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Review Article

Anti-Diabetic Effect of Some Plants Acting on Oxidative Stress and Inflammation

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Keywords

- Antidiabetic plants; Brain; Diabetes; Insulin receptors; Insulin signaling

Abstract

Insulin is the most effective pharmacological treatment for the control of hyperglycemia. The liver is the main target tissue for the action of insulin and insulin resistant liver can lead to hyper-insulinemia and eventually hyperglycemia. The receptors of insulin and their downstream pathways are extensively distributed in the brain. These receptors play crucial roles in the regulation of different central nervous system tasks. Therefore, dysfunction at different levels of insulin signaling and metabolism can contribute to the development of a bunch of clinical disorders.

Recent studies have detected that many bioactive compounds, derived from plants; have an array of beneficial functions and could be important sources of potential novel therapies for chronic diseases and for attenuating symptoms related with diabetes, especially oxidative stress and inflammation. The precise molecular mechanisms by which the dysfunction of insulin signaling and metabolism induce these health problems are not yet clear. Hence, the aim of this work was to carry out recapitulating reviews of the current works on this issue in order to find the role of antidiabetic plants in resolution of health problems associated with this dysfunction.

ABBREVIATIONS

AD: Alzheimer's Disease; Abeta: Amyloid-beta; BBB: Blood-brain Barrier; BMI: Body Mass Index; CNS: Central nervous system; T2D: Diabetes Type 2; ER: Endoplasmic Reticulum; ENS: Enteric Nervous System; FR: Free Radicals; GLUT 1: Glucose Transporters; Hpc: Hypercholesterolaemia; IRE1: Inositol-requiring Kinase1; IDE: Insulin-degrading Enzyme; IGF-1: Insulin-like-growth Factor 1; IRS-1: Insulin Receptor Substrate; OS: Oxidative Stress; MHC: Major Histocompatibility Complex; MetS: Metabolic Syndrome; NSCs: Neural Stem Cells; PD: Parkinson's Disease; PPARs: Peroxisome Proliferator-Activated Receptors; ROS: Reactive Oxygen Species; TLR-5: Toll-like Receptors; XBP-1: X box Binding Protein

INTRODUCTION

The receptors of insulin and their downstream pathways are extensively distributed in all the brain regions [1]. The stimulating signals of insulin and somatomedin C, also called insulin-like-growth factor 1 (IGF-1), are important hormones that participate in the regulation of various functions of the central nervous system (CNS). In fact, IGF-1 shares a lot of typical pathophysiological features as amyloid β accumulation, brain vasculopathy impaired insulin sensitivity, oxidative stress (OS), tau hyper-phosphorylation and inflammation [2]. Endotoxin induces nitric oxide synthase in the cells responsible for the production of insulin, glycogen and pancreatic polypeptides and this re-enforces the pathophysiological role of these inducible protein in the development of insulin-dependent diabetes mellitus [3].

Hyperglycemia is very common in patients who are critically ill and the survival of these patients can be improved when subjected to a 144 – 180mg/dl insulin therapy. Also, impairment in the clearance of insulin is a common event in patients with sepsis and invariably, this makes them to become more susceptible to hypoglycemia [4]. Likewise, in septic condition, the protein intermediates in the skeletal muscle of insulin/mTOR pathway may undergo changes and become agglutinated to large subsets; thus, critically affecting fatty acid and glucose metabolism (Figure 1) [5].

Recent studies have discovered that some bioactive compounds, produced from plants, possess many beneficial functions and could be important sources of potential novel therapies for chronic diseases and for mitigating symptoms related with diabetes, especially OS including inflammation. The precise molecular mechanisms through which dysfunction of insulin signaling and metabolism induce these health problems are not yet clear. Hence, the objective of this work was to carry out recapitulating reviews of the current works on this issue in order to find the role of antidiabetic plants in resolving the health problem due to this dysfunction.

