International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2022.299.306

Research Article
Neuroprotective Effect of Aqueous Extract of Ajwa Seeds via Anti-Inflammatory Pathways in Type-2 Diabetic-Induced Rats

[1]Vasudevan Mani, [2]Minhajul Arfeen, [1]Sultan Sajid and [3]Yasser Almogbel

[1]Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Buraydah, Kingdom of Saudi Arabia
[2]Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, Qassim University, Buraydah, Kingdom of Saudi Arabia
[3]Department of Pharmacy Practice, College of Pharmacy, Qassim University, Buraydah, Kingdom of Saudi Arabia

Abstract

Background and Objective: Diabetes mellitus is considered a highly prevalent metabolic disorder that causes brain dysfunction, especially memory and cognitive decline. The present study aims to investigate the effects of Aqueous Ajwa date Seeds Extract (AASE) on type 2 diabetes mellitus-induced neuroinflammation in a rat model. **Materials and Methods:** A total of 30 male Sprague Dawley rats with body weight in the range of 200-250 g and age of 3 months were randomly allocated/divided into 5 groups (n = 6). Type 2 diabetes was induced among 4 groups using nicotinamide (120 mg kg^{-1}, i.p.) followed by streptozotocin (60 mg kg^{-1}, i.p.), while one group was considered as non-diabetic group control. About 200 and 400 mg kg^{-1} of AASE were orally administrated for 30 days after diabetes induction. At the end of the treatment, the brain was isolated and evaluated for neuroinflammatory parameters [cyclooxygenase 2 (COX-2), Tumour Necrosis Factor-alpha (TNF-α), Interleukin IL-6 and IL-10 and Transforming Growth Factor-beta 1(TGF-β1)]. **Results:** Administration of AASE significantly decreased COX-2 and proinflammatory cytokines (TNF-α and IL-6) levels and increased ($p<0.05$) anti-inflammatory cytokines (IL-10 and TGF-β1) at the above-mentioned doses. **Conclusion:** The overall results supported that the neuroprotective effects of AASE by inhibiting the neuronal inflammation in type 2 diabetes by altering both proinflammatory and anti-inflammatory cytokines levels. It is concluded that the extract of AASE has the potential to improve the cognitive deficit in type 2 diabetic patients.

Key words: Neuro-production, Ajwa dates, streptozotocin, type 2 diabetes, neuroinflammation, cytokines, cyclooxygenase 2

Citation: Mani, V., M. Arfeen, S. Sajid and Y. Almogbel, 2022. Neuroprotective effect of aqueous extract of Ajwa seeds via anti-inflammatory pathways in type-2 diabetic-induced rats. Int. J. Pharmacol., 18: 299-306.

Corresponding Author: Minhajul Arfeen, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, Qassim University, Buraydah, Kingdom of Saudi Arabia Tel: +966 53 643 9056

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 combination of metabolic disorders and a lifelong (chronic) disease marked by increased blood sugar levels (hyperglycemia) that has long influenced the global population. Usually, diabetes results either from impaired insulin secretion or from defective insulin secretion causing the effects or both[1]. The health risk of diabetes has been gradually rising worldwide. Crucial factors contributing to global increases in diabetic prevalence are included an increase in population, ageing, diet, urbanization and reduced physical activity[2]. In 2019, the International Diabetes Federation (IDF) estimated that 463 million individuals were living with diabetes at age between 20-79 years. These numbers are projected to rise by 578 million in 2030 and 700 million in the year 2045[3].

There are several complications caused by long-term elevation of blood glucose in diabetes mellitus, such as metabolic disturbances, enhanced oxidative stress and inflammatory process and also these complications lead to disorders in various physiological systems including cardiovascular, nervous and renal. In general, hyperglycemia's harmful effects are usually categorized into macrovascular and microvascular complications. The macrovascular complications are stroke, peripheral artery diseases and coronary artery diseases. The microvascular complications include retinopathy, neuropathy and diabetic neuropathy[4]. The effect of diabetes on the brain is also evident. Recent studies have suggested the term "type 3 diabetes mellitus" for AD resulting from insulin resistance and thus confirming the involvement of diabetes in various brain-related issues[5].

