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REVIEW ARTICLE

Advancing Diabetes Treatment: Neuroprotective Roles of Medicinal Plant Extracts

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ABSTRACT
T2DM is a chronic metabolic disorder characterized by resistance to insulin and high blood sugar, which presents with a broad range of complications, extending to impaired cognitive performance. Cognitive decline in patients with T2DM is multifactorial, entailing insulin resistance in the brain, oxidative stress, neuroinflammation, and vascular damage. Current pharmacological interventions aim at glycaemic control, and a minimal likelihood exists of affecting cognitive outcomes while managing T2DM-related cognitive dysfunction remains a huge challenge. To assess the effects of different strategies for managing Type 2 diabetes mellitus on cognitive function and the incidence of dementia. Since monotherapy frequently doesn't work after a while, several medications are required for good glycaemic control. Recent studies have pointed out that combination therapies, a mixture of traditional antidiabetic drugs with medicinal plants, could be a better holistic approach to the management of glycemic levels and cognitive decline. Medicinal plants like curcumin, Ashwagandha, Amla, Jamun, and berberine enhance conventional antidiabetic treatments by providing neuroprotection and improving insulin sensitivity, potentially mitigating cognitive dysfunction in T2DM patients through multiple pathways. This review explores combining conventional antidiabetic drugs with medicinal plants for managing T2DM and cognitive impairment. Key considerations include drug-herb interactions, extract standardization and personalized treatments. It highlights the need for clinical trials to assess such integrative therapy's safety, efficacy, and long-term benefits.
Keywords: *Type 2 diabetes mellitus, cognitive impairment, Combination therapy, Medicinal Plants, Neuroprotection, Insulin resistance.*

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INTRODUCTION

Diabetes mellitus is the most diverting disease that can affect multiple organs in human beings. Diabetes is the most causative end-stage renal disease in the United States and is also a common cause of vision loss, neuropathy, and cardiovascular disease [1]. It is a group of chronic diseases characterized by high blood sugar levels due to the body's inability to produce or effectively use insulin. There are two main types: Type 1 Diabetes: an autoimmune condition where the pancreas produces little to no insulin. It often develops in childhood or adolescence [2]. Type 2 diabetes is more prevalent and often strikes adults. It is linked to obesity, inactivity, and hereditary factors and involves insulin resistance. It has been shown that patients with both type 1 and type 2 diabetes mellitus have cognitive impairments that are related to their condition. Diabetes can have various effects on cognitive abilities. i.e. Blood sugar levels: Variations in blood sugar levels, whether high (hyperglycemia) or low (hypoglycemia), can affect cognitive function and cause issues with memory, focus, and decision-making. ii. Chronic inflammation: The inflammatory processes that impact cognitive performance and brain health are linked to neurodegeneration. iii. Oxidative stress: This condition can be brought on by high glucose levels, which harm neurons and impair cognition [3]. Diabetes has the potential to damage blood vessels, which raises

the risk of stroke and lowers blood supply to the brain, both of which can enhance cognitive loss. Hormonal imbalances brought on by it disturb the balance of hormones that affect cognition, including insulin, which is critical for proper brain function. Dementia and cognitive impairment are more likely to occur in older persons with diabetes, especially in those whose illness has been present longer. The cognitive impairment may also be exacerbated by conditions like obesity and hypertension, which are frequently linked to diabetes. Even with extensive study, the pathogenesis of this problem remains unclear, and the best ways to identify, manage, and prevent cognitive impairment in diabetes need to be discovered [4]. Furthermore, the area of diabetes-related cognitive impairment is still in its infancy. Remember that the processes underlying the relationship between diabetes and cognitive impairment are currently being investigated, despite the fact that there have been several important contributions on the subject and numerous theories based on it [5].

DIABETES AND COGNITIVE FUNCTION

Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) have both been linked to aberrant brain MRI structural and functional features as well as decreased performance on several cognitive function domains [6]. Even in the very early stages of diabetes, cognitive abnormalities can arise, and the metabolic syndrome makes them worse. The kind and severity of cognitive impairment may vary depending on the length of diabetes and glycaemic management, but we are still unable to identify who is most at risk of cognitive impairment. Although a failure in any of the interconnected pathways eventually results in discordance in metabolic signalling, the pathophysiology of cognitive impairment is multifaceted. Because type 2 diabetes is becoming more common and people are living longer, diabetes-related cognitive impairment may pose a significant threat to the need for future health resources. Understanding the disease's pathogenesis and identifying the molecular targets and pathways that might eventually result in more effective treatment. Two of the biggest public health issues facing our aging population are dementia and type 2 diabetes, or diabetes for short. Globally, 374 million people have prediabetes and 463 million adults have diabetes [6]. 50 million individuals have dementia at the same time. Diabetes is linked to vascular damage, which can exacerbate Alzheimer's disease and vascular dementia. Due to its effects on brain blood flow and neurodegeneration, type 2 diabetes has been linked to an increased risk of dementia, according to research. It is estimated that 20% of individuals 65 years of age or older have cognitive impairment, which is frequently a prodromal stage of dementia. Type 2 diabetes is characterized by insulin resistance, which has been linked to dementia and cognitive impairment. Chronic hyperglycemia causes oxidative stress and neuroinflammation, which impede cognitive function. Because of these instances, around one-third will proceed to dementia within five years. Alzheimer's disease is characterized by amyloid-beta buildup and tau phosphorylation, two brain pathologies that diabetes exacerbates. A well-known risk factor for dementia that almost doubles the risk is diabetes (Fig. 1) [7].

