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Elucidation of Ameliorative Role of 3-Acetyl-11-Keto-Beta-Boswellic Acid Through PPAR-Γ/MPO'S/ BDNF Regulation in Diabetic Neuropathy Rats

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KEYWORDS
HFD, STZ, AKBA, Diabetic neuropathy

ABSTRACT:

Background: The resinous part of *Boswellia serrata* possesses monoterpenes, diterpenes, triterpenes, tetracyclic triterpenic acids, and pentacyclic triterpenic acids. Boswellic acids have been thoroughly investigated for their possible role in neuroprotection in an *in-vivo* model. Anti-diabetic effects via inhibition of DPP4 and GLP-1 and Insulin receptors can be potential biological targets of boswellic acid. **Aim & Objective:** To study the effect of 3-acetyl-11-keto-β- Boswellic acid in a high-fat diet (HFD) with Streptozotocin (STZ) induced diabetic neuropathy in rats. **Methodology:** Totally 5 groups of rats were used for the study. control, HFD+STZ-induction, Pioglitazone (10mg/kg), and 2 test groups (AKBA at 10 and 30 mg/kg). Behavioral studies such as Hot plate, Pin-prick, and Sciatic functional index and biochemical studies like Oxidative marker levels, Lipid marker levels, and Lipid peroxidation marker levels in Serum estimation were performed. Moreover, the histology of the Sciatic nerve and Pancreas were performed. **Results:** The administration of AKBA (10 and 30 mg/kg) reversed the changes in behavioral, biochemical, Lipid parameters, and Peroxidation levels in HFD+STZ-induced rats. Histopathological analysis demonstrated the improvement in the Sciatic nerve and Pancreas tissue on AKBA administration when compared to the control and negative control group. **Conclusion:** The study concludes that AKBA can be a potent drug to treat diabetic neuropathy induced by HFD+STZ-induced in rats.

1. Introduction

Diabetic neuropathy represents one of the most prevalent and debilitating complications of diabetes mellitus, affecting a significant proportion of individuals with both type 1 and type 2 diabetes [(1)]. It encompasses a heterogeneous group of peripheral nerve disorders characterized by progressive damage to the nervous system, leading to sensory, motor, and autonomic dysfunction [(2)]. Among various animal models utilized to study diabetic neuropathy, rats have emerged as particularly valuable tools due to their physiological similarities to humans and the feasibility of inducing diabetes experimentally [(3)]. This introduction aims to provide a comprehensive overview of diabetic neuropathy in rat models, highlighting key pathophysiological mechanisms, experimental techniques, and therapeutic interventions [(4,5)]. The pathogenesis of diabetic neuropathy is multifactorial, involving a complex interplay of metabolic, vascular, and neurodegenerative processes [(6)]. Hyperglycemia, the hallmark feature of diabetes, is considered a central driver of nerve damage, leading to the accumulation of advanced glycation end products (AGEs) and oxidative stress [(7)]. These metabolic abnormalities contribute to

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microvascular dysfunction, impaired nerve conduction, and axonal degeneration [8]. Additionally, dysregulated insulin signaling, neuroinflammation, and mitochondrial dysfunction have been implicated in the pathophysiology of diabetic neuropathy [9]. Despite the significant progress made in elucidating the pathophysiological mechanisms of diabetic neuropathy in rat models, effective therapeutic interventions remain elusive [10]. Current treatment strategies primarily focus on glycemic control, symptomatic relief, and management of comorbidities. However, emerging therapeutic approaches targeting specific molecular pathways implicated in diabetic neuropathy, such as neuroinflammation and oxidative stress, hold promise for future clinical translation [7]. Furthermore, developing novel animal models that more closely mimic the clinical heterogeneity of diabetic neuropathy and the implementation of advanced imaging modalities may facilitate the identification of novel therapeutic targets and the evaluation of treatment efficacy in preclinical studies [11]. The effect of nutrition, especially high-fat meals, in aggravating diabetic neuropathy is one important environmental component that has attracted attention recently [43]. High-fat diets, which are defined as consuming large amounts of cholesterol and saturated fats, have been linked to the onset, development, and complications of diabetes. Research indicates that eating a high-fat diet can lead to the development of insulin resistance, dyslipidemia, and persistent low-grade inflammation. These conditions are recognized to have a role in the etiology of diabetic neuropathy. Moreover, streptozotocin (STZ), a substance that specifically kills pancreatic beta cells and causes insulin insufficiency and hyperglycemia, is frequently administered in experimental models of diabetic neuropathy. Comparing STZ-induced diabetic rats to those on a normal diet, the former show rapid development and greater severity of neuropathic symptoms when paired with a high-fat diet. Boswellia serrata's resinous part contains monoterpenes, diterpenes, triterpenes, and four major pentacyclic triterpene acids. Its oleo-gum resin is used to treat inflammation [15], asthma [12], colitis [14], headaches, and arthritis [13]. It has antioxidant, immune system modulation, anti-inflammatory, and neuroprotective properties [44,45].

2. Materials and Methods

Chemicals: AKBA (3-O-Acetyl-11-keto-β-Boswellic Acid) from Natural remedies, Pioglitazone HCL, and Streptozotocin from Sigma-Aldrich.

Experimental animals:

Male Sprague rats (n=30) weighing 150- 200g were obtained from Biogen laboratory animal facility, Bangalore (Biogen Laboratory Animal Facility, Bangalore, Reg. No:971/bc/06- CPCSEA). Rats were kept in separate cages (6 animals per cage) and housed with husk as a bedding material under normal room temperature (25±2º C), 12/12 hr light-dark cycle as well as constant relative humidity (55±5%) throughout the experimental period according to CCSEA guidelines. Project Proposal Number (KMCRET/ReRc/M.Pharm/74/2023).

High fat and high Sugar Diet:

Vanaspati ghee and coconut oil were combined in a 3:1 (v/v) ratio to create high fat. The dosage administered to the rats every day, based on body weight, was 3 milliliters per kilogram. Rats were given a high-sugar diet that included 25% fructose by oral [16].

