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Histological and immunohistochemical study of the neuroprotective potentials of trans-cinnamaldehyde in Wistar rat model of insulin resistance

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ABSTRACT

INTRODUCTION: The incidence of insulin resistance is on the increase globally. Earlier reports linked impaired insulin signaling and glucose intolerance to cognitive decline, suggesting that improving insulin signaling could enhance neuronal survival. Trans-cinnamaldehyde (TCA) is an active component of cinnamon and has many pharmacological importance. However, the effects of TCA on insulin resistance-induced neurodegenerative changes are unclear. This study, therefore, aimed at evaluating the effects of trans-cinnamaldehyde on hippocampal histoarchitecture in insulin-resistant rats.

METHODS: Twenty adult Wistar rats were fed with a high-fat diet for 8 weeks and then injected with a low dose of STZ (30 mg/kg body weight intraperitoneally). 60mg/kg of TCA was orally administered once daily for 4 weeks. Histological and immunohistochemical techniques were used to investigate the ameliorative potentials of TCA on the hippocampus of Wistar Rats.

RESULTS: TCA administration to insulin-resistant rats histologically and immunohistochemically reduced pyknosis, astrogliosis, and neurodegenerative changes in the hippocampus when compared with untreated insulin-resistant rats.

CONCLUSION: TCA prospect as a novel therapy in insulin-resistant subjects with neurogenerative diseases could be further explored.

Keywords: High-fat Diet; Hippocampus; Insulin-resistant; Trans-cinnamaldehyde

INTRODUCTION

Insulin resistance (IR) is a state of impairment in the blood glucose-lowering effect of circulating or injected Insulin, which is the central feature of type 2 diabetes mellitus (T2DM) and metabolic syndrome [1,2].

In the pathogenesis of Alzheimer's disease (AD) IR has been implicated. AD shares some molecular and biochemical features with IR; hence, it is referred to as "type 3 diabetes" [3]. The association between diabetes and AD may partly be due to the systemic mitochondrial dysfunction that is common to these pathologies [3].

Long-term IR in the peripheral tissues promotes IR in the brain by suppressing the uptake of

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Insulin and accelerating the accumulation of Aβ in the brain [4], it has been proposed that neurons can develop hyperinsulinemia-induced insulin resistance [1]. Chronic hyperinsulinemia may lead to a compromise in the blood-brain barrier and subsequently abrogate insulin activity. Prolonged neuronal exposure to a hyperinsulinemic environment has been reported to result in irreversible cognitive dysfunction and neuronal degeneration [5].

Deficits in hippocampal function have been attributed to peripheral insulin resistance and hyperlipidemia induced by a high-calorie diet [6,7]. Several findings linked impaired insulin function and glucose metabolism to the risk of developing AD-type neurodegeneration [8].

High-fat diet (HFD) intake containing mainly saturated fats is on the increase globally, leading to increased incidence of insulin resistance, diabetes, and other metabolic syndromes [2]. This increased intake of HFD has directly or indirectly resulted in an exacerbation of dementia [9].

Hence, there is a need to explore the therapeutic potentials of trans-cinnamaldehyde, which has been reported to possess anti-inflammatory and other neuroprotective properties on the hippocampal histomorphology and functions in insulin resistance [10].

METHODS

Animal Acquisition and Handling: Twenty (20) adult Wistar rats weighing 160 ± 10 g were purchased from the Department of Anatomy, Ladoke Akintola University, Ogbomosho. The rats were housed in the Animal House of the Faculty of Basic Medical Sciences, University of Ilorin, Nigeria. The rats were allowed to acclimatize for fourteen days. The rats were fed daily with rat pellets from Ogo-Oluwa feed and Flour Mill Limited, Sango, and Ilorin. The rats had access to water ad libitum. Standard guidelines for animal handling as approved by UERC were followed.

