer's Disease, Type-3 diabetes, bioactive compounds, plant-based medicine, flavonoids, polyphenols, alkaloids

1. Introduction

The rising incidence of type 2 diabetes, a complicated chronic disease associated with ageing, is a major cause for public concern. Diabetes mellitus affects around 400 million people globally, and experts predict that figure will rise sharply over the next 30 years. [1,2] Type 2 diabetes, which is characterised by insulin resistance in cells and chronic inflammation, speeds up the ageing process and increases the risk of early death and morbidity.[3] Diabetes mellitus (T2DM) is now known to have serious consequences for the brain, including an increased likelihood of cognitive decline and dementia. One out of ten instances of dementia globally may be caused by type 2 diabetes, and the likelihood of dementia over time is roughly doubled in people with T2DM.[4,5] The reason why these chronic disorders are so closely related in terms of prevalence is because diabetes and dementia both cause brain damage. Among such characteristics, the most significant ones include deficient insulin sensitivity, Aβ buildup tau hyper-phosphorylation, vascular damage, and inflammation (Figure 1).

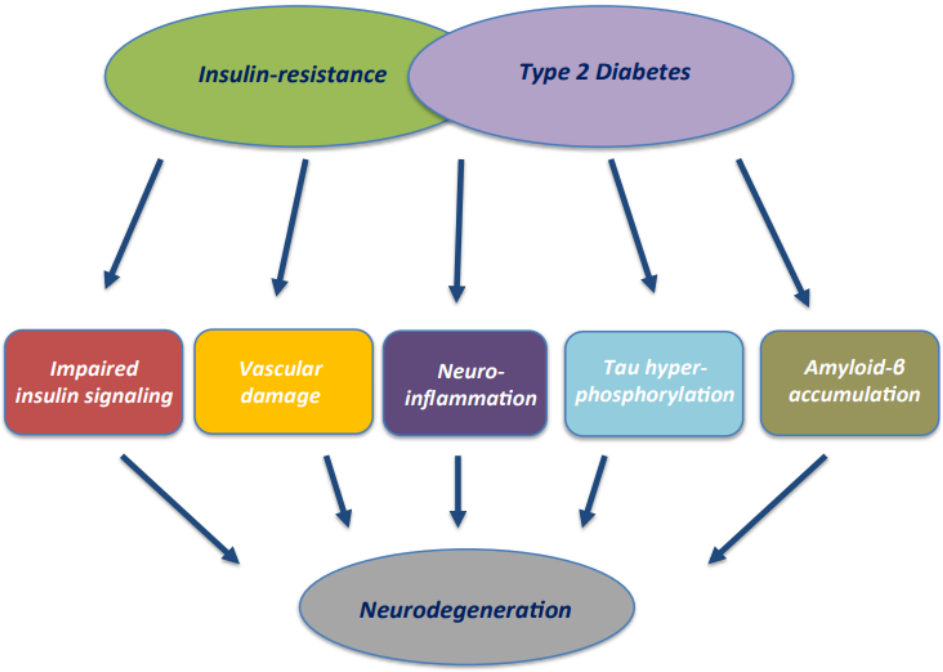

Figure 1: Link between T2DM and Neurodegeneration

2. Pathology

2.1 Impaired glucose metabolism in brain:

There must be a basic underlying mechanism that causes neurodegeneration, given the consistently aberrant clinical, pathophysiological, and neuropathological features of the Alzheimer's disease progression. Integrating apparently unrelated diseases using evidence-based methods to establish their commonness will be crucial in our rethinking of its idiopathic underpinnings. Although deficiencies in energy metabolism in the brain, especially glucose utilisation in Alzheimer's disease, have been known for a while, newer methods like PET imaging using (18)F-fluoro-deoxyglucose (FDG) have made it possible to reliably identify neurodegeneration in its earliest phases. Also, compared to healthy control brains, AD brains show an overall decline in glucose metabolism, which is one of the most important discoveries from several research.[6] These findings are noteworthy because glucose metabolism is essential for the majority of brain activities, including the cognitive, behavioural, and morphological processes that are most severely affected by Alzheimer's disease. The metabolic abnormalities related to the brain's use of glucose and oxygen deteriorate as the disease progresses.Due to their key role as fuels, deficiencies in their utilisation lead to brain malnutrition (Figure 2). As the illness progresses, insulin's activities progressively become compromised, which plays a significant role in the metabolic dysfunction of the brain in Alzheimer's disease.[7-9]