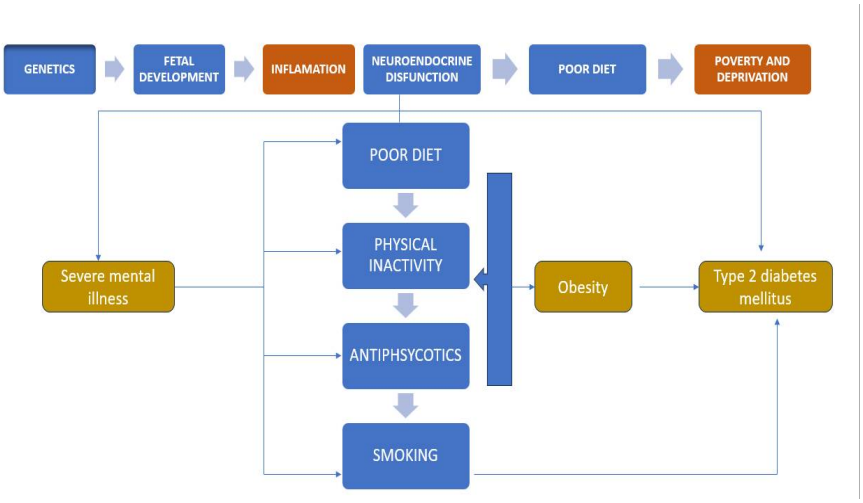

Figure 1: Severe mental illness and Type 2 Diabetes mellitus: Pathology.

DEMENTIA AND ALZIEMERS

When memory, logic, or other cognitive abilities deteriorate, a set of symptoms known as dementia occurs. Dementia can be of several forms and be brought on by a wide range of illnesses. When many

dementia types manifest simultaneously in the brain, it is referred to as mixed dementia. Alzheimer's disease is the most common cause of dementia, accounting for 60-80% of dementia cases. Alzheimer's is a degenerative brain disease that is caused by complex brain changes following cell damage. It leads to dementia symptoms that gradually worsen over time. The most prevalent sign is difficulty recalling new knowledge since the brain region linked to learning is usually affected first by the condition. Intracellular neurofibrillary tangles of hyperphosphorylated tau protein and extracellular depositions of β-amyloid, which constitute the majority of senile plaque, are the neuropathological hallmarks of Alzheimer's disease (AD) [8]. A new research framework focussing on diagnosing AD using three biomarkers was recently revealed by the National Institute on Aging and Alzheimer's Association (NIA-AA) [9]. The biomarkers were categorized into tau and β-amyloid. The disparity between the severity of brain dysfunction and its clinical symptoms is the source of cognitive reserve (CR). Individual vulnerability to age-related brain alterations or AD-related brain neuropathology is taken into consideration by the reserve concept. CR is measured using surrogate lifestyle markers, although they have several innate shortcomings. As we have shown before, the model that represents the entire neuropathology of AD (A-T-N) may also represent the neurodegeneration (A/T/N) and the characteristics of CR in a cross-sectional study protein. Numerous underlying pathophysiological processes may be the cause of the clinical condition of dementia, which is marked by new functional dependency based on gradual cognitive deterioration. The most prevalent of them are frontotemporal lobar dementia (FTLD; 5%), dementia with Lewy bodies (DLB; 5%), vascular dementia (VaD; 20%), and Alzheimer's disease (AD; 50–75%) (Fig. 2) [10]. Their relative rates are best estimates due to the substantial clinical and pathological overlap between these processes 1, 6. Huntingdon's illness, Creutzfeldt-Jakob disease, HIV/AIDS, and multiple sclerosis are less frequent causes (3%) than the others.

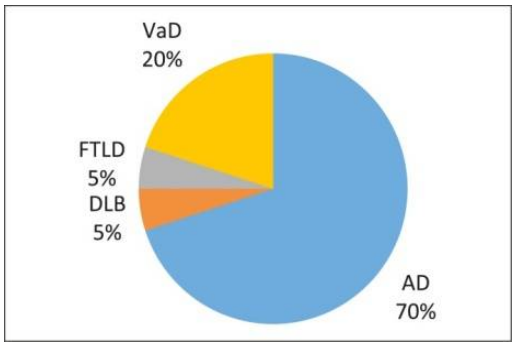

Figure 2: Prevalence of major dementia subtypes. Alzheimer's disease (AD) is the most common form of dementia (70%), followed by vascular dementia (VaD; 20%), dementia with Lewy bodies (DLB; 5%), and frontotemporal lobar dementia (FTLD; 5%). These conditions are associated with various underlying pathophysiological mechanisms, contributing to progressive cognitive decline and functional impairment.

The less common causes (3%) include Huntingdon's disease, Creutzfeldt-Jakob disease, HIV/AIDS, and multiple sclerosis [11]. The clinical characteristics of these illnesses will be discussed first, followed by their pathological aspects. Memory, executive function, language, visuospatial ability, personality, and behavior are the five primary categories into which cognitive deficits important to the diagnosis of dementia can be divided. Any type of dementia will eventually deepen and spread its cognitive deficits, affecting additional domains and increasing functional impairment [11]. Identifying dementias with distinct aetiologies might therefore prove challenging as they progress (Table 1). In the initial phases, nonetheless, the arrangement of noticeable symptoms can aid in determining the most probable underlying pathophysiological mechanism. It is important to look for neuropsychiatric signs. Cognitive deficits can result from depression or be caused by it, and symptoms like delusions and hallucinations are frequently not reported until certain questions are asked [12].