Experimental design:

A high-fat, high-sugar diet was used to induce diabetes for 12 weeks. During the fourth week, intraperitoneal injection of streptozotocin (35 mg/kg) was given. Following 3 days, rats' blood sugar levels were assessed, and those exceeding 250 mg/dL were classified as diabetic. The diabetic rats were separated into several groups.

Group 1: Throughout the trial, the animals in this group were fed a regular pellet diet and were given purified water to drink for 24 hours. They were regarded as the control group.

Group 2: Throughout the trial, the animals were given a conventional pellet food, a water bottle containing 25% fructose for 24 hours, and 3 millilitres of a high-fat diet. This group was referred to as the induction group.

Group 3: Following six weeks of research, pioglitazone at a dose of 10 milligrams per kilogram was given to the animals. This group was regarded as standard and got a standard pellet food, 3 milliliters of high-fat diet, and 23% fructose in a water bottle for 24 hours.

Group 4: After six weeks of research, AKBA at a dose

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of 10 milligrams per kilogram was given to the animals throughout the study and was referred to as Test Group 1. The animals also received a normal pellet meal and 24 hours of 23% fructose in a water bottle and 3 milliliters of a high-fat diet.

Group 5: Following six weeks of research, AKBA at a dose of 30 milliliters per kilogram was given to the animals, which is regarded as Test Group 2. The animals also received a normal pellet food, 24 hours of 23% fructose in a water bottle, and 3 milliliters of a high-fat diet.

Body weight analysis:

The animal's body weight was analyzed on initial week, 4th week, 7th week, and 12th week.

Estimation of fasting blood glucose levels:

Using a glucometer and glucose oxidase-peroxidase reactive strips, blood samples were drawn from the tip of the rat tail vein, and glucose levels were calculated. On the 26th, 30th, 63rd, and 84th days, the blood glucose levels were estimated.

Behavioral assessment of mechanical sensitivity by Pin-prick method:

A 90°-bent gauge needle was used to touch the rat's rear paw to ensure that the needle had not pierced the skin; instead, a pick was made. All groups' reflexive withdrawal reactions were noted and observed. The paw withdrawal was timed and recorded in seconds, with a 20-second cutoff. All group outcomes were documented [(17)].

Behavioral assessment of thermal hyperalgesia by Hot-plate method:

Inside the restrainer, each animal was placed separately on Eddy's hot plate, which was kept at 55±1°C. The timer went off. The rats were timed to see if they would leap or lick their paws in response to the thermal pain, which yielded the reaction time (in seconds) latency period or nociceptive threshold. To prevent harm to the paw, the cut-off time was set at ten seconds [(18)].

Behavioral assessment of Sciatic nerve function:

One technique for assessing walk track analysis has been SFI. It's applied in the evaluation of nerve and motor function. After dipping the rat hind paws in ink and letting them roam around freely, the SFI of the pictures on a piece of white paper was calculated. To get enough footprints on the white paper, each animal only needed to take one stroll. Following analysis of the footprints, the following foot lengths were determined. Print length (PL): The distance from heel to toe; Toe spread (TS): The distance from the first toe to the fifth; Intermediary toe-spread (IT): The distance from the second to the fourth toe; All these measurements were taken from the experimental (E) and normal sides (N). The factors were calculated as follows: Print Length Factor (PLF) = (EPL-NPL)/NPL; Toe Spread Factor (TSF) = (ETS-NTS)/NTS; Intermediary Toe Spread Factor (ITF) =(EIT-NIT)/NIT; Where, EPL = experimental print length, NPL = normal print length, ETS = experimental toe spread, NTS = normal toe spread, EIT = experimental intermediary toe spread, NIT = normal intermediary toe spread, These factors were incorporated into the SFI formula derived by Bain *et al.*,1989; **SFI=-38.3 *PLF + 109.5 * TSF + 13.3 x*ITF - 8.8**. An SFI of 0 is normal and -100 indicates total impairment due to a complete transaction of the sciatic nerve [(19)].

Blood Biochemical Analysis:

Blood was collected from the animals and subjected to centrifugation to obtain the serum. The serum level of Superoxide dismutase (SOD), Catalase (CAT), Reduced glutathione (GSH), Glutathione peroxidase (GPx), malondialdehyde (MDA), Lipid Peroxidation (LPO), Total Cholesterol (TC), Triglycerides (TG), LDL cholesterol, HDL cholesterol, VLDL cholesterol, Atherogenic index, and Total protein was measured.

Histopathological assessment:

The animals were sacrificed using high doses of anesthesia and cervical dislocation. The animals were cut and the Pancreas and Sciatic nerve were instantly dissected out, excised, and rinsed in ice-cold saline solution. A portion of the Pancreas and Sciatic nerve was fixed in 10% neutral formalin fixative solution, was fixed in 10% formalin, dehydrated in alcohol, and then embedded in paraffin. Microtome sections of 4-5µm thickness were made by using rotary microtome. The sections were stained with hematoxylin-eosin (H&E) dye to observe the histopathological changes.

Statistical analysis:

Data will be expressed as Mean ± SD. Statistical analysis will be carried out by one-way ANOVA followed by post hoc analysis Tukey's multiple comparison test and two-way ANOVA followed by Bonferroni test using prism 5.0, considered as statistically significant. Data will be analyzed using Graph Pad Prism 5.0 (la Jolla, CA. USA).

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3. Results

AKBA treatment on Body weight in HFD-induced diabetic neuropathy rats

HFD+STZ-treated rats showed [P<0.001] increased body weight when compared to the control in the 4th week **(fig 2)**. HFD+STZ-treated rats showed [P<0.001] decreased body weight when compared to the control on the 7th week **(fig 3)**. HFD+STZ-treated rats showed [P<0.001] increased body weight when compared to the control on the 12th week **(fig 4)**.