Inflammation is an immune reaction to many causes, including infection and disorders. Acute inflammatory reactions are effectively resolved and under physiological settings, inflammation levels recover to baseline. However, owing to unnecessary pro-inflammatory signalling, the resolution process is not reached under the situation of chronic inflammation and may cause adverse outcomes[6]. Literature review of recent publications emphasized that DM is correlated with the immune system's activation and inflammation in various pathogenesis events under both T1DM and T2DM. Moreover, microglia have a prominent role in the occurrence of neurodegenerative diseases and appears to have an active role in metabolic diseases including DM[7]. Continuous, activation of microglia may release pro-inflammatory cytokines like IL1β, IL-6 and Tumour Necrosis Factor-alpha (TNF alpha) and lead to potential cellular damage[8]. Additionally, cognitive dysfunction is commonly associated with national inflammation as well[9].

The date palm (*Phoenix dactylifera* L.) is found in the Middle East, North Africa and throughout the globe for thousands of years. It is widely spread around the Arab World and is known for its nutritional and medicinal benefits. Among verities of dates known to the Arab world, Ajwa dates are cultivated in the western Saudi Arabian district of Al Madinah and is considered unique because of their richness of dietary fibre, essential minerals, fats, proteins and vitamin contents[10]. Phytochemical studies demonstrate that Ajwa dates have excellent quantities of flavonoid and phenolic constituents and are the main ingredients for their antioxidant properties[11]. Ajwa dates are reported to demonstrate various pharmacological properties, like antioxidant, anti-microbial, anti-inflammatory, anti-mutagenic and anti-tumour activities. Additionally, its extracts display hepatoprotective, nephroprotective, hypolipidemic and gastroprotective beneficent effects[12]. In STZ-diabetic model rats, Ajwa dates seeds extracts showed antidiabetic effects with the restoration of liver and kidney functions and antioxidant activity, especially with prolonged treatment[13]. Similarly, Ajwa seed extract exhibited the ability to normalize glucose and liver enzyme levels in alloxan-induced diabetic rats to a certain extent[14].

Due to the lack of significant research evidence about the effects of Ajwa date seeds on the CNS, especially in neuroprotection, the current work aims to explore the effects of aqueous extract of Ajwa dates seeds on type 2 diabetes-induced neuroinflammation in rat models.

MATERIAL AND METHODS

Study area: The study was carried out at Pharmaceutical Chemistry Lab, Department of Medicinal Chemistry and Pharmacology Research Laboratory, Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Saudi Arabia from October, 2020-February, 2021.

Drugs and chemicals: The fine chemicals Streptozotocin (STZ), metformin hydrochloride and nicotinamide were purchased from Cayman Chemicals, USA. ELISA kits for TNF-α, IL-6, IL-10, TGFβ1 and COX-2 was obtained from Cloud-Clone Corp., USA. All other chemicals and solvents were procured from local suppliers and were used of analytical grade.

Plant material and extraction: Ajwa dates (*Phoenix dactylifera* L., Arecaceae) were purchased from the date farm of Al-Madinah. The dates were identified by Prof. Mohamed Motawei, Professor in Genetic Molecular, Department of Plant

Production and Protection in College of Agriculture and Veterinary, Qassim University, Saudi Arabia. The seeds were separated from the fruit pulp and were washed with an adequate amount of water. After drying at room temperature for 2-3 days, the seeds were crushed into small pieces and coarse powder was obtained by grinding with a coffee grinder. Each 100 g of the collected seed powder was soaked into 1 L of distilled water for 3 days at room temperature. The mixture was concentrated under a vacuum. The collected extract was freeze-dried and stored for further studies[13].

Animals: In this experiment, a total number of 30 adult male Sprague Dawley rats (3 months old, 200-250 g body weight) were collected from the animal facility of the Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Kingdom Saudi Arabia. Female Sprague Dawley (SD) rats of similar age were used for acute toxicity studies. Rats were acclimatized for one week in standard laboratory conditions at 25±1°C and relative humidity (60±5%) with 12 hrs light and dark cycle. Rats were randomly divided into 5 groups with every group consisting of six animals each. Three rats/propylene cages were housed and were permitted free access to food and water during the experiment. The experimental procedures for the present study were approved by the Animal Ethical Committee, College of Pharmacy, Qassim University, Kingdom of Saudi Arabia (Approval ID 2020-CP-5).