INSULIN RESISTANCE AND DYSREGULATION

Insulin resistance and dysregulation are strongly linked to cognitive impairment in individuals with diabetes. Insulin's cognitive effects depend on brain areas that house insulin receptors (IRs), notably the frontal cortex and the hippocampus [18]. Because IRs are found all across the brain, insulin and insulin-like growth factor 1 can function biologically. Diabetes is characterised by insulin resistance and hyperinsulinemia, which have a deleterious effect on amyloid formation and processing. This results in tau hyperphosphorylation, decreased β-amyloid clearance, and increased intraneuronal β-amyloid

accumulation. Insulin resistance affects blood-brain barrier integrity and cognitive performance at the same time [19]. Moreover, chronic low-grade inflammation, or "meta-inflammation," frequently coexists with insulin resistance. Neuroinflammation may result from an inflammatory illness, which can also affect the brain. There are several cognitive problems linked to chronic neuroinflammation [20].

Table 1: The model table for the potential association between Type 2 diabetes (T2D) and cognitive impairment (Type 3 diabetes):

Stage	Description	Examples of Factors	References
Upstream Risk Factors	Early risk factors contributing to metabolic dysregulation and cognitive impairment risk	- Genetics (e.g., family history of diabetes) - Age - Lifestyle (e.g., poor diet, lack of exercise)	[13]
Metabolic Precursors	Metabolic dysfunctions that precede the development of T2D and cognitive decline	- Insulin resistance - Obesity - Dyslipidemia - Chronic inflammation	[14]
Pathways	Biological mechanisms linking metabolic precursors to cognitive impairment and T2D	- Impaired glucose metabolism - Increased oxidative stress - Reduced insulin signaling in the brain	[15]
Subclinical Pathology	Early pathological changes observed before the onset of full disease	- Mild cognitive impairment (MCI) - Brain atrophy - Microvascular damage (e.g., cerebral vasculature)	[16]
Disease Outcome	The manifestation of clinical symptoms of T2D and Type 3 diabetes (cognitive impairment)	- Type 2 diabetes - Alzheimer's disease-like cognitive impairment (Type 3 diabetes) - Dementia	[17]

This table outlines the potential pathway linking Type 2 diabetes with cognitive impairment, often described as Type 3 diabetes, in terms of upstream risks, metabolic precursors, and outcomes.

CASE STUDY

Acute and temporary cognitive disturbances linked to hyperglycemia are frequently reported by diabetic patients. Such impacts could have an impact on daily functioning and quality of life. They could also reveal indicators that help patients recognize hyperglycemia earlier [21]. A hospital clamp trial observed a significant slowing of visual reaction time at a blood glucose level of 16.7 mmol/L; however, this effect was not reproducible when using an auditory reaction-time task. Additionally, cognitive performance deficits, including a 9.5% reduction in IQ, were associated with blood glucose levels in the 20–30 mmol/L range among children with type 1 diabetes. At a blood glucose level of 16.7 mmol/L, a hospital clamp study found a substantial shortening of visual reaction time; however, this effect was not replicable when employing an auditory reaction-time test. Furthermore, in children with type 1 diabetes, blood glucose levels in the 20–30 mmol/L range were linked to cognitive performance abnormalities, including a 9.5% decrease in IQ. In 67% of the kids surveyed, performance IQ declined. tested cognitive performance in persons with type 2 diabetes using a hyperinsulinic glucose clamp at 14.5 and 16 mmol/l. Tests of cognitive ability, such the four-choice reaction time, showed notable abnormalities with hyperglycemia. On certain neuropsychological tests, other researchers, however, were unable to observe a decline in cognitive-motor performance under hyperglycemia [22].

HYPERGLYCEMIA AND COGNITIVE IMPAIRMENT

The lack of a well-defined physiological mechanism explaining how hyperglycemia impairs brain function is a major obstacle to research on the impact of hyperglycemia on cognitive-motor performance, including hypoglycemia and its related neuroglycopenia [23]. Nonetheless, studies point to a number of potential processes. Short-term hyperglycemia can lead to microvascular disruption in the blood-brain barrier. Some theories include variations in insulin availability to the brain or changed synthesis or reuptake of monoamine neurotransmitters as a result of altered precursor availability to the brain. Uncontrolled diabetic may have complex impacts on peptide neurotransmitters [24]. Each of these mechanisms might not be enough on its own, and some of them might work better together than others. Currently, no precise mechanism or mechanisms that may be responsible for potential short-term

cognitive impairment can be concluded. Verifying hyperglycemia's disruptive effects on cognitive-motor functioning is necessary before delving into potential physiological explanations [25].
This study specifically tests three hypotheses: i) hyperglycemia is linked to cognitive-motor dysfunctions; ii) hyperglycemia impairs cognitive-motor functioning in adults with type 1 or type 2 diabetes; and, iii) hyperglycemia-related disruptions to cognitive-motor functioning are specific to each individual. The last hypothesis is based on our earlier discoveries that the glycaemic threshold for incidence and individual vulnerability of symptoms and cognitive motor disturbances linked to hypoglycemia vary (12–14) [26].

COGNITIVE IMPAIRMENT

Diabetic brain damage is mostly impacted by its effects on the microvascular and macrovascular systems [27]. Microvascular problems such as diabetic retinopathy, neuropathy, and nephropathy are caused by hyperglycemia. Cardiovascular and cerebrovascular disorders are examples of macrovascular problems. Diabetes impairs the integrity of the neurovascular units that control cerebral blood flow. The transport of nutrients to nerve tissue is impacted by structural alterations in the microvasculature, such as capillary reduction and arteriovenous shortcuts [26]. This increases the brain's vulnerability to oxygen deficiency, which may result in cognitive decline. Chronic hyperglycemia is a hallmark of the metabolic illness diabetes mellitus (DM). The eyes, kidneys, heart, and brain are just a few of the organs that might be negatively impacted by DM's secondary consequences [28]. Cognitive impairment is the most frequent consequence of hyperglycemia on the brain. According to estimates, 20–70% of DM patients experience cognitive impairments. Cognitive impairment is the most frequent consequence of hyperglycemia on the brain. According to estimates, 20–70% of DM patients experience cognitive impairments. Important brain regions that are involved in memory, learning, and spatial navigation are impacted by high blood sugar, and the brain's anatomical complexity predisposes it to several pathological conditions, including type 2 diabetes. According to studies, diabetics may experience cognitive deterioration that goes unnoticed for years at a time. Additionally, extensive impacts on several brain regions are shown by studies on brain imaging in T2D patients. Whether hyperglycemia or a co-occurring T2D issue is the cause of diabetes-associated cognitive deterioration is yet unknown. The precise processes that cause diabetes-related cognitive impairment are not well understood, although aberrant insulin action and poor glucose metabolism are likely major contributors. The impact of hyperglycemia on the structure and functioning of the brain, as well as the possible mechanisms driving T2DM-associated cognitive deterioration, have all been attempted to be summarised in this study [28].