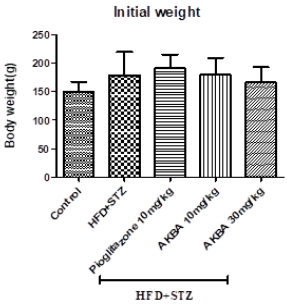

Fig 1

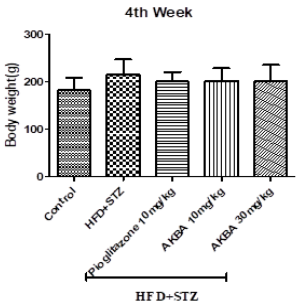

Fig 2

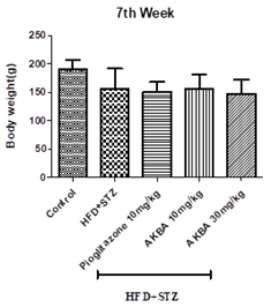

Fig 3

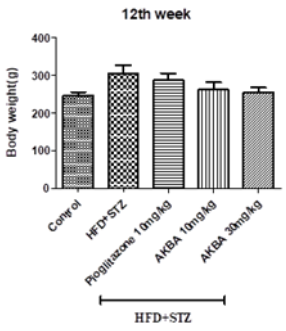

Fig 4

Mean±SD, n = 6. Statistical analysis was carried out in one-way ANOVA followed by post hoc analysis Tukey's multiple comparison tests using Graph Pad Prism 5.0. Statistical significance. ###P < 0.001, ##P < 0.01, #P < 0.05 vs control. ***P < 0.001, **P < 0.01, *P < 0.05 vs HFD+STZ induced group.

Effect of AKBA on Fasting Blood Sugar Level

HFD+STZ-treated rats showed [P <0.001] increased blood sugar levels when compared to the control **(fig 6)**. HFD+STZ-treated rats showed [P <0.001] increased blood sugar levels when compared to the control on the 63rd day **(fig 7)**. HFD+STZ-treated rats showed [P<0.001] increased blood sugar levels when compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.001], and 30mg/kg [P < 0.001] markedly decreased blood sugar levels when compared to the HFD+STZ treated group on the 84th day **(fig 8)**.

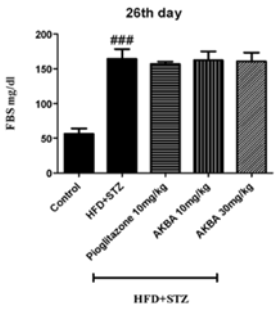

Fig 5

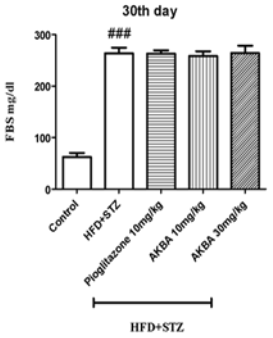

Fig 6

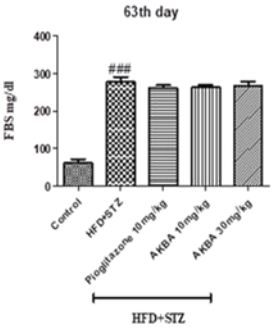

Fig 7

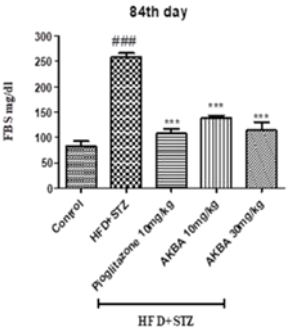

Fig 8

Mean±SD, n = 6. Statistical analysis was carried out in one-way ANOVA followed by post hoc analysis Tukey's multiple comparison tests using Graph Pad Prism 5.0. Statistical significance. ###P < 0.001, ##P < 0.01, #P < 0.05 vs control. ***P < 0.001, **P < 0.01, *P < 0.05 vs HFD+STZ induced group.

Effect of AKBA on Hot Plate and Pinprick Methods

HFD+STZ treated rats showed [P <0.001] decreased latency time towards thermal hyperalgesia compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly increased latency time towards thermal hyperalgesia when compared to the HFD+STZ treated group **(fig 9)**. HFD+STZ treated rats showed [P <0.001] decreased latency time towards mechanical allodynia

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compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly increased latency time towards mechanical allodynia when compared to HFD+STZ treated group **(fig 10)**.

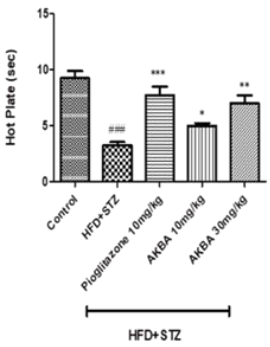

Fig 9

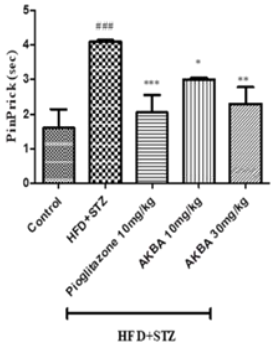

Fig 10

Mean±SD, n = 6. Statistical analysis was carried out in one-way ANOVA followed by post hoc analysis Tukey's multiple comparison tests using Graph Pad Prism 5.0. Statistical significance. ###P < 0.001, ##P < 0.01, #P < 0.05 vs control. ***P < 0.001, **P < 0.01, *P < 0.05 vs HFD+STZ induced group.

Effect of AKBA on Sciatic Functional Index

HFD+STZ treated rats showed [P <0.001] decreased Print length compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.01], and 30mg/kg [P < 0.001] markedly increased Print length when compared to the HFD+STZ treated group **(fig 11)**. HFD+STZ-treated rats showed [P <0.001] decreased toe spread compared to the control. Treatment with Pioglitazone [P < 0.01], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly increased toe spread when compared to the HFD+STZ treated group **(fig 12)**. HFD+STZ-treated rats showed [P <0.001] decreased intermediate toe spread compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly increased intermediate toe spread when compared to the HFD+STZ treated group **(fig 13)**. HFD+STZ-treated rats showed [P <0.001] decreased sciatic functional index compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly increased sciatic functional index when compared to the HFD+STZ treated group **(fig 14)**.