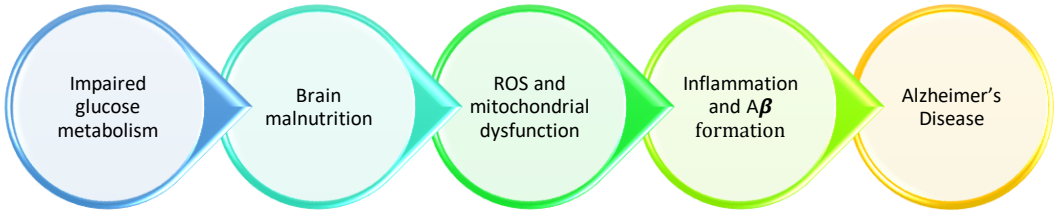

Figure 2: Role of insulin/ IGF resistance in the pathology of AD

2.2 Insulin and Insulin-Like Growth Factor (IGF) dysfunctioning

Brain areas prone to Alzheimer's disease neurodegeneration have high levels of insulin, IGF-1, and their receptors.[10] Dyer et al. [11] found that networks of insulin and IGF-1 signalling control neuronal survival, adaptability, growth, metabolism, and restoration, and that these networks impact cognitive processes, motor functions, behaviour, and memory. Research has shown that the amount of insulin in the brain and cerebrospinal fluid (CSF) are lower in the initial and intermediate forms of Alzheimer's disease and that administered insulin enhances cognition and working memory.[12, 13] These results emphasise the etiopathic significance of insulin related to metabolic impairment in AD.Furthermore, numerous experimental findings have proposed that insulin and Aβ may have opposing regulatory functions. These findings are partially corroborated by human research that indicate that insulin and IGF-1 deficits are associated with elevated Aβ and AGE levels in the brain and that using insulin improves Aβ clearance.[14, 15] Pathology in both white and grey matter structures might be caused by deficits in insulin or IGF-1, as both trophic factors control survival and other activities of neuronal and oligodendroglial cells.[16] Despite the limited research on the correlation between insulin and IGF signalling impairments and pathology in white matter and oligodendrocytes in AD patients, there is abundant evidence that both grey and white matter structures experience shrinkage and neurodegeneration as the disease advances.[17]