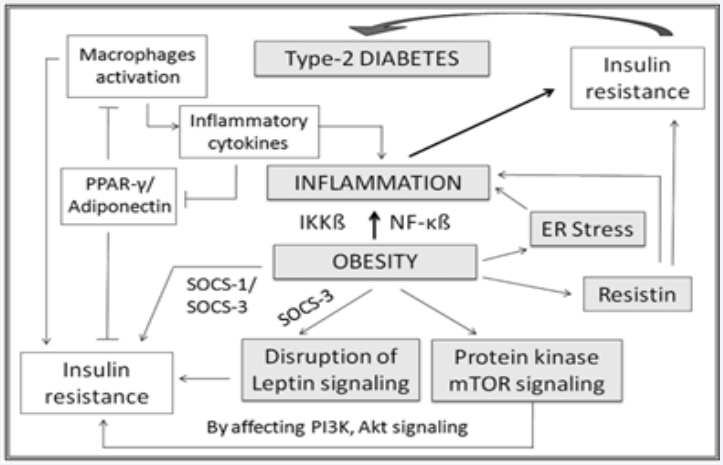

Figure 1 Insulin/mTOR pathway undergoing changes and become agglutinated to large subsets; thus, critically affecting fatty acid and glucose metabolism.

DIABETES AND THE BRAIN

Hyperglycemic as well as hypoglycemic conditions are known to have detrimental effects on the brain. These fluctuations in glucose, are usually overcome through the blood brain barrier, endowed with active glucose transporters (Glut 1), and glucose sensing cells that are found in abundant in different anatomical sites such as the CNS. The regulation of energy and glucose homeostasis in the CNS are usually done by the insulin sensing cells which send signals to hypothalamic neurocircuits and higher brain circuits like the dopaminergic system. It is known that the hyperinsulinemia of the fetus, because of maternal over nutrition or other metabolic conditions such as obesity or diabetes, can disrupt the fetal development of hypothalamic neurocircuit, a situation which can predispose the affected individual to metabolic disorders later in life [6].

Chronic overconsumption of animal fats causes diabetes mellitus and obesity which underlie the molecular mechanisms encompassing resistance to leptin, decline in rewarding effects of physical activities, xanthine oxidase-induced oxidative stress in vasculature and peripheral tissue, impaired activation of incretin signaling, and deviation in food preference [7]. Obesity is a New World Syndrome [8], and it is principally caused by excess of glucose and fat in the body which, sometimes, co-occur with body weight increase defined as the body mass index (BMI) ≥ 30 units in the adult people [9]. The risk of developing dementia as well as cognitive weakening has been highly correlated with the consumption of high-fat food and hyperglycemia, both of which have been linked to metabolic syndrome (MetS). Moreover, excess consumption of high-fat foods as well as hyperglycemia increases the release of systemic inflammatory cytokines, and accelerates hippocampal gliosis and immune infiltration in cerebral hemispheric tissue [10]. In addition, hyperglycemia has been highly associated with the induction of hippocampal microglial numbers and astrocytosis, including the mobilization of peripheral leukocytes to the cerebrovasculature. However, these effects of hyperglycemia are not seen in systemic inflammation.

THE INFLAMMATORY RESPONSE

The systemic application of insulin could hamper injuries of the cerebral cortex and prevent brain swelling as well as the alterations of blood-brain barrier (BBB), caused by kaliotoxin 2. Hence, it can beneficially reduce the risk of developing systemic diseases, production of excess serum cytokines, markers of oxidative stress and inflammation, and decrease damages to the tissue. The action of insulin on neuroprotection can be attributed to its ability to regulate inflammatory response processes [11]. Toll-like receptors (TLR-5) are pattern-recognition receptors of the innate immune system that are activated during infections. TLR-5 activation in the insulin-producing tissue brings about a considerable decline in insulin secretion and a boost in the production of anti-inflammatory heat-shock protein, nitric oxide, major histocompatibility complex (MHC) class I transporter including pro-inflammatory cytokines [12].

Insulin resistance could predispose the development of Parkinson's disease (PD), due to diminished capacity of dopaminergic neurons to cope with 6-OHDA mediated neurotoxicity [13]. Changes in glucose levels has been shown to mobilize neuroendocrine response which mediates in the correction and prevention of excess glucose in the blood. The principal area of the brain in charge of regulating glucose homeostasis is the hypothalamus, consequently, obesity, diabetes and other metabolic diseases are closely associated with the imbalance in this control [14]. Zeng *et al.* [15], suggest that defects in fatty acid metabolism deplete Yhhu981; a robust novel compound that stimulates fatty acid oxidation and exerts pleiotropic effects on lipid metabolism by activating AMPK; and as a result, contribute to insulin resistance and obesity pathogenesis (Figure 2).