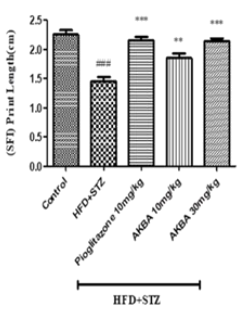

Fig 11

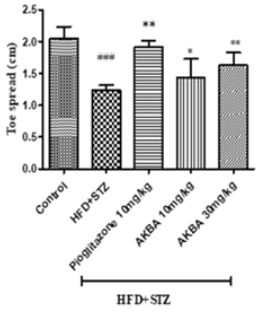

Fig 12

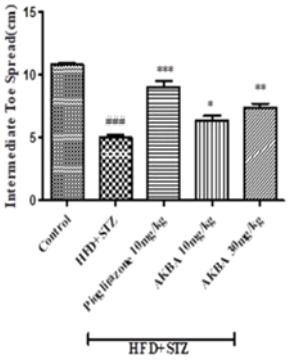

Fig 13

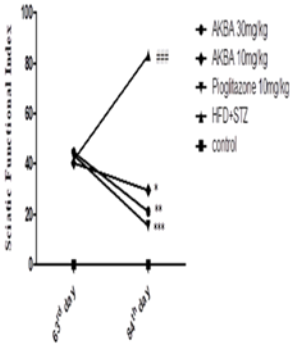

Fig 14

Mean±SD, n = 6. Statistical analysis was carried out in one-way ANOVA followed by post hoc analysis Tukey's multiple comparison tests using Graph Pad Prism 5.0. Statistical significance. ###P < 0.001, ##P < 0.01, #P < 0.05 vs control. ***P < 0.001, **P < 0.01, *P < 0.05 vs HFD+STZ induced group.

Effect of AKBA on Total Cholesterol Level

HFD+STZ-treated rats showed [P <0.001] increased levels of Cholesterol compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.01], and 30mg/kg [P < 0.01] markedly decreased levels of Cholesterol when compared to the HFD+STZ treated group **(fig 15)**.

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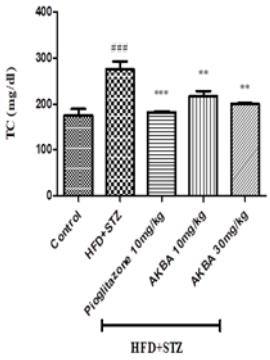

Fig 15

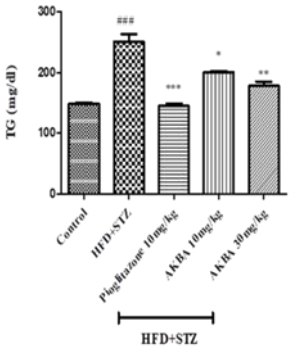

Fig 16

Mean±SD, n = 6. Statistical analysis was carried out in one-way ANOVA followed by post hoc analysis Tukey's multiple comparison tests using Graph Pad Prism 5.0. Statistical significance. ###P < 0.001, ##P < 0.01, #P < 0.05 vs control. ***P < 0.001, **P < 0.01, *P < 0.05 vs HFD+STZ induced group.

Effect of AKBA on Serum Triglycerides Level

HFD+STZ-treated rats showed [P <0.001] increased levels of Triglycerides compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly decreased levels of Triglycerides when compared to the HFD+STZ treated group **(fig 16)**.

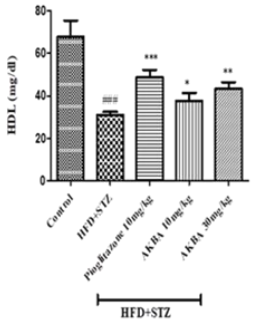

Fig 17

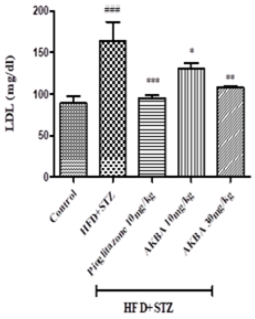

Fig 18

Mean±SD, n = 6. Statistical analysis was carried out in one-way ANOVA followed by post hoc analysis Tukey's multiple comparison tests using Graph Pad Prism 5.0. Statistical significance. ###P < 0.001, ##P < 0.01, #P < 0.05 vs control. ***P < 0.001, **P < 0.01, *P < 0.05 vs HFD+STZ induced group.

Effect of AKBA On Serum HDL Level

HFD+STZ-treated rats showed [P <0.001] decreased levels of HDL compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly increased levels of HDL when compared to the HFD+STZ treated group **(fig 17)**. Mean±SD, n = 6. Statistical analysis was carried out in one-way ANOVA followed by post hoc analysis Tukey's multiple comparison tests using Graph Pad Prism 5.0. Statistical significance. ###P < 0.001, ##P < 0.01, #P < 0.05 vs control. ***P < 0.001, **P < 0.01, *P < 0.05 vs HFD+STZ induced group.

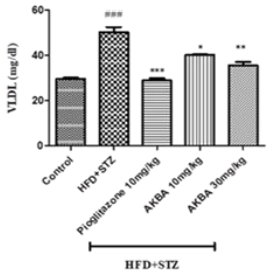

Fig 19

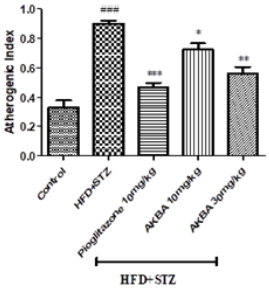

Fig 20

Effect of AKBA on Serum LDL Level

HFD+STZ-treated rats showed [P <0.001] increased levels of LDL compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly decreased levels of LDL when compared to the HFD+STZ treated group **(fig 18)**. Mean±SD, n = 6. Statistical analysis was carried out in one-way ANOVA followed by post hoc analysis Tukey's multiple comparison tests using Graph Pad Prism 5.0. Statistical significance. ###P < 0.001, ##P < 0.01, #P < 0.05 vs control. ***P < 0.001, **P < 0.01, *P < 0.05 vs HFD+STZ induced group.