Animal grouping and Induction of Insulin-resistance: To induce Insulin- resistance, rats were fed a high-fat diet, as previously described [12], for eight weeks. They administered a single dose of 30 mg/kg STZ (Sigma-Aldrich Inc., St. Louis, MO, USA Lot #MKCD4749) intraperitoneally [13] at the end of the eighth week. Blood samples were withdrawn from the tail veins of the rats, the Wistar rats were fasted overnight, and the fasting blood glucose level was checked using a digital glucometer (Accu-Check, Roche, Belgium). Wistar rats with fasting blood glucose concentrations not less than 200 mg/mol were included in the study.

Trans-cinnamaldehyde treatment: Following the induction of insulin resistance, 60 mg/kg of TCA (Sigma-Aldrich Inc., St. Louis, MO, USA Lot #MKCD4749) was administered daily for four weeks orally. The rats were randomly assigned into four (4) groups: Control, Insulin resistance control, TCA only, and Insulin resistance + TCA (60mg/kg)

Histopathological Studies: The rats were anesthetized with intramuscular injection of ketamine 30 mg kg−1 and perfused transcardially with sterile Phosphate Buffered Saline (PBS), following 10% formol-saline, and their hippocampus was then excised and then fixed in 10% formalin for histological examination using hematoxylin and eosin (H&E), cresyl fast violet (CFV) and Immunohistochemical staining techniques. Immunohistochemical techniques were used to quantify the level of beta-amyloid, Glia Fibrillary Acidic Protein (GFAP) for astrocyte distribution and Neuronal nuclei (NeuN) for nuclei protein expression using the beta-amyloid, GFAP, and NeuN kits (Santa Cruz, Germany) according to the manufacturer's instructions and modified method[14]. Stained sections were viewed under a light binocular microscope (Olympus, NJ, USA) attached to an Amscope Digital Camera (MD500, CA, USA).

The approval for this research was given by the University of Ilorin Ethical Review Committee (UERC) with approval number UERC/ASN/2018/1157. The research was conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals [11].

RESULTS

Trans-cinnamaldehyde Treatment Restores Insulin-resistant Induced Hippocampal Cytoarchitectural Distortion

Microscopic examination of the CA3 region of the control and the TCA-alone treated group shows normal basic histological features of the hippocampus. The histological presentations of these groups were dominated by distinct cellular