Likewise, gestational obesity might alter the developmental program of specific fetal brain cell-networks. These defects could underlie pathologies such as metabolic syndrome and possibly, some neurological disorders in the offspring at a later age [16].

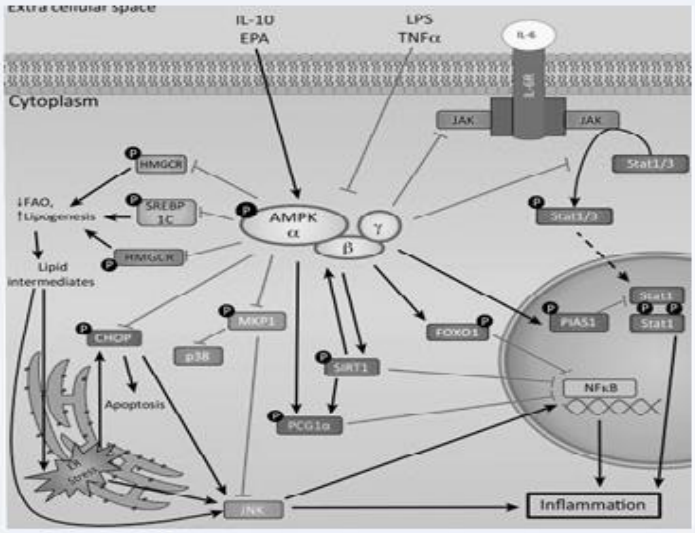

Figure 2 The figure showing lipid metabolism by activating AMPK; and as a result, contribute to insulin resistance and obesity pathogenesis.

DIABETES AND ALZHEIMER'S DISEASE

In epidemiological studies, high adiposity level has been associated with the manifestations of Alzheimer's disease (AD) and dementia. In middle and old-aged life, obesity and excessive body weight have been linked to an increased risk of dementia [17], and presently, these disorders are considered as a potential risk factor for different neurodegenerative failures (Figure 3) [18].

Environmental factors that operate in gestational and postnatal periods can adversely modify the vulnerability of genes and stress factors; thus, negatively impacting on brain evolution and growth, both in the aspects of structure and function which, in old-aged life, may show up as a diseased state. Aging is a process known to desynchronize the biological systems and undoubtedly, such event critically increases brain entropy and degeneration. In AD conditions, such desynchronizing events usually involves stress components, cortisol and noradrenaline, reactive oxygen species, and membrane damage and consequently, an insulin resistant brain state with decreased glucose/energy metabolism [19]. In the study conducted by Ariaans *et al.* [20]. it was found that treatment with cancer drugs (chemotherapy, glucocorticoids, hormonal therapies and targeted drugs) induced insulin resistance.

In a complex and changing environment, the necessity for survival is crucial in all living organisms and the neural systems are principally in charge of making this a success by identifying and responding to salient stimuli. Genetic variation as well as hormonal and metabolic status or other interindividual differences determine the neuronal responses and behavioral strategies in a critical environment. Burghardt *et al.* [21], indicated that dopamine plays integral role in pathological states such as disorders in the mood, in the use of substances, in eating and obesity which are associated with stress-induced dopaminergic function influenced by leptin.

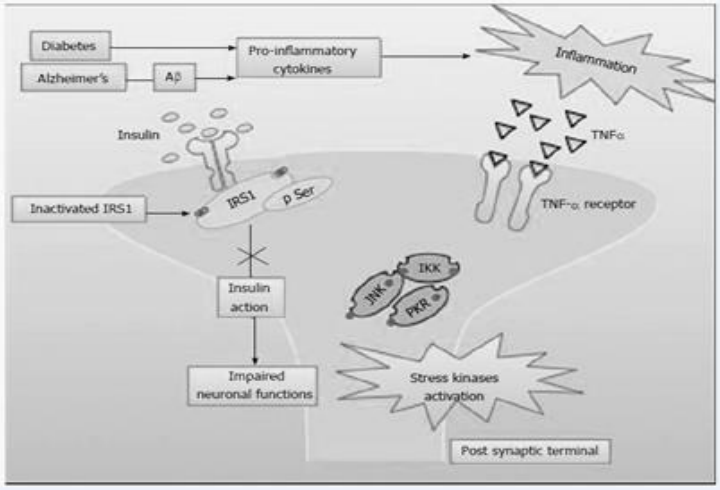

Figure 3 Figure showing disorders which are considered as a potential risk factor for different neurodegenerative failures.