Effect of AKBA on Serum VLDL Level

HFD+STZ-treated rats showed [P <0.001] increased levels of VLDL compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly decreased levels of VLDL when compared to the HFD+STZ treated group **(fig 19)**.

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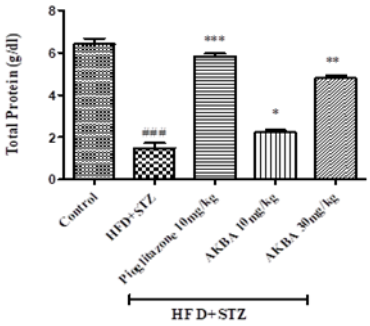

Fig 21

Mean±SD, n = 6. Statistical analysis was carried out in one-way ANOVA followed by post hoc analysis Tukey's multiple comparison tests using Graph Pad Prism 5.0. Statistical significance. ###P < 0.001, ##P < 0.01, #P < 0.05 vs control. ***P < 0.001, **P < 0.01, *P < 0.05 vs HFD+STZ induced group.

Effect of AKBA on Atherogenic Index

HFD+STZ-treated rats showed [P <0.001] increased levels of Atherogenic index compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly decreased levels of Atherogenic index when compared to the HFD+STZ treated group **(fig 20)**. Mean±SD, n = 6. Statistical analysis was carried out in one-way ANOVA followed by post hoc analysis Tukey's multiple comparison tests using Graph Pad Prism 5.0. Statistical significance. ###P < 0.001, ##P < 0.01, #P < 0.05 vs control. ***P < 0.001, **P < 0.01, *P < 0.05 vs HFD+STZ induced group.

Effect of AKBA on Serum Total Protein Level

HFD+STZ-treated rats showed [P <0.001] decreased levels of Protein compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly increased levels of Protein when compared to the HFD+STZ treated group **(fig 21)**.

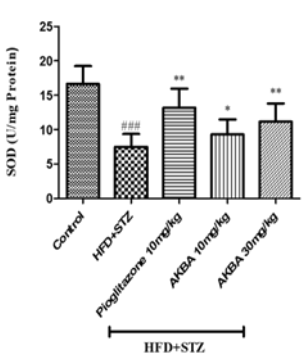

Fig 22

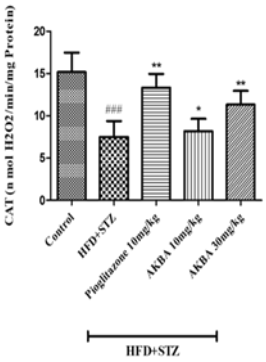

Fig 23

Mean±SD, n = 6. Statistical analysis was carried out in one-way ANOVA followed by post hoc analysis Tukey's multiple comparison tests using Graph Pad Prism 5.0. Statistical significance. ###P < 0.001, ##P < 0.01, #P < 0.05 vs control. ***P < 0.001, **P < 0.01, *P < 0.05 vs HFD+STZ induced group.

Effect of AKBA on Serum Anti-Oxidant Markers

HFD+STZ-treated rats showed [P <0.001] decreased SOD levels compared to the control. Treatment with Pioglitazone [P < 0.01], and 30mg/kg [P < 0.01] markedly increased SOD level when compared to the HFD+STZ treated group **(fig 22)**. HFD+STZ-treated rats showed [P <0.001] decreased levels of CAT when compared to the control. Treatment with Pioglitazone [P < 0.01], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly increased the level of CAT when compared to the HFD+STZ treated group **(fig 23)**. HFD+STZ-treated rats showed [P <0.001] decreased levels of GSH when compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly increased the level of GSH when compared to the HFD+STZ treated group **(fig 24)**. HFD+STZ-treated rats showed [P <0.001] decreased levels of GPx compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.01], and 30mg/kg [P < 0.001] markedly increased levels of GPx when compared to the HFD+STZ treated group **(fig 25).**

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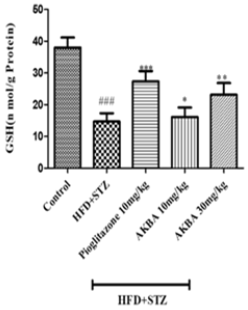

Fig 24

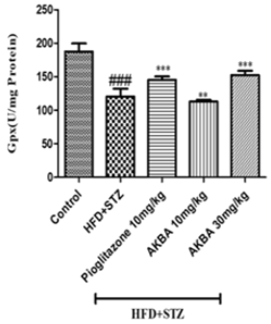

Fig 25

Mean±SD, n = 6. Statistical analysis was carried out in one-way ANOVA followed by post hoc analysis Tukey's multiple comparison tests using Graph Pad Prism 5.0. Statistical significance. ###P < 0.001, ##P < 0.01, #P < 0.05 vs control. ***P < 0.001, **P < 0.01, *P < 0.05 vs HFD+STZ induced group.

Effect of AKBA on Serum Lipid Peroxidation Markers

HFD+STZ-treated rats showed [P <0.001] increased levels of LPO compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.01], and 30mg/kg [P < 0.001] markedly decreased levels of LPO when compared to the HFD+STZ treated group **(fig 26)**. HFD+STZ-treated rats showed [P <0.001] increased levels of MDA when compared to the control. Treatment with Pioglitazone [P < 0.001], AKBA at 10mg/kg, [P < 0.05], and 30mg/kg [P < 0.01] markedly decreased levels of MDA when compared to the HFD+STZ treated group **(fig 27)**.