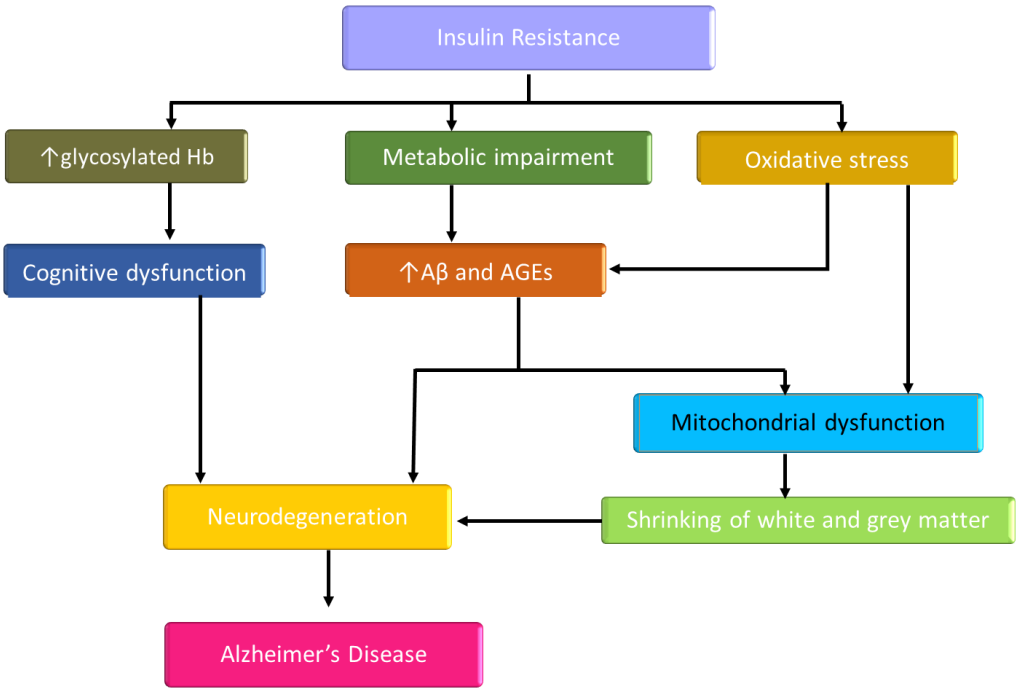

Figure 3: Other pathological mechanisms of T2DM which contribute to AD

2.3 Oxidative stress:

A state of oxidative stress (OS) is reached when the generation of reactive nitrogen species (RNS) and reactive oxygen species (ROS) is out of sync with inflammatory mechanisms that are meant to neutralise these harmful free radicals. It is reasonable to designate AD as Type 3 Diabetes since both AD and T2DM are classic cases of disease processes caused by OS.[18] Oxidative stress is especially harmful to the brain's lipid-rich membranes. Protein structural changes, including those in amyloid beta and tau, may contribute to many forms of cell damage.[19]

3. Treatment modalities

3.1 Pharmacological treatment

Metfromin: Findings supporting its usage in AD are contentious. Metformin, according to preclinical studies, passes the blood-brain barrier (BBB) and accumulates in several components of the central nervous system (CNS) at a fast pace. The molecular and clinical alterations exhibited in AD neurons

may be prevented by treating neuronal cell lines with metformin, according to in vitro tests conducted under extended hyperinsulinemic settings.[20]

Thiazolidinedione: There have been mixed results from trials evaluating rosiglitazone and pioglitazone for the treatment of Alzheimer's disease. Evidence suggests that PPARγ expression is higher in the temporal cortex of AD patients compared to control subjects, which raises the possibility of their application in AD. Additionally, preclinical research has demonstrated that PPARγ agonists can improve AD-related pathology, likely by lowering the expression of inflammatory genes and the burden of amyloid plaque.[21]

GLP-1 RA: The neuroprotective benefits of GLP-1 analogues in Alzheimer's disease have been investigated in many preclinical investigations, and the findings have been encouraging. Cognitive decline, neuronal death, and hippocampal synaptic plasticity degradation were all averted when AD transgenic mice were given liraglutide systemically for 8 weeks. In addition, litaglutide attenuated the inflammatory response as assessed by activated microglial cells and decreased amyloid plaque formation by 40-50%.[22]

DPP4 inhibitors: The effects of taking saxagliptin and vildagliptin orally were shown to reduce Aβ deposition, tau phosphorylation, and inflammatory markers, while increasing GLP-1 levels in the hippocampus and improving memory retention.[23] At this time, there is a lack of clinical evidence on the possible effects of gliptins in Alzheimer's disease patients.

Amylin: Memory, mood, and anxiety may all be influenced by amylin, which has the ability to pass the blood-brain barrier. Preclinical evidence in AD mice models suggests that pramlintide treatment may enhance cognition, decrease oxidative stress, and decrease neuroinflammation; also, amylin plasma levels are dramatically decreased in AD patients.[24]

Intranasal insulin: Insulin that is administered intranasally has a number of benefits, including improved insulin signalling in the brain, faster insulin delivery through the olfactory and trigeminal perivascular routes, and slower release via the olfactory bulb axonal transport. Insulin and insulin signalling are both diminished in Alzheimer's disease brains.[25] Crucially, neither blood insulin levels nor glucose levels are negatively impacted by intranasal insulin.

