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Research Article
Aqueous Extract from Sukkari Date Seeds Attenuates Neuroinflammation Induced by Type-2 Diabetic in Rats

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Abstract

Background and Objective: Diabetes mellitus is recognized as a global pandemic and is recently linked to cognitive and memory decline. In this study effect of Aqueous Sukkari Dates Seeds Extract (ASSE) on Type-2 Diabetes Mellitus (T2DM) associated neuroinflammation was explored. **Materials and Methods:** About 30 Sprague Dawley Male rats were divided into 5 groups with 6 rats each. Four groups of rats were induced with T2DM using nicotinamide and Streptozotocin (STZ), while one was considered as control. Among the 4 groups, two were treated with oral doses of 200 and 400 mg kg^{-1} of ASSE, the 3rd group was treated with standard drug metformin while the 4th group was left untreated and considered as diabetic-induced. The treatment with ASSE and metformin was continued for 30 days. At the end of treatment, the brain tissue was isolated and estimated for the neuroinflammatory parameters like TNF-α, IL-6, IL-10, TGF-β1 and COX-2. **Results:** The 2 doses of ASSE resulted in a significant decrease of COX-2 levels besides resulting in the decrease of proinflammatory cytokines like TNF-α and IL-6 levels. The administration of ASSE also increased an anti-inflammatory cytokine, IL-10 levels. **Conclusion:** The results support the neuroprotective effects of ASSE. Besides, it can also be concluded that the ASSE also has the potential to improve the cognitive deficit in T2DM patients.

Key words: Sukkari dates, diabetes, neuroinflammation, cytokines, cyclooxygenase 2, cognitive impairment, neuroprotective

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetes Mellitus (DM) is a major metabolic disorder and is a global pandemic. Approximately 382 million people were affected across the globe in the year 2013 and by the year 2035, the number is expected to rise by 592 million[1]. Out of these 90% of the diabetic population is suffering from type-2 diabetes. China has the world's largest diabetic population followed by India. According to the prediction of the international diabetes federation, by the year 2035 India will inhabit 109 million people suffering from diabetes[2]. Globally, Saudi Arabia is listed as the 6th among the top 10 countries with the prevalence of diabetes about 23.9% of the total population[3].

Insulin resistance and insulin deficiency is a characteristic of type-2 diabetes. The long-term hyperglycemic conditions often lead to enhanced oxidative stress linked to the inflammatory process which further causes complications to important physiological systems like the cardiovascular system, renal system and nervous system[4]. The complications of the cardiovascular system can be categorized into macro and microvascular complications. Macrovascular complications include stroke, peripheral artery diseases and coronary artery diseases while microvascular complications are retinopathy and neuropathy[5].

Inflammation is an immune reaction resulting from injury, infections, diseases and disorders. Acute inflammatory responses are generally resolved and recovered to baselines. The literature review suggests that DM causes activation of the immune system and thus inflammatory conditions which further causes various pathogenic events and ultimately adverse outcomes both under Type-1 Diabetes Mellitus (T1DM) and T2DM[6,7]. Microglia has an important role in DM and is also known to have a central role in neurodegenerative diseases[8]. Constant trigging of microglia results in the liberation of pro-inflammatory cytokines like IL-6, IL-1β and TNF-α, which causes cellular damage in neurons[9]. It is also established that memory impairment is characterized by neuronal inflammation[10]. The DM condition results in persistent oxidative stress in nerve cells and thus severe inflammatory alterations[11]. The long-term DM condition results in damage to BBB and leads to vascular complications in the brain[12]. The DM condition results in a high respiration rate in astrocytes and pericytes, which are causing the generation of a large number of reactive oxygen species and hence oxidative stress. This oxidative stress condition causes increased production of inflammatory cytokines, further activating the NF-κβ pathway and finally BBB leakage[13].