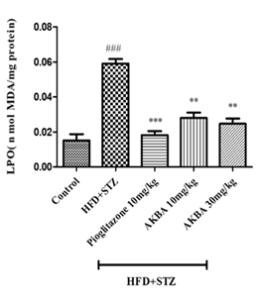

Fig 26

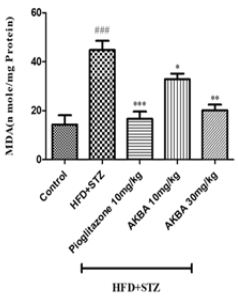

Fig 27

Mean±SD, n = 6. Statistical analysis was carried out in one-way ANOVA followed by post hoc analysis Tukey's multiple comparison tests using Graph Pad Prism 5.0. Statistical significance. ###P < 0.001, ##P < 0.01, #P < 0.05 vs control. ***P < 0.001, **P < 0.01, *P < 0.05 vs HFD+STZ induced group.

Histopathology

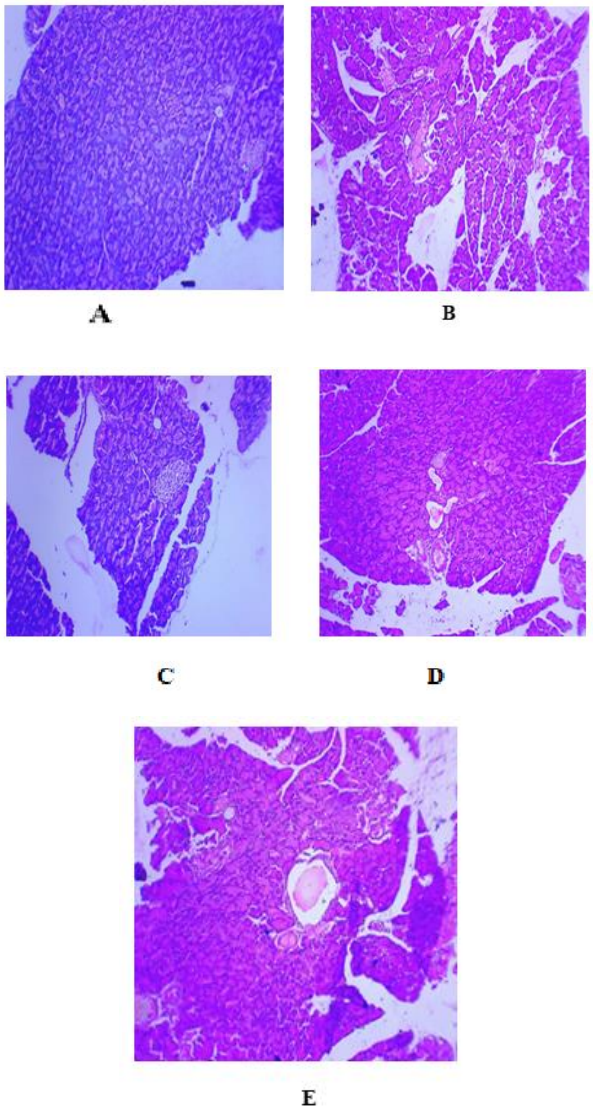

Fig 28 **pancreatic tissue**: A) shows normal pancreatic acini. Islets are normal in number and size. Blood vessels show normal in the control group. B) shows normal pancreatic acini. Islets are reduced in number and size with few showing destructed architecture and cytoplasmic vacuolation. C) shows pancreatic acini with islets. Islets show normal in number and small in size with few showing cytoplasmic vacuolation. D) shows normal pancreatic acini. Islets are reduced in number and size; few show degenerative changes. Blood vessels show no significant pathology in the AKBA 10mg/kg

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treated group. E) shows normal pancreatic acini. Islets are normal in number and size. Few show degenerative changes in cytoplasmic vacuolation. Blood vessels show no significant pathology in the AKBA 30mg/kg treated group.

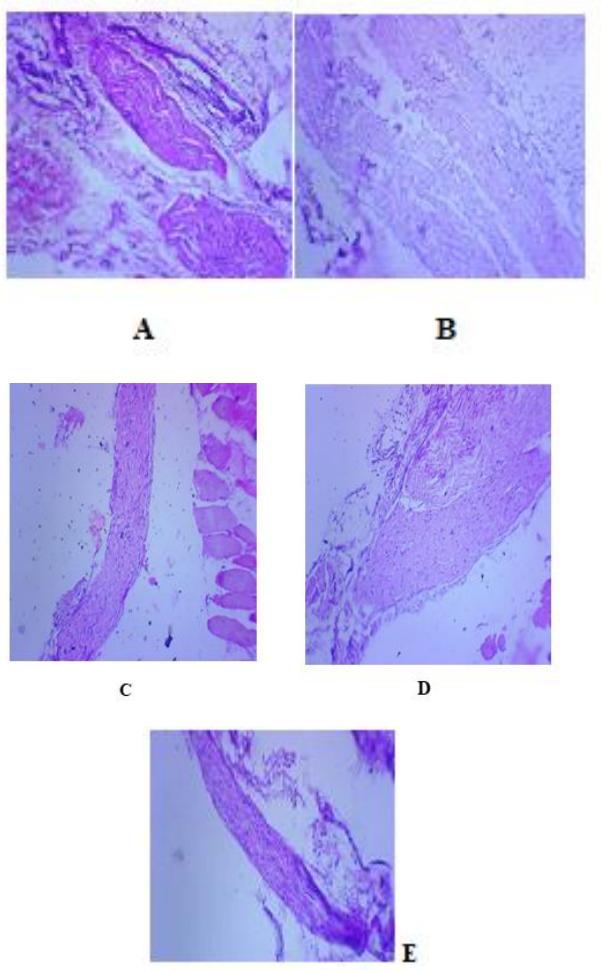

Fig 29 **sciatic nerve**: A) shows normal axons, fibrocytes, and Schwann cells. There is no evidence of toxic changes in the control group. B) shows epi, peri, and endoneurium respectively with focal mild degeneration in Schwann cells, one focal showed mild inflammatory infiltrate in the HFD+STZ induced group. C) shows normal axons, Schwann cells, and the nodes of Ranvier show normal. Fibrocytes show normal. There is no evidence of toxic changes in the Pioglitazone-treated group. D) shows normal perineurium and endoneurium respectively. Focal Schwann cell hyperplasia was noted in the AKBA treated with 10mg/kg group. E) shows normal axons, and fibrocytes show focal degeneration. Schwann cells and nodes of Ranvier show normal in the AKBA treated with 30mg/kg group.