Vehicle: AASE and metformin hydrochloride were solubilized in 0.9% (w/v) normal saline and was used for the treatment through oral route 0.1 M cold citrate buffer with pH 4.5 was used to prepare STZ solution. While nicotinamide was solubilized in 0.9% (w/v) normal saline. The solutions were injected intraperitoneally (i.p.) for inducing type 2 diabetes.

Acute toxicity study: Acute toxicity experiments were performed in compliance with the guidelines of the Organization for Economic Co-operation and Development (OECD 423)[15]. In this experiment, for each step, three female rats were allocated using a random sampling technique. Animals were subjected to overnight fasting and only kept on water. Initially, AASE was administered orally at 5 mg kg^{-1} and closely observed for toxic symptoms for the first 4 hrs and mortality for another 3 days. When two of the three animals died, the dose given was considered toxic. Whereas if only one of the three animals died, the dosage was re-evaluated to confirm toxic effects. If none of the animals died at an above lower dose, further higher doses of AASE (50, 300 and 2000 mg kg^{-1}) were employed to confirm the toxicity[16].

Experimental design and drug treatments: A total number of 30 rats were divided into six groups (n = 6) and assigned to the following groups: Control group was administered with vehicle (0.5% w/v CMC, p.o.) only, Diabetic-induced group was injected 120 mg kg^{-1} of nicotinamide followed by 60 mg kg^{-1} of STZ after 15 min by intraperitoneal route, Standard group was treated with metformin (200 mg kg^{-1}, p.o.), Extract treatment groups were subjected to AASE with the dose of 200 or 400 mg kg^{-1} through the oral route. The treatment with metformin and AASE was continued for 30 days diabetes induction.

Induction of diabetes: The rats fasted overnight before injection. Diabetes was induced by a single intraperitoneal injection (i.p.) of streptozotocin (60 mg kg^{-1}). Nicotinamide (120 mg kg^{-1}, i.p.) was injected 15 min before STZ to develop type 2 diabetes. The development of hyperglycemia was confirmed by measuring the blood glucose level after 72 hrs and then on day 7th after the induction. The rats with a fasting blood glucose level higher than 126 mg dL^{-1} were considered diabetic and were used for further studies[17].

Enzyme-linked immunosorbent assay (ELISA): At the end of treatment, all the animals were sacrificed and the whole brain was isolated for ELISA analysis. The fresh brain was homogenized in ice-cold phosphate buffer (4°C, pH 7.6), followed by centrifugation for 10 min at 4000 rpm. The cloudy supernatant homogenate aliquot was separated into 4 mL vials and stored at -80°C which were later used to determine the neuroinflammation parameters. The total protein content of samples was quantified using the Biuret colorimetric method (Crescent Diagnostics, Saudi Arabia). The samples were tested using ELISA kits for TNF-α, IL-6, IL-10, TGFβ1 and COX-2 antibodies as described in the manufacturer's (Cloud-Clone Corp., USA) protocol. Measurements were performed at 450 nm by using an ELx800 Absorbance Microplate Reader (BioTek Instruments, Inc.).

Statistical analysis: Results were indicated as Mean±Standard Error (SEM). The recorded data were analyzed using the one-way ANOVA followed by Tukey-Kramer *post hoc* test to calculate the significance level. Graph Pad version 9 (GraphPad Software Inc., United States) was employed for statistical analysis. The $p<0.05$ was considered statistically significant.

RESULTS

Acute toxicity study: The results from acute toxicity OECD 423 guidelines revealed that there was no record of any toxicity symptoms and mortality of animals from each dose of the extract via oral treatment until the higher dose of 2000 mg kg^{-1}. So, two lower doses (200 and 400 mg kg^{-1}, p.o.) were selected for further memory assessment and biochemical studies.

Treatment of AASE reduced pro-inflammatory cytokine markers in brain homogenates of diabetic-induced rats: The data in Fig. 1 and 2 illustrate the effects of AASE on two selective pro-inflammatory cytokine markers such as TNF-α and IL-6. The results from TNF-α, the diabetic-induced group was found with significant ($p<0.05$) higher levels of TNF-α in their brain homogenate as compared with the control group (Fig. 1). These elevations of TNF-α levels indicates the sign of neuroinflammation in the diabetic-induced rat's brain. Thirty days' treatment of AASE orally at 200 and 400 mg kg^{-1} significantly reduced ($p<0.05$ and $p<0.01$, respectively) TNF-α productions in the brain as compared to the diabetic-induced group. Furthermore, the standard drug metformin also significantly ($p<0.05$) reduced the TNF-α levels in the brain. Additionally, there is no significant difference between extract-treated groups and metformin.