Date palm (*Phoenix dactylifera* L.) is an indispensable fruit crop in Saudi Arabia and is known for its many nutritional and medicinal benefits[14]. Among the dates known to Arabs, Sukkari is considered as one of the famous and premium variety, because of its high economic returns to farmers and buyers. It is mainly grown in the central regions of Saudi Arabia and Iraq[15]. Date palm is known to have very little content of cholesterol and fat besides being a rich source of fibre and it is good for patients with a heart condition and digestive system[16]. Seeds from the dates are a major waste product of the dates industry and could offer a solution for the production of agents with medicinal value[14]. Date seeds besides containing minerals like potassium, calcium and magnesium are a rich source of secondary metabolites like polyphenols, flavonoids, carotenoids, antioxidants and phenolic acids[17]. Abdelaziz *et al.*[18] showed a protective effect of aqueous seed extract on liver and kidney tissues in diabetic rats. Early, the treatment of ethanolic extract from date palm seed showed hypoglycemic, hypolipidemic and antioxidant effects in alloxan-induced diabetic rats[19]. Furthermore, the aqueous extracts of Sukkari seeds were reported as a reduction in blood glucose level and glycosylated Haemoglobin (HbA1c) and also elevated serum insulin levels in STZ-induced diabetic rats. Also, the same treatment demonstrated with improvement of lipid profiles and liver as well as kindly functions in STZ-induced diabetic rats[20]. Abuelgassim *et al.*[14] demonstrated antibacterial and antioxidant activity of date seeds. The DM has a deteriorating effect on brain functions and several pieces of evidences are supporting the anti-diabetic effect of dates seeds. However, there is a lack of sufficient evidence supporting the effect of dates seeds on CNS, especially for neuroprotection. Therefore, this study aims to explore the effects of ASSE on neuroinflammation induced by LPS in mice model.

MATERIAL AND METHODS

Study area: The study was carried out at Pharmacology Research Laboratory, Department of Pharmacology and Toxicology, Qassim University, Saudi Arabia from October, 2020-April, 2021.

Drugs and chemicals: Metformin hydrochloride, nicotinamide and streptozotocin were obtained from Cayman Chemicals, United States of America. TNFα, IL-6, IL-10, TGF-β1 and COX-2 ELISA kits were obtained from Cloud-Clone Corp., United States of America. Other chemicals and solvents of analytical grade were purchased from local suppliers.

Plant material and extraction: Sukkari dates were purchased from the farms located in the Al-Qassim region. The dates were confirmed with Prof. Mohammed Motawei, Professor in Genetics Molecular, Department of Plant Production and Protection in College of Agriculture and Veterinary, Qassim University, Saudi Arabia. The seeds were separated from fruit pulp followed by their washing with water and drying at room temperature for 2-3 days. The seeds were then crushed into a coarse powder using a coffee grinder. One litre of distilled water was then added to every 100 g of coarse powder. The resulting mixture was filtered after 3 days and concentrated using a rotary evaporator (BUCHI UK Ltd, Newmarket Suffolk, UK). The concentrated extract was freeze-dried and stored for further use[20].

Experimental design and drug treatments: About 3 months old, 30 male SD (Sprague Dawley) rats with a body weight of 200-250 g were used for the assessment of neuroprotective of ASSE. The animals were obtained from the Animal Facility, Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Saudi Arabia. Five groups with each having 6 animals were labelled as follows:

- Control
- Diabetic group of animals
- Metformin-treated group
- 200 mg kg^{-1} ASSE treated group
- 400 mg kg^{-1} ASSE treated group

The rats were 1st acclimatized for 7 days under standard laboratory conditions with 12 hrs light and dark cycles. Three rats/propylene cages were housed and had free access to food and water during the entire experiment. The treatment with metformin (200 mg kg^{-1}, p.o.) and 2 doses i.e., 200 and 400 mg kg^{-1} of ASSE was conducted for 30 days. At the end of treatment, animals were sacrificed and the brain was separated and estimated for neuroinflammatory parameters like TNF-α, IL-6, IL-10, TGF-β1 and COX-2. Acute toxicity studies were conducted using female rats of similar weight and age. The animal ethical committee of the College of Pharmacy, Qassim University Saudi Arabia reviewed and approved the present experimental procedures (Approval ID 2020-CP-5).

Vehicles: The ASSE, metformin hydrochloride and nicotinamide were dissolved in 0.9% saline solution. STZ was dissolved in 0.1 M, pH 4.5 cold citrate buffer solution. A single dose of nicotinamide followed by STZ solution was injected intraperitoneally (i.p.) for inducing type-2 diabetes while ASSE and metformin were administered continuously 30 days through oral route for the treatment purpose.

Acute toxicity studies: The procedures of the study were followed as per the guidelines of the Organization of Economic Cooperation Development (OECD 423)[21]. The toxicity experiments were conducted using female rats of similar weight and age as used in the main study. Three rats were randomly allocated for each step. The food except the water was withdrawn before administering the dose of 5 mg kg^{-1}. The animals were then observed for any toxic symptoms and mortality for the first 4 hrs and 3 days, respectively. If one animal died, the dose is re-evaluated for toxicity. If none of the animals died further higher doses of 50, 300 and 2000 mg kg^{-1} were used to confirm the toxicity.