OXIDATIVE STRESS IN NEURODEGENERATIVE DISEASES

Although Ariaans *et al.* [20], suggested that diabetes is related to reduced basal dopamine (DA) levels in the nucleus accumbens, evidently, this disorder may be caused by free radicals (FR), in the CNS [22]. The antioxidant system and the generation of FR coexist in a balanced way. When this equilibrium is altered, the result is oxidative stress; a situation that produces cell injury and triggers physiologic disorders. Thus, such imbalance promotes pathologic processes like human neurodegenerative diseases, characterized by 8-oxo-7,8-dihydroguanine (8-oxodG) accumulation in the DNA of affected neurons which can occur through either direct oxidation of guanine DNA or by the incorporation of oxidized nucleotide during replication [23]. Likewise, the principal location where superoxide radicals are produced is in the mitochondrial respiratory chain, but so far, the precise mechanism and location for the production of the physiologically relevant reactive oxygen species (ROS), within the respiratory chain has not been discovered. Understanding such mechanism is relevant, because evidence has indicated that oxidative stress constitutes the key event in neurodegenerative diseases [24]. It has been reported that excessive production of ROS and RNS are injurious to target cells, and inevitably, they are involved in many human degenerative disease processes of the CNS. The effects of ROS or RNS can be beneficial or harmful, based on the species and cellular target on the neuronal signaling pathways involved in the pathophysiology of the neurodegenerative disorders [25]. On the other hand, neurodegeneration has a link with selective neuron loss. The brain regions such as the substantia nigra and hippocampus are the most vulnerable to cell damage and thus, in Alzheimer's disease [26].

LEVELS OF IMMUNOGLOBULIN G

Hypercholesterolaemia (Hpc), is a major risk factor in sporadic Alzheimer's disease and in this manner, metabolic disorders (diabetes, obesity and atherosclerosis) are linked with this pathology. Moreover, Hpc is correlated with immunoglobulin G increase in a bid to counteract oxidized lipoproteins. AD patients are known to generate autoantibodies that attack non-brain antigens. This point is buttressed by the finding that in susceptible neuronal subpopulations, there are specific Fc region receptors of immunoglobulin G. The main subunit that activates receptors of Fc is the γ-chain. It has been demonstrated that prevention of learning and memory impairment can be achieved in mice with genes where this chain is deleted without causing cholesterolemia or affecting brain and serum immunoglobulin G levels. These effects on cognitive protection may be interpreted based on the reduced loss of synapsis, accumulation of intracellular amyloid β and cortical and hippocampal pyramidal neuronal tau hyperphosphorylation. On this basis, the authors suggested the association of the receptors of Fc of the immunoglobulin G with the development of hpc-associated features of AD and proposed a novel potential target for impeding or preventing AD in hypercholesterolemic patients [27].

The neural stem cells (NSCs), in adults have multiply potentials and are present in few brain regions. In adult mice, they are abundantly present in the mediobasal hypothalamus. It has been reported that eating high-fat-diet in chronic form brings about both neurogenic impairment and depletion of htNSCs due to the activation of IKKβ/NF-κB. Li *et al.* [28], proposed that adult htNSCs are important for the central regulation of metabolic physiology. IKKβ/NF-κB-mediated impairment of adult htNSCs is a critical neurodegenerative mechanism for obesity and related diabetes.

Evidences from epidemiological facts have shown that people with obesity and diabetes type 2 (T2D) as well as nondiabetic individuals with low insulin sensitivity have a high risk of developing dementia; thus, implicating a mechanistic link between adiposity, insulin sensitivity and dementia. It has been found that an increase in insulin-induced phosphorylation of insulin receptor substrate (IRS-1), Akt and GSK-3β brings about an improvement in insulin signaling activity at the molecular level. Endoplasmic reticulum (ER) stress signals including phosphorylation of inositol-requiring kinase1 (IRE1), and activation of X box binding protein (XBP-1), splice when there is an inhibition of oxidative stress [29]. Indeed, the disruption in the action of neuronal insulin may underlie the link between diabetes and neurodegenerative disorders [30].