Table 1: Neuroprotective mechanisms of antidiabetic drugs

Compound	Potential mechanism	Reference
DA5-CH	Brings theta rhythm back to normal and decreases tau phosphorylation	[26]
DA-JC1	Counteracting disruptions to the circadian rhythm caused by $A\beta_{31-35}$	[27]
DA5-CH	Enhancement of hippocampus synaptic plasticity and PI3K/AKT signalling pathway activation	[28]
DA-CH3	Lower ER damage, decreased apoptotic signalling, and decreased brain amyloid plaque burden	[29]
Insulin	Reducing insulin receptors and preventing synapse loss caused by Aβ oligomers, while improving ER stress caused by PKR.	[30, 31]
Insulin	Cognitive function is impacted by lower insulin sensitivity in Alzheimer's disease patients who are not ε4 carriers.	[32]
Insulin	Following acute insulin treatment, verbal memory was improved in MCI AD ε4 individuals, but in ε4 carriers, it remained unchanged.	[33, 34]
Insulin	Optimal dosages of insulin for intramuscular administration improved cognitive performance in individuals with mild cognitive impairment (MCI) and early-stage Alzheimer's disease ("AD").	[35]

Insulin	Impaired working memory was only seen in female patients after therapy.	[36]
Liraglutide	Decreased tau phosphorylation; c-AMP dependent protection of insulin receipt and synaptic loss preservation	[37]
Liraglutide	Enhancement of memory impairments in the fear conditioning and new object recognition tests	[37]
Liraglutide	Improved long-term potentiation (LTP), decreased microglial activation, decreased Aβ plaque burden, and restored memory impairments in the object recognition test and Morris water maze.	[38]
Exendin-4	Reduced inhibitory phosphorylation on INK Ser312 and Ser66 and restored activating phosphorylation on IRS1 Tyr 465	[39]
Exendin-4	Cognitive enhancement in the Morris water maze; decreased amyloid plaque	[39]
Exedin4-Liraglutide	decrease of eIF2α phosphorylation	[31]
GLP-1 Exendin-4	Minimising damage to the nervous system	[40]
Rosiglitazone	Decreased levels of Aβ and improvement in memory performance on the Morris water maze and object recognition tests	[41]

3.2 Plant-based treatment

There are major health and economic concerns caused by the increasing frequency of diabetes mellitus and Alzheimer's disease on a worldwide scale. A growing body of research [42, 43] indicates that metabolic diseases, including diabetes, might worsen or possibly cause the neurodegenerative conditions that are typical of Alzheimer's disease. Because of this confluence of factors, the Alzheimer's disease subtype characterised by insulin resistance and metabolic dysfunction in the brain is now known as "Type-3 diabetes".[44] Bioactive chemicals found in food and plants contain antioxidant, anti-inflammatory, and neuroprotective characteristics that may help reduce the severity and course of diabetes and other neurological disorders.

3.2.1 Alkaloid:

Research on the pharmacological effects of trigonelline, a key alkaloid in fenugreek, has been more extensive than that of other fenugreek components, particularly in relation to CNS disorders and diabetes. It slows the onset of diabetic neuropathy in the ears and the clumping of blood platelets. Zhou et al. [45] found that it influences β-cell regeneration, insulin production, enzyme activity associated with glucose metabolism, ROS, axonal extension, and neuron excitability. Berberine (BBR) is an isoquinoline alkaloid that has shown promise in a number of studies on Alzheimer's disease. In particular, it has reduced higher levels of fasting blood glucose, triglycerides, total cholesterol, and glycosylated serum protein in diabetic rats, improved the number of cells that tested positive for TUNEL, and repaired impairments in neurons. In addition, Xuan et al. [46] found that BBR administration decreased translation of ER stress-related proteins and mRNAs. The alkaloids nuciferine and norcoclaurine, derived from the Nelumbo nucifera plant, greatly decrease fasting blood glucose levels and AChE activity in the brain, restoring cognitive function, and regulating body weight. Therefore, the plant extract has potential for the management of neurological diseases and type 2 diabetes.[47] The cognitive abnormalities in mice with type 2 diabetes were improved by total alkaloids from C. chinensis (TAC). In addition, the diabetic rats exhibited significant Aβ accumulation, neuronal damage, and loss, all of which may be ameliorated with TAC therapy, according to immunohistochemical and histopathologic analyses.[48]

3.2.2 Terpenes

Sesquiterpenes including β-caryophyllene, germacrene-D, and caryophyllene oxide are present in essential oils extracted from S. galatica (SGEOs), along with monoterpenes like α- and β-pinene.