Induction of diabetes: About 120 mg kg^{-1} of nicotinamide followed by 60 mg kg^{-1} of STZ at the gap of 15 min was injected through the intraperitoneal route for induction of T2DM. The rats were devoid of food and water before injection. Blood glucose levels were measured after 72 hrs and on the 7th day of injection to confirm the hyperglycemic state. Diabetic rats were employed in the investigation, with fasting blood glucose levels greater than 126 mg dL^{-1} [22].

Enzyme-linked immunosorbent assay (ELISA): The isolated brain was homogenized in ice-cold phosphate buffer solution (4°C, pH 7.6), centrifuged for 10 min at 10,000 rpm. The supernatant was separated into 4 m< vials and stored at -80°C for further use. Total protein content was estimated using Biuret colorimetric method (Crescent Diagnostics, Saudi Arabia). TNF-α, IL-6, IL-10, TGF-β1 and COX-2 ELISA kits were used for the estimation of the targets as per the procedures described by the manufacturers (Cloud-Clone Corp., Katy, Texas, USA). The readings were taken at the wavelength of 450 nm using an Absorbance Microplate Reader (ELx800, BioTek Instruments, Winooski, Vermont, USA).

Statistical analysis: The recorded data were examined using one-way ANOVA and Tukey-Kramer post hoc test to calculate significance level. The mean values with standard error (Mean±SEM) is used to represent the results. GraphPad 9 (GraphPad Software Inc., United States) was followed for statistical analysis. Statistical significance was defined as a $p<0.05$.

RESULTS

Acute toxicity study: No signs of toxicity and mortality were noted up till the dose of 2000 mg kg^{-1}. Therefore, 2 lower doses of ASSE (200 and 400 mg kg^{-1}, p.o.) were selected for further study.

Treatment of ASSE reduced pro-inflammatory cytokine markers in brain homogenates of diabetic-induced rats: Figure 1 displays the effect of ASSE on proinflammatory cytokine markers TNF-α. The diabetic group showed considerably higher levels of TNF-α in the brain homogenate as related to the control group ($p<0.05$). The higher levels of TNF-α confirm the development of neuroinflammation in the brains of rats induced with diabetes. The treatment of animals with two doses (200 and 400 mg kg^{-1}, p.o.) of ASSE showed a considerable ($p<0.05$ and $p<0.01$, respectively) reduction in levels of TNF-α.

Furthermore, the levels of IL-6 were noted to be suggestively higher ($p<0.001$) among diabetic rats than in the control group (Fig. 2). The oral treatment of animals with 2 doses (200 and 400 mg kg^{-1}, p.o.) of ASSE also considerably reduced ($p<0.001$) the levels of IL-6. The results from the metformin-treated groups also showed significantly reduced levels of TNF-α and IL-6 ($p<0.05$ and $p<0.001$), respectively. The results of TNF-α and IL-6 from the metformin-treated group were noted to comparative with both doses of ASSE-treated groups.

Treatment of AASE selectively elevated anti-inflammatory cytokine markers in brain homogenates of diabetic-induced rats: Figure 3 displays the results of anti-inflammatory cytokines IL-10 from the brain homogenates of animals under study. The level of IL-10 was found to be substantially ($p<0.01$) lower in the brain homogenate of the diabetic group of animals when associated with the control group of animals that indicating lower levels of anti-inflammatory activity in the brains of diabetic rats. The administration of 400 mg kg^{-1} of ASSE showed a substantial ($p<0.05$) increment in the levels of IL-10 marking an increase in the anti-inflammatory activity. The results from the animals treated with 200 mg kg^{-1} of ASSE displayed only marginal improvement in the levels of IL-10. The metformin-treated groups showed significant elevation in the levels of IL-10 ($p<0.01$) as associated to control.

Figure 4 shows the results for the levels of TGF-β1 from brain homogenate of the animal under study. The diabetic group showed significantly ($p<0.001$) reduced levels of TGF-β1 as matched to the brain homogenate of the control group.