OBESITY AND ALZHEIMER'S DISEASE

Obesity and Alzheimer's disease have a link with CNS structural resistance to insulin effects, and this resistance may originate from either genetic polymorphisms or long-term exposure to excess amounts of circulating insulin caused by peripheral insulin resistance [31]. This disorder may be produced through the liver-brain axis where toxic lipids and ceramides pass the blood brain barrier; thus, giving rise to brain insulin resistance, oxidative stress and neuro-inflammation [32]. One of the innate immune response after any aggression in the body is inflammatory reaction and this can disseminate all over the systemic circulation and into the CNS. This situation has been observed in chronic conditions including obesity and diabetes. Targeting the couple enteric nervous system (ENS)/inflammation could represent an attractive therapeutic solution to treat metabolic diseases [33]. In multiple sclerosis, Parkinson and Alzheimer`s diseases as well as in other neurodegenerative problems, CNS inflammation is part of the pathogenesis. These diseases intensify consequent to increased CNS inflammation after peripheral insult [34]. Although obesity has been associated with changes in brain structure, little is known about its associations with the rates of brain atrophy. Greater reduction in the volume of gray matter, cingulate, precuneus and orbitofrontal gyrus was detected in people who were extensively obese. The association of obesity with brain atrophy has been reported in obese middle-aged individuals witnessing the onset of cognitive impairment and dementia, while it has little effect on structural brain integrity in no demented older adults [35]. Metabolic disturbances as obesity, insulin resistance and diabetes; and neuropsychiatric disorders have been found in the studies of humans and animals; thus, suggesting the likelihood that both have the same pathophysiological mechanisms. Pleiotropic peptides such as insulin is critical to neuroplasticity, neurotrophism, and neuromodulation. Furthermore, insulin`s role highlights its relevance in the evolution of many neuropsychiatric disorders, and in the mechanisms implicated in the pathogenesis and

progression towards diabetes, obesity and neurodegenerative disorders like Alzheimer's disease [36].

THE ROLE OF PPAR IN THE TREATMENT OF DIABETES

The peroxisome proliferator-activated receptors (PPARs) are improvements that results from the finding that the activation of PPAR is endowed with anti-inflammatory effects. PPARs can regulate immune cell function by inducing metabolic changes through these nuclear receptors. Together, immune cell-specific activation of PPARs can be a promising therapeutic approach for the management of both metabolic and neurodegenerative diseases [37]. PPARγ plays a role as an organizer of lipid metabolism and glucose homeostasis, thus supporting its function as a target for antidiabetic agents.

PLANTS WITH ANTI-DIABETIC POTENTIAL

The discovery that some natural compounds and plants could activate PPARγ opens up the prospect for future development of strategies to take advantage of its therapeutic potential in diabetes [38]. At moderate concentrations, insulin exhibits neurothrophic effect. Excess brain insulin is related with decreased amyloid-beta (Abeta) clearance because both insulin and Abeta compete for insulin-degrading enzyme (IDE) which is their common and main depurative mechanism. The selectivity of IDE is more inclined to insulin than to Abeta; thus, the clearance mechanism of Abeta is affected by brain hyperinsulinism [39].

Insulin is the golden standard for the control of hyperglycemia, which essentially acts on liver tissue activating the glucose-phosphorylating enzymes [40]. Insulin resistance causes hyper-insulinemia and eventually hyperglycemia.

The incidence of diabetes worldwide has continuously been progressive and this is notable in the United States. The estimate in this country is put to a toll of more than 25 million cases consisting of either type 1 or type 2 diabetes [41]. Presently, the most common type is T2D, which, in greater degree, affects the elderly population and globally constitutes a serious health burden with its concomitant effect on the loss of brain neurons manifested as dementia. The mechanism through which diabetes can cause dementia has been evaluated in pre-clinical studies and the cornerstones of this mechanism are aggravation of neuronal insulin resistance, intensification of insulin signaling impairment, establishment of pro-inflammatory condition and mitochondrial dysfunction; as well as an increase in β-amyloid, tau proteins and GSK3β accumulations. Hence, individuals suffering glucose metabolism impairment are likely candidates to suffer early onset of dementia [42].