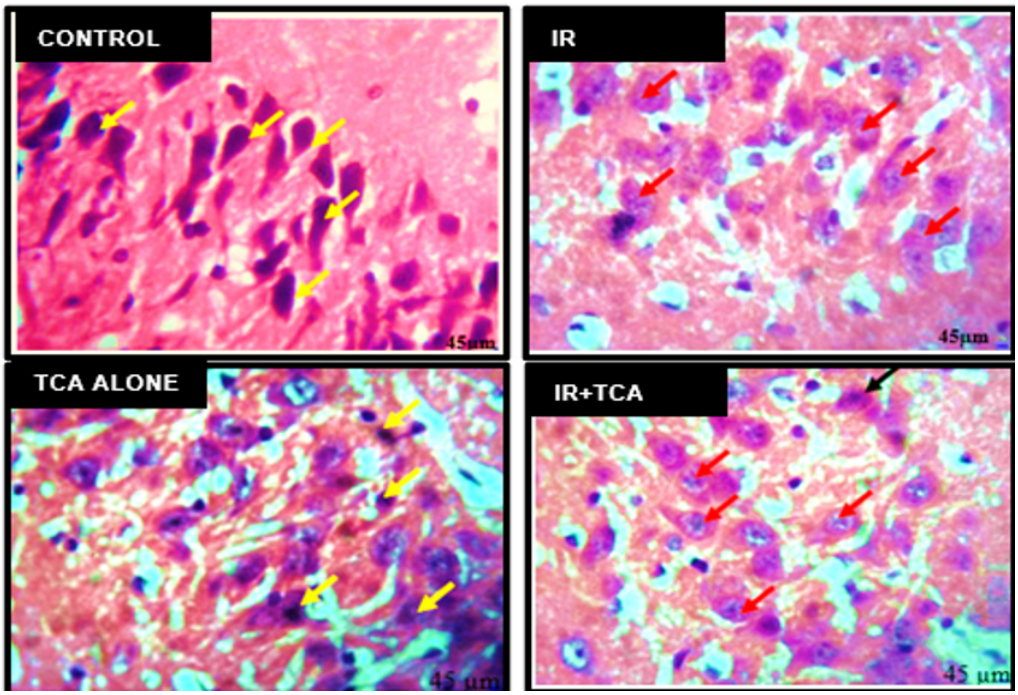

Figure 1: *Representative photomicrographs of Haematoxylin and Eosin staining of the CA3 region of the hippocampus of Wistar rats, the hippocampus of the control group presents normal neuronal layers (yellow arrows) with well-organized pyramidal cells. In contrast, the insulin-resistant group (IR) was characterized by various degenerative changes with pyknotic nuclei (red arrows), a reduced layer of neuronal cells and neuronal vacuolation. TCA alone treated group with well-organized pyramidal cells (yellow arrows), IR+TCA treated group with reduced pyknotic cells (red arrows) comparable to the control.. (TCA=Trans-cinnamaldehyde; IR=insulin-resistant)*

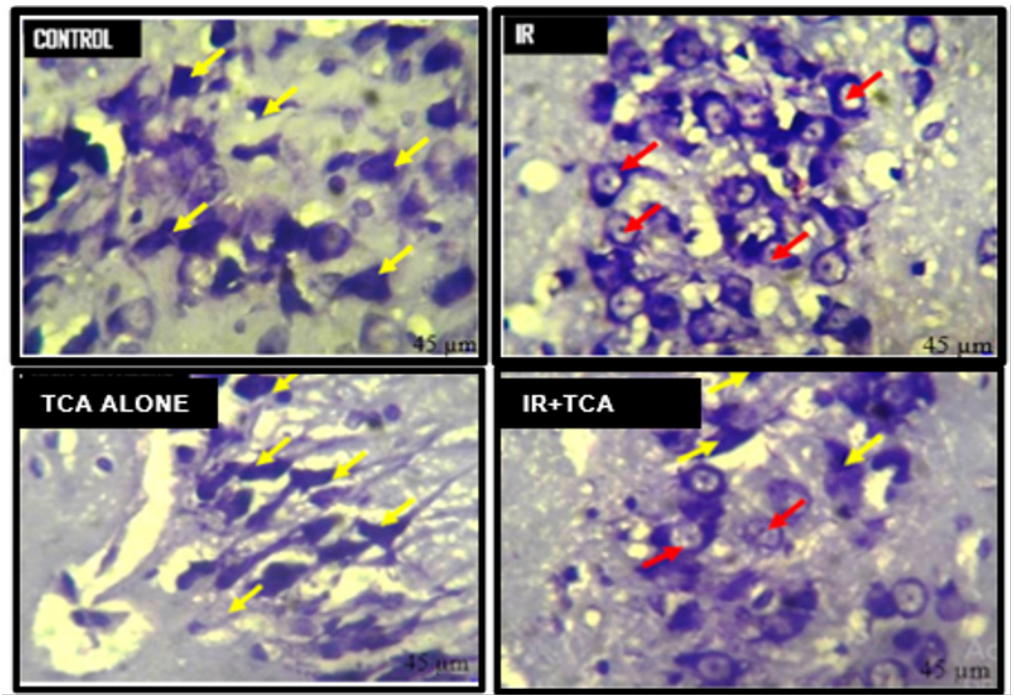

Figure 2: Representative photomicrographs of Cresyl fast violet staining of the CA3 region of the hippocampus of Wistar rats of the control group showing highly chromatogenic (yellow arrows) cells, the Insulin-resistant group (IR) showing chromatolytic cells (red arrows) with poor staining intensity. TCA alone treated group with highly chromatogenic pyramidal cells (yellow arrows), treatment of insulin-resistant rats with TCA shows improved chromatogenic properties of the pyramidal cells and neuroglia within the CA3 region of the hippocampus (yellow arrows).
(TCA=Trans-cinnamaldehyde; IR=insulin-resistant)