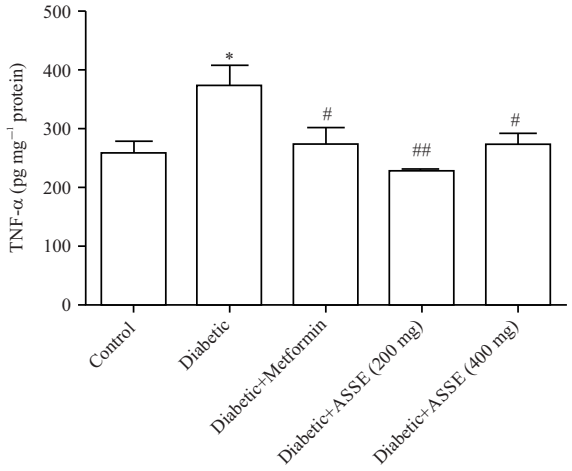

Fig. 1: Effect of aqueous Sukkari seeds extracts (ASSE) on a proinflammatory cytokine TNF-α in brain homogenates of type-2 diabetic-induced rats

Values are Mean±SEM (n = 6). One-way ANOVA [F(4,25): 5.201, $p<0.01$] followed by Tukey-Kramer multiple comparisons test, *$p<0.05$ as compared to the control group, #$p<0.05$ and ##$p<0.01$ as compared to the diabetic-induced group

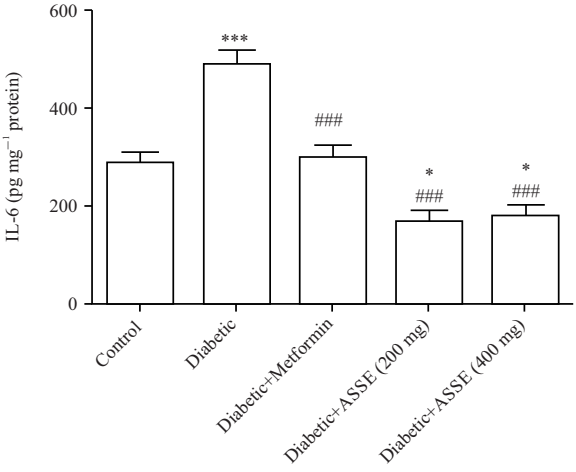

Fig. 2: Effect of aqueous Sukkari seeds extracts (ASSE) on a pro-inflammatory cytokine IL-6 in brain homogenates of type-2 diabetic-induced rats

Values are Mean±SEM (n = 6). One-way ANOVA [F(4,25): 28.32, $p<0.001$] followed by Tukey-Kramer multiple comparisons test, *$p<0.05$, ***$p<0.001$ as compared to the control group and ###$p<0.001$ as compared to the diabetic-induced group

The animals treated with 2 doses of ASSE displayed marginal improvements in the levels of brain TGF-β1, while metformin-treated groups showed greatly ($p<0.001$) higher levels of TGF-β1 in mice brains as compared to diabetic groups.

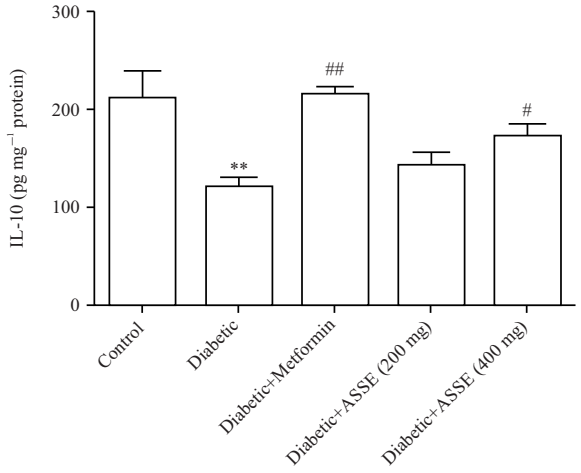

Fig. 3: Effect of aqueous Sukkari seeds extracts (ASSE) on an anti-inflammatory cytokine IL-10 in brain homogenates of type-2 diabetic-induced rats

Values are Mean±SEM (n = 6). One-way ANOVA [F(4,25): 7.465, p<0.001] followed by Tukey-Kramer multiple comparisons test, **p<0.01 as compared to the control group, #p<0.05 and ##p<0.01 as compared to the diabetic-induced group