TYPE 2 DIABETES AND COGNITIVE DECLINE

For every cell in the body, glucose serves as its principal energy source. The brain uses around 20% of daily energy intake, even though it only makes up 2% of the body weight [29]. Neurons need twice as much energy as other body cells because they must be constantly active to govern vital processes necessary for the body to survive. Beyond their essential roles, neurons are also active during sleep to regulate the sleep-wake cycle [28]. Thus, normal brain metabolism, brain viability, cerebral signal conduction, cognitive function, neurotransmission, and synaptic plasticity all depend on an uninterrupted supply of glucose [30]. Even though the brain depends heavily on glucose, chronic and severe hyperglycemia can be dangerous. Numerous studies have demonstrated the detrimental effects of diabetes on the hippocampal tissue and the promotion of neuronal death through a variety of pathways [31]. The limbic system's hippocampus, which is involved in memory as well as emotional, reproductive, and adaptive processes, is especially susceptible to high blood sugar. It also aids in the creation of new memories and the recollection of feelings and senses, such as sound and scent. The hippocampus functions as a marker for memory, guiding memories to the appropriate area of the brain for retrieval and long-term storage [32]. The hippocampus is susceptible to numerous clinical conditions, including type 2 diabetes, due to its intricate anatomical structure [33]. Because of its intricate structural makeup, the hippocampal region is vulnerable to several pathological conditions, including type 2 diabetes. Type 2 diabetes contributes to cognitive decline through mechanisms such as insulin resistance, chronic inflammation, and vascular dysfunction, leading to neurodegeneration (Fig. 3). All during life, the dentate gyrus's (DG) granular layer multiplies. Anything that throws off the balance between neuronal death and proliferation in the DG region might lead to memory and learning issues. Additionally, in the CA3 area and the DG, hyperglycemia causes neuronal death (necrosis/apoptosis) and inhibits the proliferation of granular cells [28].

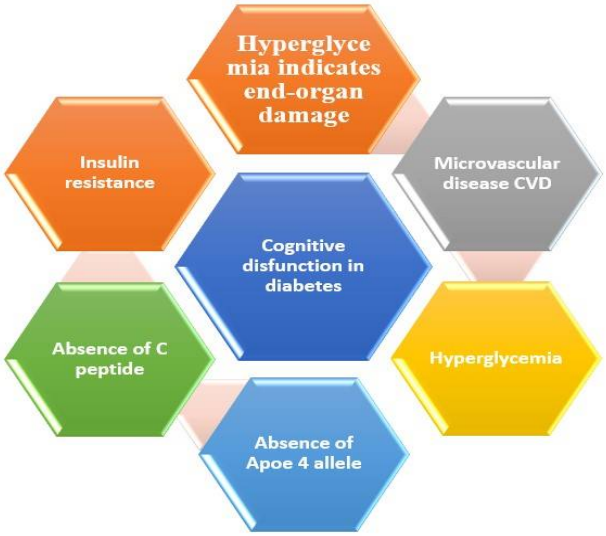

Figure 3. Pathophysiology of cognitive dysfunction in diabetes.

MECHANISMS UNDERLYING HYPERGLYCEMIA-INDUCED COGNITIVE IMPAIRMENT

In the hippocampal environment of diabetic mice, multiple preclinical investigations have reported a significant increase in apoptotic markers such as Bcl-2, Bcl-xl, Bax, and caspase 3 [34]. The most essential member of the caspases family, caspase-3, was found to have significantly increased activity in the hippocampus of STZ-induced diabetic rats [35]. Mitochondria may be responsible for the hyperglycemia-induced apoptosis in the diabetic rats' hippocampal tissues because of the considerable reduction in Bcl xL and Bcl 2 expression in these diabetic rats [35]. Multiple *in vitro* and *in vivo* studies have revealed that diabetic mice experience hippocampal cell death, which may play a crucial role in memory and learning issues [36].

HYPERGLYCEMIA ALTERS MOOD STATE AND IMPAIRS COGNITIVE PERFORMANCE IN PEOPLE WITH TYPE 2 DIABETES

Those with type 2 diabetes showed worsening mood and decreased cognitive performance after acute hyperglycemia. Because type 2 diabetics frequently experience intermittent or chronic hyperglycemia, which can negatively impact mood and cognitive function and interfere with numerous everyday tasks, these findings are practically significant [37]. Glucose levels in people with diabetes fluctuate quickly. Hypoglycemia is a common side effect of insulin administration and other antidiabetic drugs, while hyperglycemia is a common consequence of the relative or absolute insulin deficit that is inherent to diabetes [38]. Variations in blood glucose content have an immediate impact on cerebral function since the brain uses glucose continuously as its primary energy source. Acute hypoglycemia is known to have negative effects on mood and cognitive performance. Less is known, though, regarding how acute hyperglycemia affects brain function. Anecdotal accounts from diabetic patients indicate that mood swings (including heightened irritation and a sense of impaired well-being) and difficulties with fast thought occur when blood glucose levels are elevated [39].