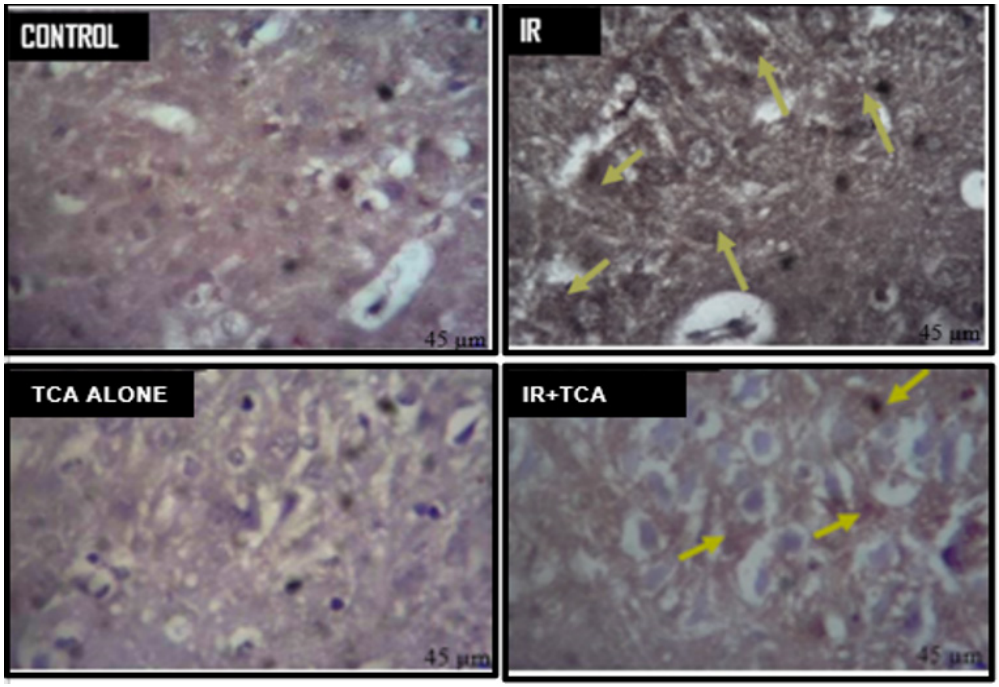

Figure 3: Representative photomicrographs of amyloid immunohistochemical staining of the CA3 region of the hippocampus of Wistar rats showing the control group with normal amyloid distribution, Insulin-resistant group (IR) with multiple amyloid deposition (yellow arrows). The TCA alone group had a normal amyloid distribution, and the insulin resistant group was treated with TCA (IR+TCA) with reduced amyloid distribution (yellow arrows). (TCA=Trans-cinnamaldehyde; IR=insulin-resistant; HFD=High Fat Diet)