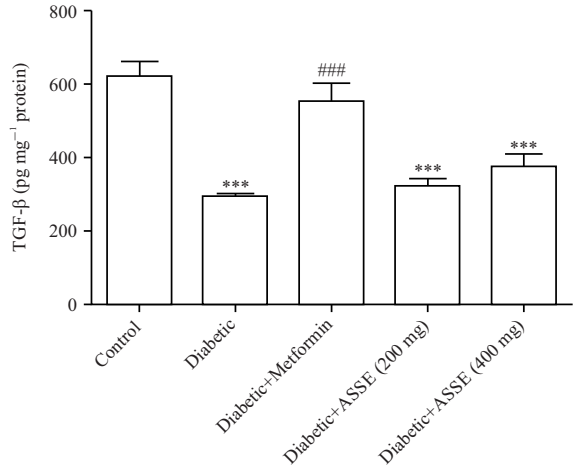

Fig. 4: Effect of aqueous Sukkari seeds extracts (ASSE) on an anti-inflammatory cytokine TGF-β1 in brain homogenates of type-2 diabetic-induced rats

Values are Mean±SEM (n = 6). One-way ANOVA [F(4,25): 18.67, p<0.001] followed by Tukey-Kramer multiple comparisons test, values are Mean±SEM (n = 6), ***p<0.001 as compared to the control group and ###p<0.001 as compared to the diabetic-induced group

Treatment of AASE reduced cyclooxygenase 2 (COX-2) activities in brain homogenates of type-2 diabetic-induced rats: Figure 5 displays the results for the levels of COX-2 in the brain homogenates of animals under study. The brain homogenate of the diabetic group showed considerably

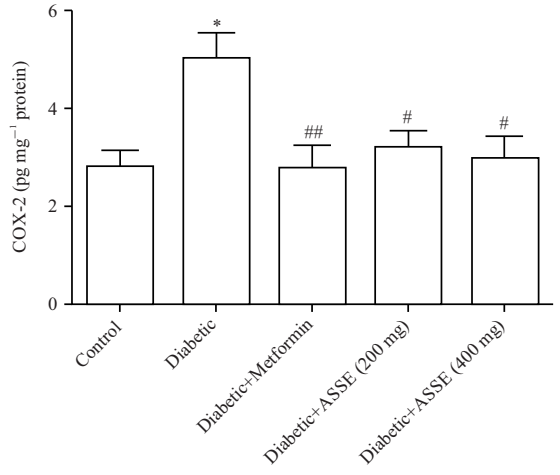

Fig. 5: Effect of aqueous Sukkari seed extract (ASSE) on cyclooxygenase-2 (COX-2) activities in brain homogenates of type-2 diabetic-induced rats

Values are Mean±SEM (n = 6). One-way ANOVA [F(4,25): 4.774, p<0.01] followed by Tukey-Kramer multiple comparisons test, values are Mean±SEM (n = 6), *p<0.05 as compared to the control group, #p<0.05 and ##p<0.01 as compared to the diabetic-induced group

higher (p<0.05) levels of COX-2 in comparison to the control group. The group of animals was treated with both doses (200 and 400 mg kg^{-1}, p.o.) of ASSE showed significantly (p<0.05) lower in the COX-2 levels. The animals treated with metformin e showed substantial lowering (p<0.05) of COX-2 enzyme as related to the diabetic group.

DISCUSSION

The present study resulted in the role of ASSE on the levels of proinflammatory parameters TNF-α and IL-6, anti-inflammatory parameters IL-10 and TGF-β1 and COX-2 enzyme. It was found that the treatment of ASSE on type-2 diabetic rats, significantly controlled the pro-inflammatory activities, moderately showed alteration in anti-inflammatory cytokines and considerably reduced COX-2 enzyme levels in the diabetic-induced brain. The research reports have linked abnormal blood glucose levels, impaired insulin activity, impaired cholinergic systems and inflammation associated damaged neurons with the decline of cognitive health and memory dysfunction[23,24].

Diabetes is a well-established and complex prolonged illness that levies significant liability on society in terms of financial cost, low productivity, early deaths and reduced quality of life[25]. The long-term hyperglycemic condition is often accompanied by a decline in cognitive health. The underlying mechanism for the decline of cognitive health-

associated because of the long-term hyperglycemic condition has not been outlined very clearly[10]. However, elevation in the levels of inflammatory parameters under hyperglycemic conditions has been very well-reported and established[26]. Besides elevation in the levels of inflammatory parameters is also associated with the decline of cognitive health and the reports mention that the patients suffering from the above-mentioned metabolic disorder have shown higher significant cognitive deficit or memory impairment[8].