Evidence from two research shows that during hyperglycemia as opposed to euglycemia, there are deficits in verbal abilities and IQ. According to other research, acute hyperglycemia has little influence on mood or cognitive performance. Because the study groups had chronically poor metabolic control, cerebral adaptation to the high blood glucose concentrations that were prevalent may have occurred. However, the study only employed two tests to assess cognitive function. Subsequent research revealed that in non-diabetic patients, short-term hyperglycemia (blood glucose concentration 17.1 mmol/l) with physiological hyperinsulinemia was linked to decreased motor latency and higher sensory nerve conduction velocity [40].

Prior research has only included individuals with type 1 diabetes. There is mounting evidence that individuals with type 2 diabetes have an increased risk of cognitive impairment (Table 2). This is most likely the result of the interaction between the structural and functional changes that the aging process causes to the central nervous system, and the metabolic disturbances linked to diabetes. Short-term variations in blood glucose levels may put people with type 2 diabetes at risk for cognitive impairment.

This study looked at how acute hyperglycemia affected several critical cognitive functions and essential emotional states in a group of type 2 diabetics [41]. Several mechanisms explain the link between type 2 diabetes and cognitive impairment, including insulin resistance, vascular damage, and Inflammation (Table 2).

Table 2: **Mechanisms Linking Type 2 Diabetes and Cognitive Impairment.**

Mechanism	Link Between Type 2 Diabetes & Cognitive Impairment	References
Insulin Resistance	Insulin resistance in the brain impairs glucose metabolism, reducing energy supply to neurons, which leads to cognitive decline and dementia, especially Alzheimer's disease.	[42]
Hyperglycemia	Chronic high blood sugar can damage blood vessels and neurons in the brain, contributing to neurodegeneration, cognitive decline, and vascular dementia.	[43]
Oxidative Stress	High glucose levels increase oxidative stress, leading to neuronal damage and inflammation, which accelerates cognitive decline and neurodegenerative diseases.	[44]
Inflammation	T2DM induces chronic inflammation, which can affect brain structures like the hippocampus and increase the risk of dementia and cognitive decline.	[45]
Vascular Damage	Diabetes damages small and large blood vessels, reducing cerebral blood flow, causing ischemia and increasing the risk of vascular dementia and stroke-related cognitive decline.	[46]
Amyloid β Deposition	Insulin resistance and hyperinsulinemia may promote amyloid β deposition in the brain, a hallmark of Alzheimer's disease, linking T2DM with cognitive impairment.	[47]
Advanced Glycation End-Products (AGEs)	AGEs accumulate in diabetic patients, contributing to oxidative stress and inflammation, which leads to cognitive decline and brain aging.	[48]
Cerebral Atrophy	Chronic hyperglycemia and insulin resistance are associated with brain atrophy, particularly in regions involved in memory and cognition, such as the hippocampus.	[49]
Mitochondrial Dysfunction	Impaired insulin signaling affects mitochondrial function, leading to reduced energy production, neurodegeneration, and cognitive impairment in T2DM patients.	[50]
Hypoglycemia Episodes	Frequent episodes of hypoglycemia in diabetes patients may cause neuronal damage and cognitive deficits, particularly in older adults.	[51]

COGNITIVE FUNCTION TESTS

Validated tests of information processing, tests of memory, and tests of attention were administered during each study condition.

Test of Information Processing

Trail-Building B. This handheld computer-based test evaluates motor skills in addition to complicated visual scanning [52].

Digit-Symbol Examination

This code was written quickly for testing purposes.

Reaction Time Evaluation

This is an information processing and psychomotor speed test. Together with the coefficient of variation, the SDs of the Simple and Four-Choice Reaction Times were computed to provide an indication of intra-individual variability [53].

Tests of Memory

The study's memory and learning assessments were selected based on prior research demonstrating their susceptibility to metabolic disruptions like hypoglycemia [54].

Verbal Memory Tests

i. Auditory Verbal Learning Test, immediate and delayed. This is a test of immediate memory capacity, retrieval efficiency, and learning. The delayed component measures longer-term retention.

ii. Logical Memory Test, immediate and delayed. The Logical Memory test, a test of verbal learning, measures immediate and delayed recall following auditory presentation [55].

Tests of Visual Memory

Instant and delayed visual reproduction. After a nonverbal visual presentation, this exam assesses both immediate and delayed recall. Second, the Benton Visual Retention Test. This exam measures instantaneous visual recollection [56].

Working memory exercises

i. Digit Forward and Backward Span. Throughout the exam, the participant is given verbal presentations of a variety of items that get longer and longer.

ii. Number/Letter Sequencing. Voice presentations are made of many lists containing both numbers and letters [57].

Tests of Attention

The attention was assessed using the Test of Everyday Attention battery, which includes measures for divided, sustained, auditory, visual, and attention switching [58]. To reduce any learning impact between the two research conditions, parallel versions of the Auditory Verbal Learning Test, Logical Memory, Benton Visual Retention Test, and Test of Everyday Attention battery were employed in this investigation. The battery of tests was administered in a predetermined order over the duration of the trial [59].