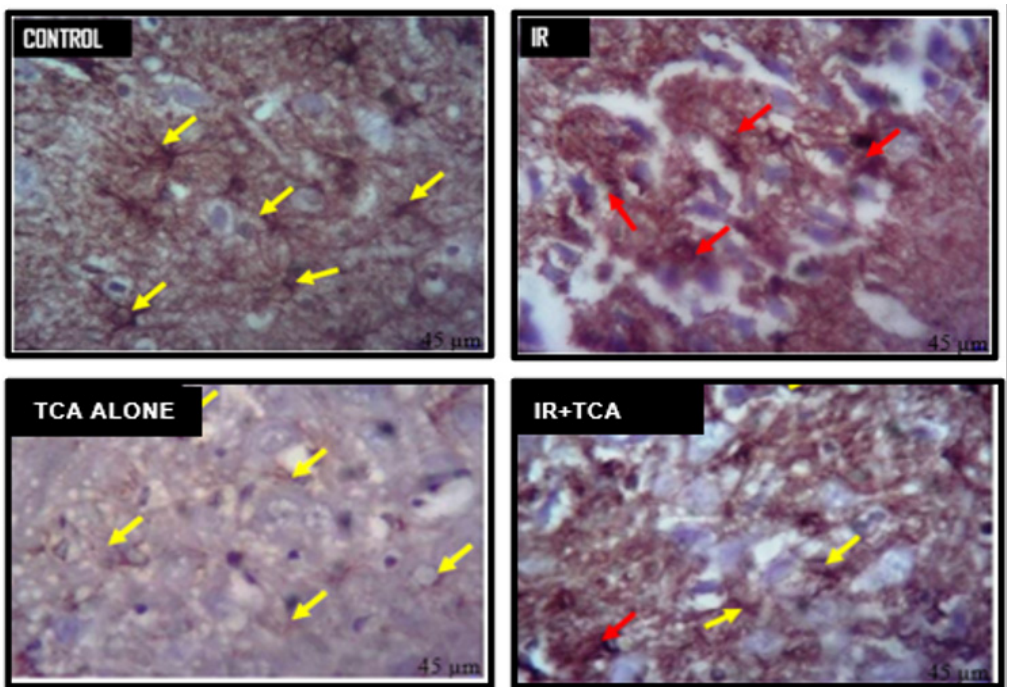

Figure 4: Representative photomicrographs of immunohistochemical staining of the CA3 region of the hippocampus of Wistar rats using GFAP immunostaining. The control group shows normal astrocytic morphology and distribution with normal processes (yellow arrows). On the other hand, the astrocyte of the insulin-resistant group (IR) is characterized by increased GFAP staining, astrogliosis and increased astroglia size (red arrows). TCA alone group was characterized by normal astrocytic expression with regular distribution (yellow arrows), and the Insulin resistant group treated with TCA (IR+TCA) had normal astrocytic morphology (yellow arrows).

morphology with normal staining intensity, distinctly arranged pyramidal cell layers (Figure 1) with highly chromatogenic cells and cellular cytoarchitecture (Figure 2), the well-arranged hippocampal cellular layer and neuronal morphology in these groups suggest appropriate interconnectivity within the hippocampus. However, the insulin-resistant group (Figure 1-IR), shows disorganization of neuronal cell layers, with degenerating and pyknotic nuclei, and chromatolytic cells with poor staining intensity (Figure 2-IR). The pyramidal cells were however preserved in the insulin-resistant treated groups (IR-TCA), with improved chromatogenic properties of the pyramidal cells and neuroglia within the CA3 region of the hippocampus (Figure 2- IR-TCA) were also observed, this result shows that TCA was able to protect the histo-architectural morphology of the hippocampus following HFD/STZ administration.

Trans-cinnamaldehyde Treatment Reduces the Expression of Beta-amyloid Plaques

Immunohistochemical examination of the CA3 region of the hippocampus with amyloid immunostaining of the control and TCA-alone groups shows normal amyloid distribution (Figure 3) however, there was an observed multiple deposition of amyloid plaque in the CA3 region of the hippocampus of the insulin-resistant group (Figure 3-IR). Treatment with TCA (IR+TCA) shows a reduced amyloid burden comparable to the control in the CA3 region of the hippocampus of Wistar rats.

Trans-cinnamaldehyde Intervention Reduces Astrogliosis

Examination of the control group using GFAP immunostaining shows normal astrocytic morphology and distribution with normal processes (Figure 4). On the other hand, the astrocyte of the insulin-resistant group (Figure 4-IR) is characterized by increased GFAP staining, prominent astrogliosis, and increased astroglia size (red arrows), the presence of hypertrophied reactive astrocytes surrounding amyloid plaques with increased thickness of their cytoskeletal processes was demonstrated in the insulin-resistant group (Figure 4; IR) compared to the control. TCA alone group was characterized by normal astrocytic expression with regular distribution (yellow arrows), while the Insulin resistant group treated with TCA (Figure 4; IR+TCA) had normal astrocytic morphology