The production of cytokine IL-6 was noted to be significantly ($p<0.001$) higher in the diabetic-induced group as compared to the control group (Fig. 2). The oral treatment of AASE at selected doses (200 and 400 mg kg^{-1}, p.o.) and metformin significantly ($p<0.001$) attenuated the increased IL-6 levels in the rat's brain as compared to the diabetic-induced group. Besides, there were no significant differences between AASE and metformin administrated groups.

Treatment of AASE selectively elevated anti-inflammatory cytokine markers in brain homogenates of diabetic-induced rats: The data in Fig. 3 and 4 show the effects of AASE on anti-inflammatory cytokine markers such as IL-10 and TGF-β1 in brain homogenates of type 2 diabetic-induced rats. The levels of cytokine IL-10 in diabetic-induced rats were reported significantly ($p<0.01$) lower as compared to the control rats (Fig. 3). This indicates lower anti-inflammatory activity in diabetic-induced rats' brains. However, the administration of a higher dose (400 mg kg^{-1}, p.o.) of AASE significantly ($p<0.05$) increased IL-10 levels in the brain as compared to the diabetic-induced group. As expected, metformin also significantly ($p<0.01$) elevated IL-10 activity in the brain. The other low dose (200 mg kg^{-1}, p.o.) did not show any significant changes in brain IL-10 levels as compared to the diabetic-induced group.

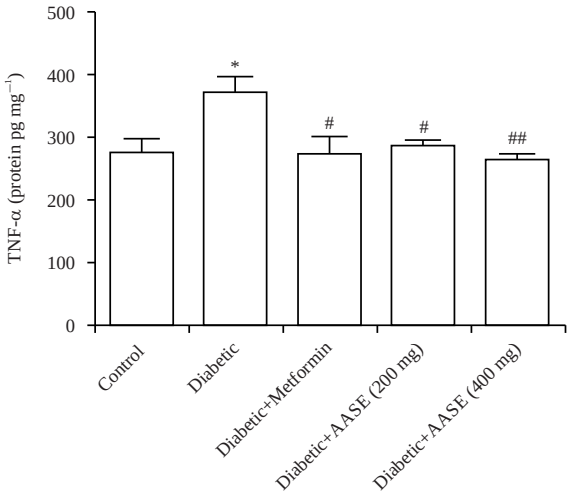

Fig. 1: Effect of Aqueous Ajwa Seeds Extracts (AASE) on a pro-inflammatory cytokine TNF-α in brain homogenates of type 2 diabetic-induced rats

Values are Mean±SEM (n = 6). One-way ANOVA [F (4.25) = 4.757, $p<0.01$] 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

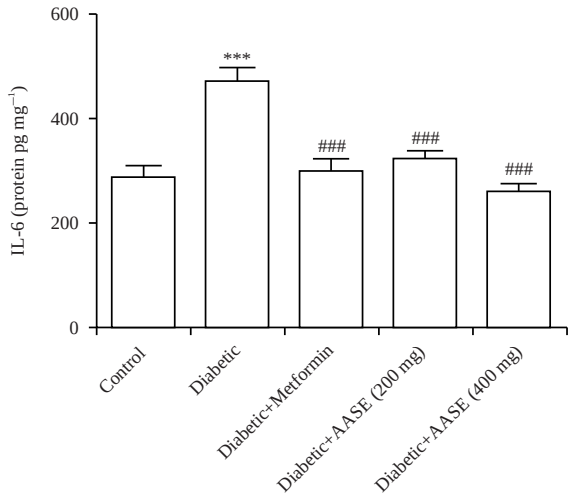

Fig. 2: Effect of Aqueous Ajwa Seeds Extracts (AASE) on a pro-inflammatory cytokine IL-6 in brain homogenates of type 2 diabetic-induced rats