Studies on therapeutic and preventive potentials of substances derived from plants for the treatment of type 2 diabetes mellitus (T2DM), and obesity are currently the hallmark of extensive researches. Several plant materials possess beneficial bioactive compounds that would be used in the treatment of diabetes; thus, it is essential to consummate a comprehensive knowledge of their effects at the molecular level [43].

The prevalence of diabetes continues to increase in spite of all the effort and progresses in its detection, prevention and insulin therapy. Lifestyle intervention, particularly physical

Table 1: Plants with anti-diabetic potential capable of controlling blood glucose levels.

Compounds	Effects	Ref.
Didymin found in various citrus fruits	Didymin activates insulin receptor substrate (IRS)-1 by increasing phosphorylation at tyrosine 895 and enhancing phosphorylation of phosphoinositide 3-kinase (PI3K), Akt and glycogen synthase kinase-3(GSK-3).	[44]
Incretins are intestinal peptides	Therapies with this substance have shown to be a useful tool to treat diabetic patients (glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide)	[45]
Catalpol and its 10-O-trans-p-coumaroyl derivative, geniposide, harpagoside loganin seco-iridoids, oleuropein and its aglycone and oleocanthal	These substances increase the expression of insulin degrading enzyme (IDE), neprilysin (NEP), PPAR-γ α-secretase decrease the expression of β-secretase (BACE-1) to reduce the levels of Aβ oligomers ($A\beta_0$) deposition in brain neurons, related with neurological disorders as AD and PD	[46]
Sonchus oleraceus Linn (CE), chlorogenic acid and caffeic acid	Attenuate insulin resistance and modulate glucose uptake. They also prevent the inactivation of the PI3K/AKT pathway, as well as the diminution of GLUT4 levels induced by high glucose	[47]
Cocoa-rich	Has antihyperglycemic effect which appears to be mediated through the diminution of phosphoenolpyruvate-carboxykinase (PEPCK), glucose-6-phosphatase (G-6-Pase), sodium-glucose-co-transporter-2 (SGLT-2) and glucose-transporter-2 (GLUT-2) levels.	[48]
Pomegranate aril juice (PAJ)	Alleviates most of the signs of type 2 diabetes including body-weight loss, insulin resistance (IR) and hyperglycemia by decreasing serum tumor necrosis factor-α concentration and the expression of hepatic c-Jun N-terminal kinase by increasing the skeletal muscle weight and the expression of hepatic insulin receptor substrate-1, as well as by oxidative stress.	[49]
Indigo	Aryl hydrocarbon receptor (AhR) ligand agonist is a potent inducer of IL-10 and IL-22 and functions as a protector against high-fat diet (HFD)-induced insulin resistance and fatty liver disease	[50]
Herbacetin and sorbaria sorbifolia	Have an energy-binding (>8.0 kcal/mol) substances and dissociation constant, herbacetin and sorbaria sorbifolia were the most suitable ligands for management of diabetes mellitus.	[51]