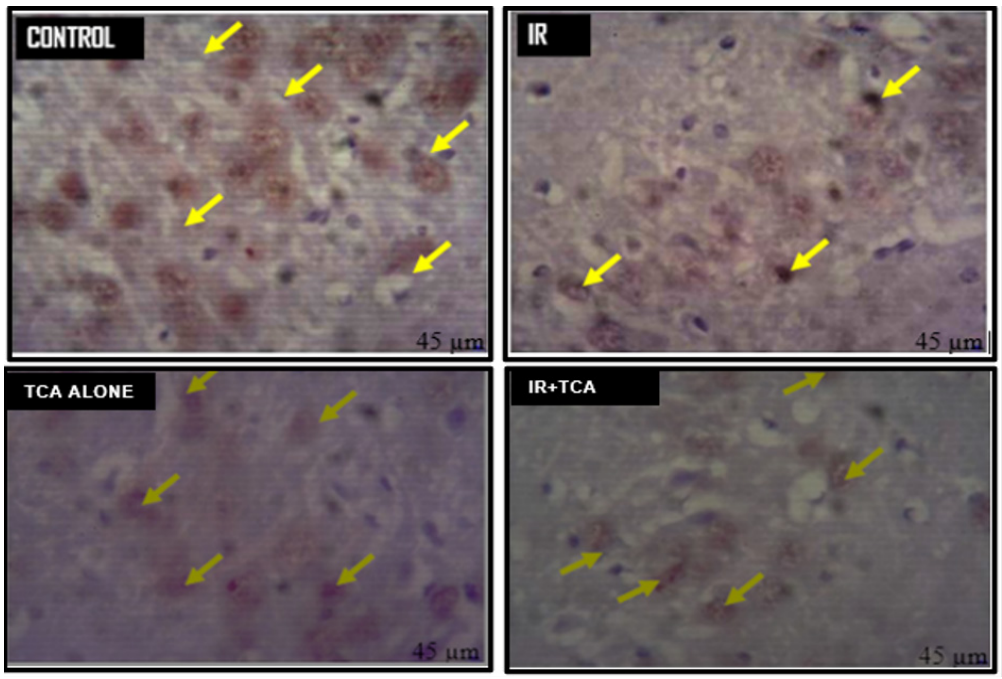

Figure 5: Representative photomicrographs of NeuN immunohistochemical staining of the CA3 region of the hippocampus of the control characterized by increased NeuN immunoreactivity with normal cellular architectural layout (yellow arrows) and insulin-resistant group (IR) with decreased NeuN immunoreactivity and nuclear degeneration (yellow arrows); TCA alone showing normal NeuN immunoreactivity and nuclear content (yellow arrows), treatment of Insulin resistant rats with TCA (IR+TCA) shows improved NeuN immunoreactivity

(yellow arrows) and reduction in the thickness of these processes compared to the insulin-resistant control group.

Trans cinnamaldehyde Treatment Restores Neuronal Loss

NeuN is a neuron-specific nuclear protein expressed in the nucleus and cytoplasm of most neuronal cell types in vertebrate nervous systems. The control and TCA-alone groups show normal cellular architecture of the CA3 region of the hippocampus with increased NeuN immunoreactivity and normal cellular layout (Figure 4), however, there were observed degenerative changes and loss of NeuN immunoreactivity in the insulin-resistant group.

Treatment of insulin-resistant rats with TCA shows an improved NeuN immunoreactivity in the CA3 region of the hippocampus of Wistar rats.

DISCUSSION

Neurons are metabolically active insulin-dependent tissues; while in insulin-resistant state, the ability to respond properly to the neurotrophic properties of Insulin is lost, resulting in neuronal injury, neuronal dysfunction, AD, and related diseases [1]. It was shown from the result that the hippocampus of the control and the group treated with TCA had normal basic histological features of the hippocampus comparable to the normal control (Figure 1). The histological presentations of these groups were dominated by distinctly arranged pyramidal cell layers. The well-arranged hippocampal cellular layer with high chromatogenic cells (Figure 2) and neuronal morphology in these groups suggest an appropriate interconnectivity within the hippocampus. Insulin resistant group, however, shows disorganization of neuronal cell layers, with degenerating pyknotic and chromatolytic cells. Such alteration in cellular morphology may be responsible for the behavioral deficits observed in Y-Maze and MWM tests earlier reported [10]. This result shows that TCA was able to protect the histo-architectural morphology of the hippocampus following neurotoxicity.