One-way ANOVA [F (4.25) = 15.28, $p<0.001$] followed by Tukey-Kramer multiple comparisons test. ***$p<0.001$ as compared to the control group, ###$p<0.001$ as compared to the diabetic-induced group

Furthermore, there was a significant ($p<0.001$) reduction in cytokine TGF-β1 levels in the diabetic-induced group, when

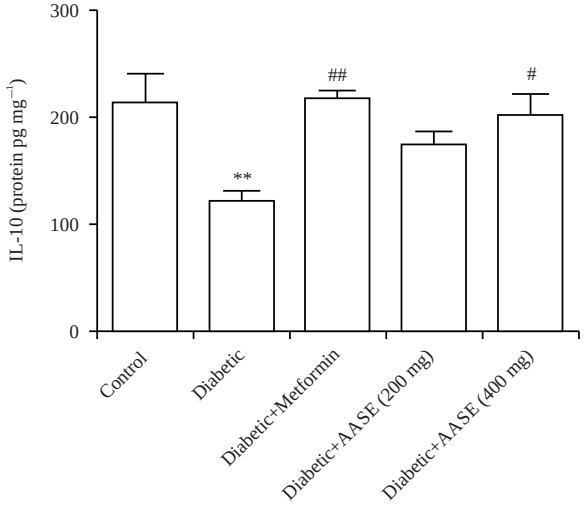

Fig. 3: Effect of Aqueous Ajwa Seeds Extracts (AASE) on an anti-inflammatory cytokine IL-10 in brain homogenates of type 2 diabetic-induced rats

Values are Mean±SEM (n = 6). One-way ANOVA [F (4.25) = 5.521, p<0.01] 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

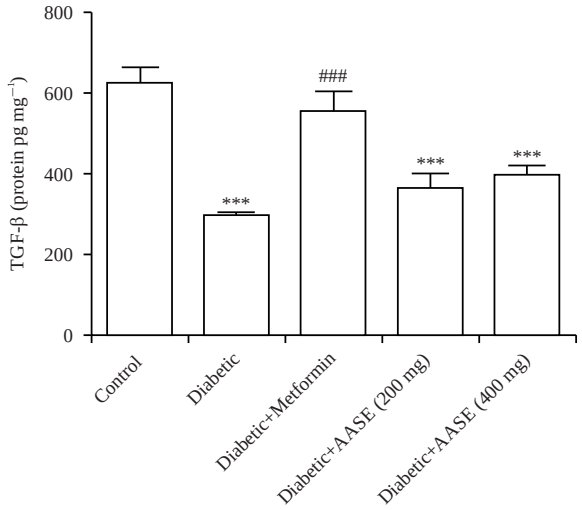

Fig. 4: Effect of Aqueous Ajwa Seeds Extracts (AASE) on an anti-inflammatory cytokine TGF-β1 in brain homogenates of type 2 diabetic-induced rats

One-way ANOVA [F (4.25) = 15.92, p<0.01] followed by Tukey-Kramer multiple comparisons test. The values are Mean±SEM (n = 6). ***p<0.001 as compared to the control group, ###p<0.001 as compared to the diabetic-induced group

compared to control groups (Fig. 4). Administration of AASE at both the dose levels (200 and 400 mg kg^{-1}, p.o.) did not change the neuronal TGF-β1 levels as compared to diabetic-induced rats. Treatment of metformin showed significant (p<0.001) improvement in the brain TGF-β1 levels as referred to the diabetic-induced group.

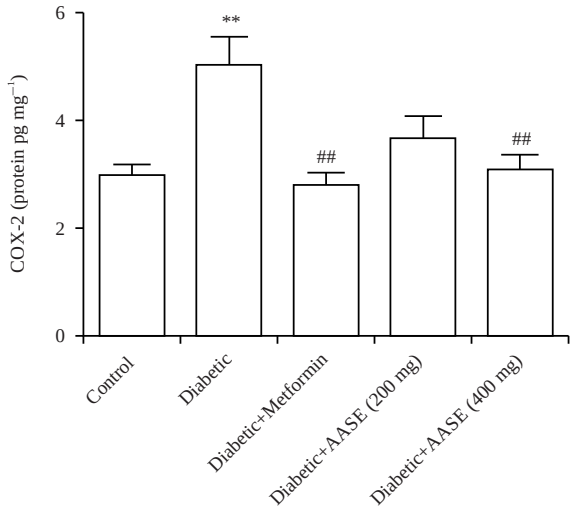

Fig. 5: Effect of Aqueous Ajwa Seeds Extracts (AASE) on cyclooxygenase-2 (COX-2) activities in brain homogenates of type 2 diabetic-induced rats