Inhibitory actions against acetylcholiesterase, butrylcholinesterase, α-amylase, and α-glucosidase suggest that SGEOs may be useful in treating type 2 diabetes and Alzheimer's disease.[49] The peel of a Diamante citron, which contains sesquiterpenes and monoterpenes including limonene and γ-terpinene, shown its ability to lower blood sugar levels and inhibit the enzyme known as cholinesterase. Its primary mechanism of action is the restoration of antioxidant function, which may halt or slow the development of certain degenerative illnesses, such as diabetes and Alzheimer's.[50]

3.2.3 Glycosides

a) Saponin glycosides: The diabetic rats' learning capacity was greatly enhanced by total saponins from Rhizoma Anemarrhenae (TSRA), which also lowered Aβ and TNF-α levels in the cortex and hippocampus, while having a propensity for reducing TNF-α levels in the hippocampus. Reducing Aβ buildup and inflammation in the brain and attenuating main diabetic symptoms are the components that make TSRA effective in preventing cognitive loss in rats associated with diabetes.[51] Sarsasapogenin (sar) reduced neurogenesis and neuronal loss in the hippocampus of diabetic rats while improving their learning and memory abilities. Furthermore, Sar reduced Aβ overproduction caused by increased BACE1 levels in both protein and mRNA, as well as tau hyperphosphorylation resulting from the inhibition of the AKT/GSK-3β cascade.[52] Diascin and protodioscin, the two main saponins of DA-9801, reduced ROS levels while safeguarding cortical primary neurons from hyperglycemia-induced neurotoxicity; this finding suggests that DA-9801 could be useful in treating and delaying the onset of neurodegenerative conditions in patients with diabetes.[53] Increasing neurogenesis and synaptic plasticity, ginsenoside Rb1, a triterpenoid saponin, ameliorates cognitive impairments in diabetic rats, according to recent research.[54] In addition to its anti-diabetic and anxiolytic benefits, recent research suggests that stevioside treatment enhances learning and memory in diabetic rats.[55]

b) Flavonoid glycosides:

Hesperidin: Hisperidin is a glycoside that contains flavonoids and is found in citrus fruits such as grapefruits, oranges, and lemons. Because of its antioxidant, anti-inflammatory, and neuroprotective characteristics, hesperidin has great potential as a treatment for type 3 diabetes. In rats that had been led to diabetes by STZ, hesperidin showed antidepressant effects. These effects were driven by its antioxidant and anti-inflammatory properties, in addition to a boost in regeneration.[56] Research indicated that hesperidin's ability to decrease Aβ deposition and alleviate neuroinflammatory responses might have a role in the improvement of behavioural paramters.[57] Research suggests that hesperidin has the potential to be an effective therapy for both type 2 diabetes and Alzheimer's disease, which might improve the lives of those who suffer from both conditions.

Naringin: Diabetes impairs cognitive abilities like learning and memory, according to research. Naringin, which is connected with a reduction in these abilities, may be an appropriate medication to treat diabetes-associated cognitive decline (DACD). By influencing PPARγ, its neuroprotective, antioxidant, and anti-inflammatory properties may improve DACD.[58] One way that naringin improves cognitive performance in Alzheimer's disease might be via reducing plaque load and increasing glucose absorption through the suppression of GSK-3β activity.[59] According to another research, naringin enhances mental abilities in obese mice generated by a high-fat diet (HFD) in a number of ways. One of these ways is via increasing insulin signalling and decreasing mitochondrial dysfunction via the stimulation of AMPK.[60] According to research, naringenin prevents neurodegeneration by switching Tau hyper-phosphorylation in the brain's hippocampus and cerebral cortex by downregulating GSK-3β activity and serves as an antioxidant and ChE inhibitor regarding cognitive impairment caused by type-2 diabetes.[61, 62]

Quercetin: In experimental models of Alzheimer's disease, trials have demonstrated that quercetin may enhance cognitive performance and diminish the production of amyloid plaques.[63] Furthermore, it has been shown to improve insulin sensitivity and decrease hyperglycemia in models of diabetes.[64] Because of its neuroprotective properties, quercetin enhanced learning and spatial memory in diabetic rats.[65]