HERBAL FORMULATIONS IN MEDICINE

Diabetes medication has long been administered with *Momordica charantia*_Linn. [60]. The goal of the current study was to develop and assess transdermal patches containing *Momordica charantia* Linn. Using hydroxy propyl methyl cellulose as a polymer, transdermal films containing the herbal medicinal component separated from ethanolic extract of *M. charantia* fruits were created. The films were assessed for stability tests, biochemical investigations, acute and sub-acute antihyperglycemic activity in diabetic rats, folding endurance, thickness, weight change, drug contents, and in vitro diffusion studies [61]. Transdermal patches of *M. charantia* (2 cm^2; 10 mg/patch) were reported to weigh 0.03 gm. It was discovered that the thickness of the *M. charantia* patches (2 cm^2; 10 mg/patch) was adequate. After 6 hours, the percentage release of active ingredients from *M. charantia* transdermal patches (10 mg/patch; 2 cm^2) was found to be 47.59% in 10% hydroalcoholic phosphate buffer pH 7.4.The transdermal approach caused very little skin discomfort, and the in vivo findings showed that the patches effectively lower blood glucose levels. It was determined that using contemporary pharmaceutical formulation processes, the well-known herbal remedy *M. charantia* Linn. was proven to be helpful for diabetes [61]. A list of herbal medications used in the treatment of diabetes as well as medicinal plants with demonstrated antidiabetic and related therapeutic effects is compiled. These include *Phyllanthus amarus, Pterocarpus marsupium, Tinospora cordifolia, Eugenia jambolana, Momordica charantia, Ocimum sanctum, Withania somnifera,* and *Trigonella foenum graecum* [62]. Free radical damage is one of the etiologic factors linked to the development of diabetes and its consequences, so an antidiabetic molecule with antioxidant characteristics would be more advantageous. In Indian traditional health care systems, there are several medicinal plants known as rasayana that have been utilised for over a millennium. The majority of medical professionals in Indian systems create and administer their own concoctions [63]. 21,000 plants are registered by the World Health Organisation (WHO) as being used medicinally worldwide. Of these 2500 species, 150 are used on a reasonably considerable scale in commercial settings in India. India is known as the world's botanical paradise and is the world's largest producer of medicinal plants. The current research focuses on plant preparations and herbal medication used to treat diabetes mellitus, a serious illness that cripples people worldwide and causes enormous financial losses (Table 3) [62]. Natural goods made from fruits and vegetables; nutraceuticals offer a number of health advantages. Over the past 20 years, natural substances like flavonoids that have antidiabetic properties have drawn scientific attention [64]. Flavonoids, which have antiviral, antiallergic, antibacterial, and anti-inflammatory properties, are regarded as a class of physiologically active secondary metabolites of plants called pigment makers that give flowers their colour and scent. Additionally, they function as antioxidants, which prevent disease by counteracting the effects of nitrogen and oxygen species and reducing oxidative stress in the body. The modulation of glucose absorption, insulin signalling, insulin secretion, adipose deposition, and carbohydrate digestion is all supported by flavonoids' antidiabetic action [65]. They target many molecules involved in the regulation of several pathways, such as boosting insulin secretion, lowering apoptosis, improving β-cell proliferation, and alleviating hyperglycemia by controlling the liver's metabolism of glucose. The major liver, colon, and intestinal enzymes are hydrolysed and conjugated by flavonoids [66] flavonoids (from plant sources), which may help reduce brain inflammation.

Table 3: Mechanisms of herbal medicines for diabetes and cognitive impairment its experimental clinical evidences.

Herbal Medicine	Mechanism/Action	Experimental Evidence	Clinical Evidence	References
***Curcuma longa* (Turmeric)**	Anti-inflammatory, improves insulin sensitivity	Curcumin improves insulin resistance and reduces oxidative stress in animal models of diabetes	Limited clinical trials show improvement in cognitive function and glucose control in diabetic patients	[67]
Ginkgo biloba	Antioxidant, neuroprotective, improves blood circulation	Ginkgo biloba has shown improvements in cognitive function in diabetic models with cognitive impairment	Some clinical trials report modest cognitive improvements in diabetic patients with mild cognitive impairment	[68]
Panax ginseng	Enhances insulin sensitivity, reduces oxidative stress	Animal models show improved glucose metabolism and reduced amyloid beta accumulation in brain	Clinical studies report improved glucose levels and cognitive function in diabetes patients	[69]
***Bacopa monnieri* (Brahmi)**	Antioxidant, neuroprotective, improves memory	Improves memory and cognitive function in diabetic models with cognitive impairment	Limited clinical trials suggest improvements in cognitive function in diabetes patients	[70]
***Cinnamomum verum* (Cinnamon)**	Improves insulin sensitivity, anti-inflammatory	Animal studies show reduced blood glucose levels and improved cognitive performance	Some human trials indicate better glucose control and possible cognitive benefits in diabetes patients	[71]
Gymnema sylvestre	Increases insulin production, regenerates beta cells	Improves insulin production and cognitive performance in diabetic animal models	Limited clinical evidence, but preliminary studies suggest better glucose control and memory retention	[72]
***Withania somnifera* (Ashwagandha)**	Anti-inflammatory, anti-hyperglycemic, neuroprotective	Shows improvement in cognitive function and glucose levels in diabetic models	Early clinical trials show potential in improving cognitive function and blood sugar control in type 2 diabetes	[73]
***Momordica charantia* (Bitter melon)**	Enhances insulin sensitivity, reduces glucose levels	Animal studies show improved glucose metabolism and potential cognitive benefits in diabetic models	Limited human trials suggest potential benefits in controlling blood sugar, with limited evidence on cognitive function	[74]
***Salvia officinalis* (Sage)**	Enhances cognitive function, improves insulin sensitivity	Animal models show improved memory and glucose metabolism in diabetes	Early clinical trials suggest modest improvements in cognitive function and glucose levels	[75]
Aloe vera	Reduces blood glucose, improves cognitive function	Improves memory and reduces glucose levels in diabetic animal models	Some human trials show better glucose control and potential cognitive benefits in diabetes patients	[76]
***Syzygium cumini* (Jamun)**	Antioxidant, anti-hyperglycemic, neuroprotective	Animal studies show reduced blood glucose, improved insulin sensitivity, and enhanced memory and cognitive function	Limited human trials; preliminary evidence suggests better blood sugar control and slight cognitive benefits	[77]
***Allium cepa* (Onion)**	Anti-hyperglycemic, antioxidant, anti-inflammatory	Onion extract reduces blood glucose, improves insulin sensitivity, and enhances cognitive function in diabetic models	Early human studies suggest improvement in blood glucose levels, limited evidence on cognitive function	[78]

This Table 3 provides an overview of the potential mechanisms and effects of various herbal medicines on diabetes and cognitive impairment, based on available experimental and clinical evidence.