4. Discussion

The glycation was involved in the binding of excess glucose molecules to proteins and lipids, which led to the formation of AGEs [22]. Due to the elevated blood glucose levels, mitochondrial function was affected and impaired in energy production which contributed to nerve damage [23]. Our current study showed elevated blood glucose levels may be related to previous research, by the formation of AGEs and mitochondrial energy impairment which contribute to nerve damage in HFD+STZ-induced animals [24], The study showed that AKBA had an anti-diabetic against STZ induction and our current study also decreased the blood glucose levels.

Diabetes-related neuropathy is frequently studied in diabetic rodents, such as rats or mice. These animals, which are frequently used to represent painful neuropathy, show features of sensory-motor dysfunction, such as stimulus-evoked allodynia (pain owing to typically non-painful stimuli) and hyperalgesia (increased sensitivity to painful stimuli) [25]. By encouraging inflammation and oxidative stress, the development of AGEs can lead to several problems, including neuropathy [26]. Diabetes-related neuropathy is believed to cause nerve injury due to mitochondrial malfunction, which can result in reduced energy production and cell death [27]. The formation of AGEs and mitochondrial energy impairment, which contribute to sensorimotor dysfunction in HFD+STZ-induced animals, may also be linked to previous research, as our study also lengthens the time withdrawal from the hot plate test. A study found that AKBA had an anti-inflammatory effect against STZ induction [28].

Diabetes-related neuropathy is frequently studied in diabetic rodents, such as rats or mice. These animals, which are frequently used to represent painful neuropathy, show features of sensory-motor dysfunction, such as stimulus-evoked allodynia (pain owing to typically non-painful stimuli) and hyperalgesia (increased sensitivity to painful stimuli) [25]. By encouraging inflammation and oxidative stress, the development of AGEs can lead to several problems, including neuropathy [26]. Diabetes-related neuropathy is believed to cause nerve injury due to mitochondrial

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malfunction, which can result in reduced energy production and cell death [27]. The formation of AGEs and mitochondrial energy impairment, which contribute to sensorimotor dysfunction in HFD+STZ-induced animals, may also be linked to previous research, as our study also disrupts sensory-motor dysfunction. A study found that AKBA had an anti-inflammatory effect against STZ induction, and our study also reduced the duration of time withdrawal from the pin-prick test [28].

Diabetic neuropathy is primarily caused by a pathologic breakdown of the blood-nerve barrier. The BNB typically controls the flow of chemicals between blood and nerves, protecting the integrity of the peripheral nervous system. This equilibrium is upset and neuropathy is exacerbated by dysfunction of the blood-nerve barrier [29]. The disruption of the blood-nerve barrier in HFD+STZ-induced animals lead to nerve damage; this imbalance may be related to earlier research, as our study also increases the regenerative ability of peripheral nerves. A study found that AKBA had a regenerative ability for injured peripheral nerves against STZ induction [30].

Reactive oxygen species that injure nerves can be triggered by AGEs [31]. The high levels of fatty acids brought on by insufficient insulin action can cause mitochondrial dysfunction, which is exacerbated in neurons and axons in the diabetic neuropathy state [32,33]. Our study also found that AKBA had an anti-hyperlipidemic effect against a high-fat diet and STZ induction. Previous research has shown that elevated cholesterol levels may be related to increased fatty acid flux on nerve cells in HFD+STZ-induced animals [24] and our study also found a decrease in cholesterol levels.

Triglycerides can cause an increase in the flow of fatty acids into nerve cells, which can lead to mitochondrial dysfunction, aberrant DNA structure, and the production of proteins through the downregulation of transcription factors such as SIRT 1, PGC-1 α, and TFAM [32,33]. The increased fatty acid flux on nerve cells in HFD+STZ-induced animals, as demonstrated by our study's elevated triglyceride levels, may be related to earlier research which found that AKBA had an anti-hyperlipidemic effect against both high-fat diet and STZ induction [24]. Our study also found a decrease in triglyceride levels.

HDL possesses several antiatherogenic qualities, including the ability to transport cholesterol in reverse and to have antioxidative and anti-inflammatory effects. There are changes in the enzymatic activity linked to HDL, including lipoprotein-associated phospholipase 2 (Lp-PLA2) and paraoxonase 1 (PON1). The HDL proteome takes on a proinflammatory profile as a result of oxidative alteration and glycation, which compromises HDL properties and greatly reduces HDL's capacity to dampen inflammatory signals [34]. By altering PON 1 and lp-PLA2 enzymes, which contribute to nerve damage in HFD+STZ-induced animals, our current study also suppresses inflammatory signals that may be related to earlier research. A study found that AKBA had an anti-hyperlipidemic against high-fat diet and STZ induction [24]. Additionally, our study increased HDL levels.

According to a study, lower motor fiber conduction velocities in nerves are linked to elevated LDL-C levels, suggesting that there is damage to the nerves [35]. When proteins or lipids are exposed to sugars and glycated, AGEs are produced. These can cause malfunctions in the mitochondria. Diabetes problems might arise and worsen as a result of this malfunction, which can reduce cellular energy production and raise oxidative stress [37,38]. The creation of AGEs and mitochondrial energy impairment, which contribute to nerve damage in HFD+STZ-induced animals, may be linked to earlier research. A study found that AKBA had an anti-hyperlipidemic effect against a high-fat diet and STZ induction [24]. Our study also found a decrease in LDL levels.