3.2.4 Tannins

Proanthocyanidins: It is well acknowledged that proanthocyanidins (PACs) have antioxidant properties and may enhance cognitive abilities. The results showed that rats that received a combination of PACs and insulin showed greater improvements in their memory and spatial learning abilities, as well as better neuronal survival in the prefrontal cortex and pancreatic β-cells, in comparison to rats that received either insulin or PACs separately.[66] PAC therapy ameliorated diabetic encephalopathy pathological alterations in rats by regulating the AGEs/RAGE/NF-κB p65 pathway, a significant factor in this condition.[67]

Ellagic acid: Ellagitannins are hydrolyzable tannins that are abundant in foods such as pomegranates, strawberries, raspberries, walnuts, and wines that have been aged in oak barrels. Ellagic acid (EA) is produced when these substances are hydrolyzed in the intestines. The overexpression of Nrf2 and Bcl-2, inhibition of NF-κB, triggering of CREB, and IRS/PI3K/Akt/GS3Kβ axis are connected with the neuroprotective impact of EA on the hippocampus and memory function of rats.[68] Further research by Kumar et al. [69] found that EA protects rats' memory against STZ-induced PI3-kinase-eNOS signalling disruption.

3.2.5 Carotenoids:

Carotenoids are pigments that give many fruits and vegetables their vibrant colours, including red, orange, and yellow. Some important carotenoids include lutein, beta-carotene, zeaxanthin, lycopene, and astaxanthin. The anti-inflammatory and anti-oxidative properties of these chemicals have made them well-known in the medical field, especially in relation to their protection against neurodegenerative disorders and diabetes.

Beta-carotene: A study conducted by Lim et al. [70] found that diabetic rats that were given beta-carotene supplements had less AChE activity and less vascular dementia. This suggests that beta-carotene may be able to slow the cognitive loss that occurs in Type 3 Diabetes.

Lutein: There is some evidence that lutein may reduce inflammation and slow down neuronal degeneration in the CCT, two complications of diabetes. It greatly reduced the elevated levels of thiobarbituric acid reactive substances (TBARS), caspase-3, tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6 that are caused by diabetes. Another study found that lutein reduced the downregulation of BDNF, NGF, and IGF caused by diabetes.[71]

Zeaxanthin: Researchers found that using zeaxanthin supplements improved cognitive function, decreased blood glucose levels, increased p-AKT levels, decreased levels of cleaved caspase-3, and inhibited NF-κB nuclear transcription in the hippocampus. Additional benefits included increased survival of brain cells. Zeaxanthin may protect brain cells from hyperglycemia via the AKT/NF-κB signalling pathway, which may explain how it improves cognitive deficits associated with diabetes.[72] Another research found that people whose diets included lutein and zeaxanthin had better cognitive function, lending credence to the idea that these antioxidants may have neuroprotective benefits for diabetics.[73]

3.2.6 Polyphenols

Resveratrol (RES): Research suggests that RES may have effects on insulin signalling pathways, blood sugar, and brain function. By enhancing mitochondrial activity, delaying or preventing major pathological markers of Alzheimer's disease (AD), aberrant Aβ, and tau, RES may enhance spatial learning and memory skills in AD. It does this via anti-oxidation, anti-inflammatory, and other mechanisms. These roles are associated with the activation of SIRT1 and insulin-related signalling pathways, which are comparable to its fundamental anti-diabetes process.[74] Researchers have shown that resveratrol improves memory function and decreases brain oxidative damage in diabetic rats.[75] New research suggests that resveratrol may boost synaptic plasticity and decrease oxidative stress, two factors that impair cognitive performance in diabetic rats.[76]

Epigallocatechin Gallate (EGCG): Among the several catechins found in green tea, EGCG stands out as a powerful antioxidant. Because of its capacity to regulate important biological processes, it has shown great promise in a number of medical domains. Research showed that diabetic rats with impaired cognitive function showed considerable improvement after receiving EGCG. Better insulin signalling and less brain oxidative stress were linked to the benefits.[77] By improving mitochondrial

function and lowering oxidative stress, it may help enhance cognitive performance in diabetic mice. To maintain healthy neurons, it is essential to maintain mitochondrial integrity and function, and this is where EGCG comes in.[78] Cognitive performance and brain oxidative stress are both improved by EGCG, according to studies in diabetic rats.[79] Another research found that the antioxidant effects of EGCG significantly improved learning and memory in diabetic rats.[80]