Symphyocladia latiuscula (Harvey) Yamada	It is a good source of bromophenols with numerous biological activities inhibitors of tyrosine phosphatase 1B (PTP1B) and α-glucosidase. It enhances insulin sensitivity and glucose uptake.	[52]
Thymus praecox subsp. skorpilii var. skorpilii methanolic extract (TPSE)	Elevates plasma insulin levels and normalizes blood glucose levels. Also, it improves the values of AMPK in liver and GLP-1 in pancreas. Moreover, it increases α-glucosidase, PEPCK, GLUT-2 and SGLTs levels	[53]
Aspalathin-enriched green rooibos extract (GRE)	It has a strong potential to ameliorate hepatic insulin resistance by improving insulin sensitivity through the regulation of PI3K/AKT, FOXO1 and AMPK-mediated pathways.	[54]
Black ginger (BG)	Contains several kinds of polymethoxy flavones and has PPARγ ligand-binding capacity *in vitro*. It prevents obesity and insulin resistance independent of adiponectin secretion	[55]
Lupinus angustifolius L.	Simulates lupin hydrolysate mechanism and stimulates insulin secretion via $G\alpha_q$ mediated signal transduction ($G\alpha_q$/PLC/PKC) in the β-cells	[56]
Aged black garlic (ABG)	Partially improves the metabolic and vascular alterations induced by a high-fat/high-sucrose diet in rats through modifications in the gene expression of proteins and neuropeptides involved in inflammation, fat metabolism and food intake regulation.	[57]
Clinopodium chinense (Benth.) O. Kuntze	Inhibits the inflammatory response and alleviates impaired insulin signaling in the vascular endothelium by suppressing TLR4-mediated NF- κ B and MAPK pathways	[58]
Boswellia serrate (BS)	Reduces significantly the hippocampal elevated levels of caspase-3, cholinesterase (ChE), GSK-3β, TNF-α, IL-1β, IL-6, MDA alleviates insulin resistance and hyperlipidemia	[59]
Edible Chrysanthemum (EC)	Shows antidiabetic effects such as improvement in insulin resistance and the down-regulation of the blood glucose level	[60]
Scutellariae Radix (SR) and Coptidis Rhizoma (CR)	Mitogen-activated protein kinase (MAPK) signaling pathway has been suggested to play a critical role during the process of inflammation, insulin resistance T2DM. Hyperglycaemia, dyslipidemia, inflammation insulin resistance in T2DM were ameliorated by SR and CR.	[61]
Aronia melanocarpa (chokeberry)	Decreases body weight, serum triglyceride (TG) low-density lipoprotein cholesterol (LDLC) levels and improves insulin sensitivity	[62]
β-elemene	Suppresses insulin-driven cell growth and the activation of mTOR and PI3K in tumor cells	[63]
Cajanonic acid A (CAA)	Reduces the serum fasting levels of total cholesterol, triglycerides and low-density lipoprotein cholesterol and restores the transduction of insulin signaling by regulating the expression of PTP1B and associated insulin signaling factors.	[64]
Astragalus polysaccharide (APS)	Enhances tyrosine phosphorylation of insulin receptor substrate 1 (IRS1, $p < 0.05$) and phosphor-Akt content ($p < 0.01$). Besides, phosphorylated AMP-activated protein kinase (AMPK) content and improves insulin sensitivity by enhancing glucose uptake, possibly through AMPK activation	[65]
Balanites aegyptiaca (BA)	BA treatment produced a reduction in plasma glucose, HbA_{1c}, lactic acid, lipid profile, malondialdehyde levels and increased insulin. Also, glutathione levels, catalase and superoxide dismutase activities were reduced by this treatment. The hypoglycemic effect is due to the inhibition of SAPK-JNK pathway	[66]
Citrus sinensis fruit peel (CSMe)	Increases the expression of PPARγ in the adipose tissue and signaling molecules GLUT4 and insulin receptor	[67]

activity, and the use of an adequate insulin regimen plus timely initiation and intensification of insulin therapy in combination with antidiabetic plants that may improve blood glucose levels are key factors in achieving optimal glycemic control (Table 1). For example, the administration of a natural dietary supplement that contains Curcuma longa, silymarin, guggul and chlorogenic acid; in combination with insulin can lower RNS, ROS and lipid peroxidation levels; and cause a decline in i-NOS, IL-6, p-ERK, HSP60, H-Oxy, GFAP, p-ERK, IL-1β, and NF-kB expressions; as well as in CD4 positive cell infiltration; thus, decreasing the rate of the accumulation of brain fat, and down turning the establishment of oxidative stress and inflammatory conditions, as well as improving brain insulin resistance [68].

CONCLUSION

Indeed, since time immemorial, herbal drugs have been successfully used for the treatment of multiply diseases and disorders with unsurpassed advantages, which can be summarized in lesser side effects, easily and abundantly available and low cost.

DECLARATIONS

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Availability of data and material

All data analyzed during this study is included in this published article. Besides, any additional data/files may be obtained from the corresponding author.

Author Contribution

DCG[1,2,3,4,5], AVP[2,3,5], HJO[2,3,4,5], MPS[3,4,5], FTJ[3,4,5]

(1) Contributed to conception and design. (2) Contributed to acquisition, analysis, or interpretation of data. (3) Critically revised the manuscript for important intellectual content. (4) Drafted manuscript. (5) Gave final approval

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