Mitochondrial dysfunction may be indicated by alterations in the expression of all proteins, including those found in the mitochondria. Studies have revealed that mitochondrial proteases are expressed less often in diabetic rats. This might lead to increased proteotoxicity and decreased activity of the electron transport chain, which is essential for mitochondrial function [36]. When proteins or lipids are exposed to sugars and glycated, AGEs are produced. These can cause malfunctions in the mitochondria. Diabetes problems might arise and worsen as a result of this malfunction, which can reduce cellular energy production and raise oxidative stress [37,38]. As AGEs and mitochondrial energy impairment contribute to nerve damage in HFD+STZ-induced animals, our study also found lower total protein expression in nerves. Previous research [24] found that AKBA had higher total protein levels against a high-fat diet and STZ induction, and our study also found lower total protein levels.

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A non-enzymatic reaction between proteins and sugars forms AGEs, which can further exacerbate oxidative stress. Superoxide dismutase (SOD) is an important antioxidant enzyme that helps mitigate oxidative stress by converting superoxide radicals into less harmful molecules. Oxidative stress in diabetic neuropathy is exacerbated by the interaction between AGEs and their receptor (RAGE), which can result in functional protein degradation and further production of ROS. But in the case of diabetes, excessive ROS generation might overpower SOD and other antioxidant defense mechanisms, resulting in oxidative damage [39]. Our study also raised SOD levels. Previous research [24] found that AKBA had an anti-oxidant property against high-fat diet and STZ induction, and our study also increased SOD levels. This suggests that decreased SOD levels may be related to this finding.

As an antioxidant enzyme, catalase reduces oxidative stress by transforming the reactive oxygen species hydrogen peroxide into oxygen and water [42]. A non-enzymatic interaction between proteins and carbohydrates produces AGEs, which build up and potentially worsen oxidative stress. Oxidative stress in diabetic neuropathy is exacerbated by the interaction between AGEs and their receptor (RAGE), which can result in functional protein degradation and further production of ROS. However, in the case of diabetes, excessive ROS generation might overwhelm the body's defense mechanisms against oxidative stress, such as CAT [39]. The present investigation revealed that the lower CAT levels could be linked to earlier findings, which indicated that animals induced with HFD+STZ produced more reactive oxygen species. Additionally, a study [24] demonstrated that AKBA exhibited antioxidant properties against both STZ induction and a high-fat diet, and our study also found that the CAT levels were elevated.

Strong antioxidant GSH is essential for shielding the mitochondria from oxidative damage. Oxidative stress results from a disruption in the equilibrium between the generation of reactive oxygen species (ROS) and antioxidant defense mechanisms in diabetic neuropathy [40]. AGEs interfere with regular cellular processes and raise oxidative stress, which can lead to mitochondrial dysfunction [33]. This dysfunction can affect the generation of energy required for nerve cell survival and function [39]. Our study also increased GSH levels. Previous research [24] found that AKBA had an anti-oxidant property against high-fat diet and STZ induction, and our study also increased GSH levels. This suggests that decreased GSH levels may be related to this finding. By converting free hydrogen peroxide to water and lipid hydroperoxides to their corresponding alcohols, the enzyme GPx aids in the body's defense against oxidative damage [39]. By interfering with regular cellular processes and raising oxidative stress, AGEs lead to mitochondrial malfunction. This dysfunction can reduce the energy production required for nerve cell survival and function [33,39]. The present investigation revealed that the observed reduction in GPx levels could potentially be linked to earlier findings, as our study also observed an increase in reactive oxygen species production in animals induced with HFD+STZ. Additionally, a study [24] demonstrated that AKBA exhibited antioxidant properties against both a high-fat diet and STZ induction. MDA is a reactive aldehyde that is produced when polyunsaturated fatty acids peroxide and is used as an indicator of oxidative stress. A typical characteristic of diabetic neuropathy is increased oxidative damage within cells, which can be shown by elevated MDA levels.

LPO: This process, which results in cell damage, is the oxidative destruction of lipids caused by free radicals "stealing" electrons from the lipids in cell membranes. LPO creates MDA and other reactive chemicals that can exacerbate cellular damage, especially in nerve cells [41]. AGEs interfere with regular cellular processes and raise oxidative stress, which can lead to mitochondrial dysfunction [41]. This dysfunction can affect the generation of energy required for nerve cell survival and function [39]. Our study also found that MDA and LPO levels were decreased. Previous research [24] demonstrated that AKBA had an anti-oxidant property against high-fat diet and STZ induction, and our study also found that increased levels of MDA and LPO may be related to this. This is because increased production of reactive oxygen species was seen in HFD+STZ-induced animals.

Rats were used to evaluate the histology of the sciatic nerve of rats. In the control group, the myelin staining revealed normal nerve fiber size, density, and distribution and clear, unswollen axons. The nerve fibers in the HFD+STZ-induced group were loosely distributed, there was unequal myelin edema, even

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demyelination, and notable axon changes. Following AKBA treatment, nerve fiber pathological damage was greatly reduced, and nerve fiber configurations were more evenly spaced [21].

The pancreatic histology in the Control group demonstrates the organ's typical anatomy. In the HFD+STZ-induced group, islet β-cells are virtually destroyed. Following the administration of AKBA, Islet β-cell pathological damage was reversed [20].

Results of this study suggest AKBA is an effective compound for the Protection against diabetic neuropathy in rats.

5. Conclusion

In the present study, the administration of AKBA reversed the changes in behavioral, and biochemical parameters levels in HFD+STZ-induced animals. The changes observed in the sciatic nerve and pancreas treated with AKBA were further confirmed by histopathological analysis. The study concluded that AKBA can be a potent drug to treat diabetic neuropathy induced by HFD+STZ in rats.

Acknowledgment

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