Curcumin: The pathophysiology of Alzheimer's disease may be mitigated by using this turmeric component, which has been demonstrated to suppress amyloid-beta aggregation and tau hyperphosphorylation.[81] There is some evidence that curcumin may improve insulin signalling and decrease inflammation in diabetic animals.[82] According to Miao et al.,[83] diabetic rats that were given curcumin showed a considerable increase in their cognitive performance and a decrease in brain oxidative stress. Supplementing diabetic rats with curcumin enhanced their spatial memory and decreased neuroinflammation, according to recent research.[84]

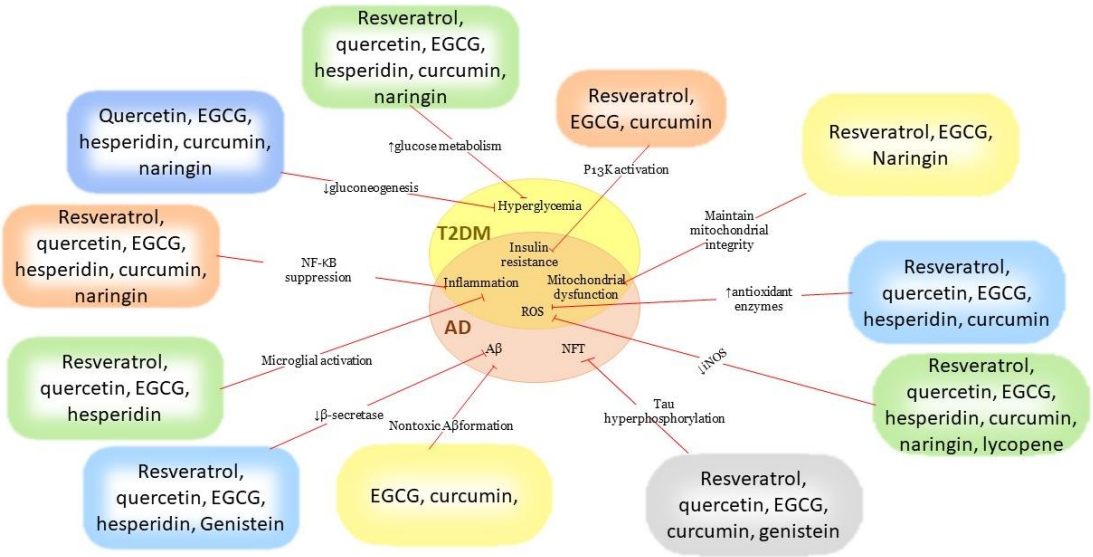

Figure 4: Mechanisms of bioactive compounds in the treatment of common pathologies of T2DM and AD

4. Future prospects:

The possibility of bioactive substances in controlling diabetic Alzheimer's disease is suggested by the encouraging outcomes of preclinical investigations. More study is needed to determine the best doses, the effects over the long term, and any interactions with other medications before these results can be put into clinical settings. The unfulfilled medical demands of those afflicted by this devastating condition can only be met by more study into the curative abilities of plant-based therapies.

Challenges and Considerations

- One factor that can restrict the medicinal potential of bioactive substances is their bioavailability. Improving stability and absorption should be a top priority when developing new formulations.
- Long-term safety and effectiveness studies are essential for determining the chemicals' suitability for human usage.
- One area of study in personalised medicine is the study of individual differences in reaction to bioactive substances. This knowledge may then be used to develop therapies that are both effective and safe for patients.
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5. Conclusion:

Type-3 diabetes, in which diabetes worsens the development and advancement of Alzheimer's disease, has encouraging therapy options in plant-based medicine. The cognitive impairment that comes with type 3 diabetes may be lessened by specific plant-derived chemicals that have anti-inflammatory and neuroprotective effects, according to research. More clinical studies are required

to confirm the effectiveness and safety of plant-based therapies designed to treat type 3 diabetes, but preliminary findings seem promising. The entire promise of plant-based medicine in fighting this complicated ailment can only be realised by optimising dosing regimes and understanding the mechanisms behind their therapeutic benefits.

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