ANTIDIABETIC ACTIVITY OF POLYHERBAL FORMULATION IN STREPTOZOTOCIN – NICOTINAMIDE INDUCED DIABETIC WISTAR RATS

Synthetic medications can effectively and specifically treat diabetes and cognitive impairments, but they frequently have negative side effects. Alternative or complementary approaches with possible advantages

are provided by herbal remedies and polyherbal mixtures (Table 4). Throughout India, *Glycosmis pentaphylla, Tridax procumbens,* and *Mangifera indica* are well-known herbs that are frequently used to cure a variety of ailments, including diabetes mellitus [79]. Though it's unknown what the combined effects will be, the separate plant parts' antidiabetic activity is well documented. Low doses of individual herbs combined with enhanced therapeutic effectiveness from polyherbal compositions lessen side effects. Create a polyherbal formulation and assessing its potential to prevent diabetes in animals is the current study's goal. The stem bark of *G. pentaphylla*, the entire plant of *T. procumbens,* and *M. indica* leaves were ethanol extracted and used to create the polyherbal mixture. *G. pentaphylla, T. procumbens*, and *M. indica* ethanol extracts are included in the polyherbal formulation in a 2:1:2:1 ratio. The World Health Organization's requirements for the quality control of herbal materials were followed in evaluating the final product's quality [79]. The polyherbal formulation's quality testing parameters were within permissible bounds. The polyherbal formulation's fingerprint analysis demonstrated effective separation at 366 nm and demonstrated that the active chemicals contained therein were identical to those found in all three extracts. In doses up to 2000 mg/kg over 14 days, the polyherbal formulation's acute toxicity trials revealed no adverse effects. The oral antidiabetic effect of the polyherbal formulation (250 and 500 mg/kg) was tested in rats with diabetes mellitus produced by streptozotocin (50 mg/kg; i.p.) + nicotinamide (120 mg/kg; i.p.) [79].

The polyherbal formulation's impact on blood glucose levels was monitored on a regular basis during the course of the investigational drug's 21-day administration. All of the animals' blood samples were taken for biochemical estimate at the conclusion of the study, and the animals were slaughtered so that the liver and pancreas tissues could be taken for histopathologic examination. Significant antidiabetic efficacy was demonstrated by the polyherbal formulation at 250 and 500 mg/kg, respectively, and this impact was similar to glibenclamide. Histopathologic and biochemical analyses corroborate the polyherbal formulation's antidiabetic efficacy [79].

Table 4: Drugs used for the treatment of diabetes and cognitive impairment.

Drug Class	Drug Name	Mechanism of Action	Effect on Diabetes	Effect on Cognitive Impairment	References
Biguanides	Metformin	Increases insulin sensitivity, reduces hepatic glucose production	Improves glycemic control, reduces insulin resistance	Shown to improve memory and reduce cognitive decline in animal studies	[45]
Thiazolidinediones	Pioglitazone	Activates PPAR-γ to increase insulin sensitivity	Improves insulin sensitivity, lowers blood glucose	Potential neuroprotective effects through reduced inflammation	[80]
GLP-1 Agonists	Liraglutide	Stimulates insulin secretion, inhibits glucagon, slows gastric emptying	Reduces blood glucose, supports weight loss	Shows potential in reducing cognitive decline in Alzheimer's models	[81]
DPP-4 Inhibitors	Sitagliptin	Inhibits DPP-4 enzyme, prolonging action of incretin hormones	Lowers postprandial blood glucose, enhances insulin secretion	May have protective effects on memory through incretin signaling	[82]
SGLT2 Inhibitors	Empagliflozin	Inhibits glucose reabsorption in kidneys, leading to increased glucose excretion	Lowers blood glucose, supports weight loss, reduces cardiovascular risk	Shown to reduce neuroinflammation in preclinical studies	[83]
Insulin Therapy	Insulin	Facilitates cellular glucose uptake	Lowers blood glucose, essential for type 1 and advanced type 2 diabetes	Some studies suggest improved cognitive function with insulin therapy	[84]
Cholinesterase Inhibitors	Donepezil	Inhibits acetylcholinesterase, increasing acetylcholine levels in the brain	No direct effect on diabetes	Improves cognitive function in Alzheimer's disease and cognitive impairment	[85] .
Nootropic Agents	Piracetam	Enhances neurotransmission and neuroprotection	No direct effect on diabetes	Improves cognitive function and memory in mild cognitive impairment	[86]

This Table 4 presents commonly used drugs for treating diabetes and their potential effects on cognitive impairment.

Combination therapies utilizing polyherbal formulations offer a holistic approach to managing diabetes and its related cognitive impairments (Table 5). Streptozotocin (STZ) is commonly used to induce diabetes in experimental models, leading to increased blood glucose levels and cognitive decline. Polyherbal formulations consist of multiple medicinal plants known for their antidiabetic and neuroprotective properties, such as Ginkgo biloba and *Withania somnifera*, which target metabolic dysregulation and oxidative stress. Studies have shown that administering these formulations results in significant reductions in fasting blood glucose and glycosylated hemoglobin levels, indicating improved glycemic control. Moreover, cognitive function has been observed to improve, as evidenced by enhanced performance in behavioral tests like the Morris Water Maze and Y-Maze, which assess memory and spatial learning. The active compounds within these herbal blends exhibit antioxidant and anti-inflammatory effects, addressing the oxidative stress and inflammation that contribute to both diabetes and neurodegeneration. By improving insulin sensitivity and supporting pancreatic function, these therapies address the underlying metabolic dysfunctions associated with diabetes, ultimately mitigating the risk of cognitive impairments. This underscores the potential of integrating polyherbal formulations into comprehensive diabetes management strategies.