An increased deposition of amyloid plaque was observed in the hippocampus of HFD/STZ-treated rats. Alzheimer's disease is primarily characterized by the formation of amyloid β (Aβ) plaques, amyloidal angiopathy, neurofibrillary tangles, and loss of neurons and synapses [15]. However, treatment with TCA reduced amyloid plaque burden (Figure 3). This may be due to the anti-inflammatory and hypoglycemic activities of TCA earlier reported in this study [10]. Previous works have shown that cinnamon has activities against neurological disorders, such as Parkinson's and Alzheimer's diseases [16, 17]. The increased Aβ accumulation in the HFD/STZ may partly be due to increased levels of TNF-α earlier reported [18]. AD-like pathological changes such as abnormal Aβ deposition and tau hyperphosphorylation were observed in patients with insulin resistance and type II diabetes and diabetic animal models [19]. High levels of amyloid beta in the brain can lead to neuronal structure deterioration [17], which may be responsible for the poor cognitive performance observed in the neurobehavioral tests conducted in this study. Treatment with TCA significantly ameliorated cognitive deficits, with significant decreases in amyloid burden and TNF-α levels via inhibition of NF-κB in the brain as well as attenuation of hyperglycemia and hyperinsulinemia.

In this study, GFAP was significantly increased in the insulin-resistant group compared to the control and TCA alone groups (figure 4), which disagrees with findings [20] that reported a decrease in GFAP activity in the insulin resistance model. The reaction of astrocytes has been reported to be the earliest response of the brain tissue to an altered glucose metabolism [20]. Astrocytes constitute the most abundant class of neuroglia. They are widely distributed in the mammalian nervous system, serving a wide range of adaptive functions [21]. Astrocytes interact with neurons to provide structural, tropical, and metabolic support. They are now emerging as key components in many aspects of brain development, function, and disease [21]. Astrocytes have increasingly been implicated in most demyelinating diseases. Astrocytes are critical for the survival of neurons in the central nervous system (CNS) by playing a role in energy metabolism, maintenance of the blood-brain barrier, vascular reactivity, regulation of extracellular glutamate levels, and protection from reactive oxygen species. These cells react to the neuronal damage resulting from physical or chemical insults by over-expression of the glial fibrillary acidic protein, an intermediate cytoskeletal filament protein specific for astrocytes. The presence of reactive astrocytes surrounding amyloid plaques, which appeared hypertrophied with increased thickness of their cytoskeletal processes, was demonstrated in the insulin-

resistant control group compared to control TCA treatment shows a reduction in the thickness of these processes compared to the insulin-resistant control group. Moreover, prominent astrogliosis was revealed in an insulin-resistant group. These astrocytes play a vital role in the degradation of amyloid plaques through the astrocytic processes, which internalize and degrade Aβ deposits [22].

NeuN is a neuron-specific nuclear protein expressed in the nucleus and cytoplasm of most neuronal cell types in vertebrate nervous systems [23]. In this work, there was an observable decrease in NeuN immunoreactivities. Studies have suggested that quantitative changes in NeuN immunoreactivity can be a determinant of neuronal loss in several pathologies, including neurodegenerative diseases [23]. Neuronal degeneration and cognitive impairment are the most typical features of Alzheimer's disease [24], which can have a direct impact on the ability of the patient to recall or recognize new information processed in the hippocampus [24]. In the insulin-resistant group (figure 5), NeuN immunoreactivity was lost. However, the administration of TCA restores the immunoreactivity. This is in accord with numerous studies which have reported neurogenesis in hippocampal neurons [25,26]. Changes in neurogenesis have been reported to alter some hippocampal-dependent functions, such as learning and memory [27]. Neurogenesis and neuroplasticity in the hippocampus are sensitive to many pathogenic and treatment factors that are associated with metabolic diseases, including diabetes. Previous studies provide strong evidence that diabetes adversely affects the structural integrity of the hippocampus, which may contribute to diabetes-induced cognitive impairment [28].

In conclusion, this study shows that TCA reverses insulin resistance-induced neurodegenerative changes.

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