Neuroinflammation often characterizes dementia and is also known to play a pivotal role in the development of AD. It is pertinent to mention that the DM condition is also known to cause a decline in cognitive health and memory impairment through neuroinflammatory parameters[27]. In one of the earlier reports, DM is reported to be linked with aggregation of Aβ protein and increase of pro-inflammatory markers like TNF-α, IL-β1 and COX-2 in the brain which further causes memory loss. Therefore, a long-lasting DM situation causes Aβ aggregation often accompanied by neuroinflammation interacts with the brain[28]. The prostaglandin H synthase popularly also known as COX converts arachidonic acid into active prostanoids. Prostanoids are recognized to have an important function in the inflammatory process. COX-1 and COX-2 are 2 isoforms of prostanoids. COX-1 is present in almost all the cells of the body are known for their housekeeping functions. In the brain, COX-1 is expressed by microglial cells. The COX-2 causes stimulation of inflammatory responses by cytokine release and thus COX-2 enzyme can be targeted selectively and possibly used as a strategy to suppress the inflammatory response[29]. Yang and Gao[30], demonstrated upregulated expression of COX-2 enzyme in the hippocampus of diabetic rats. Consistent with these results, Liu *et al.*[28] showed significant improvement in the memory and learning abilities of diabetic rats kept on the therapy of ibuprofen, a non-selective COX inhibitor. The same treatment also reported a significant reduction in brain COX-2 expression and activity levels of diabetic rats. In alignment with these results, Yang and Gao[30] further demonstrated a significant improvement in the memory functions in diabetic rats using celecoxib a selective COX-2 inhibitor. In association with the above-mentioned reports, our results also showed a significant elevation of COX-2 expression and activity in the brains of diabetic rats as compared to animals of the control group. Our results also demonstrated a significant reduction of COX-2 levels in the brain treated with both 200 and 400 mg kg^{-1} of ASSE in diabetics.

To further confirm the role of ASSE in subsiding inflammatory response, proinflammatory and anti-inflammatory cytokines were evaluated using ELISA assays. The TNF-α and IL-6 are proinflammatory cytokines and their role is very well documented in the inflammatory response. High levels of TNF-α and IL-6 have also been documented in the brains of humans and rats model suffering from AD. TGF-β1 and IL-10 are anti-inflammatory cytokines that counteract cellular immune response and thus supplement anti-inflammatory impacts[31,32]. On similar lines TNF-α and IL-6, the neuro-inflammatory parameters were found to be circulating at elevated levels in the blood of the rodents induced with T1DM and T2DM[33]. Similarly, another study reported a decreased level of IL-10 and TGF-β1 in the T2DM mouse model[34]. In line with the reports from previous studies, our results also demonstrated an elevation of pro-inflammatory cytokines TNF-α and IL-6 levels and a decline in the anti-inflammatory cytokines TGF-β1 and IL-10 levels in the brain homogenates of T2DM induced rats. Upon administration of ASSE significantly reduced both pro-inflammatory cytokines and increased moderately an anti-inflammatory cytokine IL-10 in diabetic-induced rats brains.

The current results might validate the possible efficacy of ASSE on the reversal of T2DM influenced neuronal inflammatory deficits in the STZ-nicotinamide-induced rat model. Hence, T2DM appears to be a risk factor for neuroinflammation-related neuronal damage and neurodegeneration. The current study initiated preliminary pre-clinical exploration of finding the benefits of Sukkari dates seeds for neuroinflammatory-related neuronal degeneration. However, it is needed for extended scientific evidence to establish its clinical uses in neuronal disorders including Alzheimer's disease-induced dementia and Parkinson's disease.

CONCLUSION

Our results demonstrate the anti-inflammatory effect of ASSE at dose levels of 200 and 400 mg kg^{-1}. The effects were found to be more prominent at the dose level of 400 mg kg^{-1}. The results also demonstrated the inhibition of pro-inflammatory cytokines (TNF-α and IL-6), the elevation of an anti-inflammatory cytokine (IL-10) and the reduction of COX-2 enzyme activity with ASSE on the diabetic-induced brain. The above results establish the anti-inflammatory properties of ASSE, especially under T2DM conditions. The anti-inflammatory properties of ASSE may have the potential of a neuroprotective effect.

SIGNIFICANCE STATEMENT

Our results reveal treatment of the T2DM rat model with aqueous extract of Sukkari dates seeds has the potential to

reverse neuroinflammation by (i) Reducing the levels of IL-6, TNF-α, (ii) Elevating the levels of IL-10 and (iii) Reducing the activity of COX-2. This study will help the researcher to uncover the critical areas of management of neuroinflammation in the neurodegenerative pathological process that many researchers were not able to conclude. Thus the results from the current study provide additional information on neuroprotective benefits of Sukkari dates seeds for neuroinflammatory related memory deficits.

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