Table 5: Indian Herbal Plants in Combination Therapy for Diabetes and Cognitive Impairment.

Combination Therapy	Mechanism of Action	Clinical Findings	References
Metformin + Tulsi (*Ocimum sanctum*)	**Metformin**: Increases insulin sensitivity, and reduces hepatic glucose production. **Tulsi**: Antioxidant, improves glucose metabolism and reduces stress.	The combination improved glycemic control, reduced oxidative stress, and exhibited protective effects on brain function in diabetes patients.	[93]
Insulin Therapy + Ashwagandha (*Withania somnifera*)	**Insulin**: Regulates blood glucose. **Ashwagandha**: Adaptogen, reduces oxidative stress, and enhances neuroprotection.	Improved glycemic levels and enhanced cognitive performance in diabetic patients due to Ashwagandha's neuroprotective effects.	[94]
Sulfonylureas + Amla (*Emblica officinalis*)	**Sulfonylureas**: Stimulate insulin secretion. **Amla**: Rich in vitamin C, reduces oxidative stress, and improves glucose metabolism.	Clinical trials showed improved blood glucose control and reduced cognitive decline in diabetes patients.	[95]
Thiazolidinediones (Pioglitazone) + Neem (*Azadirachta indica*)	**Pioglitazone**: Improves insulin sensitivity. **Neem**: Anti-diabetic, reduces blood glucose levels, and has neuroprotective properties.	Enhanced glycemic control and reduced neuroinflammation observed in patients treated with this combination.	[96]
DPP-4 Inhibitors (Sitagliptin) + Turmeric (*Curcuma longa*)	**Sitagliptin**: Prolongs incretin hormone activity. **Turmeric (Curcumin)**: Potent antioxidant and anti-inflammatory, prevents neurodegeneration.	Significant improvement in glycemic control and reduction in inflammation, along with cognitive enhancement in diabetes patients.	[97]
Metformin + Jamun (*Syzygium cumini*)	**Metformin**: Increases insulin sensitivity. **Jamun**: Anti-diabetic, regulates blood glucose levels, and protects against oxidative damage.	Improved glycemic control, reduced oxidative stress, and neuroprotective effects in diabetic patients.	[98]
Insulin Therapy + Brahmi (*Bacopa monnieri*)	**Insulin**: Regulates blood glucose. **Brahmi**: Enhances cognitive function, reduces oxidative stress, and improves neuronal health.	Clinical studies showed better glycemic levels and significant improvement in memory and cognitive functions in diabetes-related cognitive impairment.	[99]
Sulfonylureas + Fenugreek (*Trigonella foenum-graecum*)	**Sulfonylureas**: Stimulates insulin secretion. **Fenugreek**: Lowers blood glucose levels and has neuroprotective properties.	Clinical findings indicate improved blood sugar control and enhanced neuroprotection in diabetes patients with mild cognitive impairment.	[100]

CONCLUSIONS

In conclusion, the best way to effectively achieve longer-term management of type 2 diabetes is to optimize combination treatment; nevertheless, at this time, a progressive approach is indicated, and combination therapy as an initial approach is not advised. Now, achieving objective standards in both glycemic control and the scope of the processes behind the early onset of macro and microvascular problems in type 2 diabetes is the true difficulty. In this regard, well-tested medications like metformin and sulfonylureas, as well as more recent ones like thiazolidinediones in combination with older and herbal formulations, show promise. The intriguing findings from current clinical research are displayed in Table No 5. The endpoints that have been highlighted, the boxes are meant to serve as thought-provoking places to start further study.

Here's a table summarizing some newer agents and traditional medicinal plants used in combination with conventional diabetes treatments (e.g., sulfonylureas, metformin) for diabetes and diabetes-related cognitive impairment, along with key findings from recent clinical studies.

This table highlights the effects of combining newer antidiabetic agents (e.g., thiazolidinediones) and traditional medicinal plants with conventional treatments like sulfonylureas and metformin. It includes promising clinical results and key references. The management of cognitive impairment in patients with Type 2 Diabetes Mellitus (T2DM) presents a significant clinical challenge, necessitating a more integrated treatment approach. Traditional pharmacological strategies primarily aimed at glycemic control may fall short in addressing the multifaceted nature of cognitive decline associated with diabetes. This review highlights the potential benefits of optimizing combination therapies that incorporate both conventional antidiabetic medications and medicinal plants with neuroprotective properties. By targeting the underlying mechanisms contributing to cognitive dysfunction, such as insulin resistance, oxidative stress, and neuroinflammation, these integrative approaches may enhance patient outcomes and preserve cognitive function.

The combination of traditional Indian herbal plants with standard diabetes treatments appears to hold great promise for improving blood sugar control and reducing complications related to diabetes, such as cognitive decline. Herbs like Tulsi (*Holy basil*), Ashwagandha, Amla, Neem, and Turmeric possess a range of beneficial properties, including antioxidant, anti-inflammatory, and neuroprotective effects, which work in harmony with conventional medications. Clinical studies indicate that these herbal combinations not only improve insulin sensitivity and glucose metabolism but also offer protection against oxidative stress and cognitive impairment. Although these findings are encouraging, more clinical trials and mechanistic research are necessary to confirm these combination therapies' safety, effectiveness, and long-term advantages across different groups of people. This holistic approach could potentially lead to the development of affordable and widely accessible treatments for diabetes and its related complications.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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