One-way ANOVA [F(4.25) = 6.542, p<0.001] followed by Tukey-Kramer multiple comparisons test. The values are Mean±SEM (n = 6). **p<0.001 as compared to the control group, ##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: The data in Fig. 5 highlights the effects of AASE on brain cyclooxygenase 2 (COX-2) levels of type 2 diabetic-induced rats. As compared to the control group, the diabetic-induced animals showed significant (p<0.01) elevation of COX-2 enzyme levels in the brain. However, the treatment of the extract (400 mg kg^{-1}, p.o.) significantly (p<0.01) lowered COX-2 activities on diabetic-induced rat's brain but there were no significant changes with low dose (200 mg kg^{-1}, p.o.) treatment.

DISCUSSION

The current study results emphasized the potential of Aqueous Ajwa Seeds Extract (AASE) treatment on selected neuroinflammatory mediators such as proinflammatory cytokines, anti-inflammatory cytokines and cyclooxygenase-2 in type 2 diabetic induced rats. It is very well established that diabetes is the world's fastest-growing disorder and is accompanied by a high number of morbidity and mortality[18].

Furthermore, cognitive functional defects, including challenges in memory functioning are commonly associated with diabetes patients. Until now, the underlying mechanisms of diabetes-associated impairment in cognitive functions have remained unknown[19]. It was observed that there is a significant rise in the number of inflammatory markers associated with type 2 diabetes. People with metabolic syndrome, linked with elevated rates of neuroinflammation have suffered significant cognitive failure[20]. Scientific reports are also highlighting the crucial role of prolonged abnormalities in blood glucose levels, lack of insulin activities, a deficit of cholinergic neuronal functions and inflammatory neuronal damages in diabetes-related cognitive and memory dysfunction[21].

The presence of neuroinflammation characterizes dementia and the development of neuroinflammation can play a vital role in the progression of Alzheimer's Disease (AD)[22]. Also, diabetes mellitus is known to develop memory complications via its brain's neuroinflammatory detrimental effects[23]. In a previous study, diabetes has been shown to cause an Aβ aggregation and increase in pro-inflammatory molecules such as TNF-α, IL-1β and COX-2 in rats' brains, followed by cognitive loss. As a result, under chronic diabetic conditions, Aβ deposition and inflammatory processes accompany and interact with the brain[24]. In the present study, the effect of AASE on type 2 diabetes mellitus induced memory deficits in rats were determined by inhibiting the neuroinflammation, cytokine levels and COX-2 activities.

The COX, also known as prostaglandin H synthase, is an enzyme that transforms arachidonic acid into bioactive prostanoids, which play a vital role in the inflammatory pathway. It comes in two isoforms: COX-1 and COX-2. COX-1 is distributed abundantly in most tissues and is expressed mainly by microglia in rodents and human brains. It has been implicated in neuroinflammatory disorders. On the other hand, COX-2 causes inflammatory stimuli through the release of cytokines, indicating that selective inhibition of COX-2 may minimize inflammation and be a possible anti-inflammatory target[25]. In the diabetic rat, a previous study exhibited that the COX-2 expression in the hippocampus was significantly up-regulated[26]. In line with these results, diabetic rats that were given chronic ibuprofen (NSAIDs) found their learning and memory abilities significantly improved. Also, ibuprofen therapy decreased COX-2 activity and expression in the brain significantly[24]. In the previous investigation, using Nonsteroidal Anti-inflammatory Drugs (NSAIDs), particularly COX-2 inhibitors, has protected memory and limited memory deficits risk[26]. In the present study, our data showed that there was a significant increase in COX-2 levels in the diabetic group as compared to the control group. In addition, there was a significant reduction in COX-2 levels at 400 mg kg^{-1} when compared to the diabetic-induced group.

To further confirmation, groups of cytokines ELISA assays were performed to support Ajwa seeds extract's an anti-inflammatory role in reducing the inflammatory response. Accordingly, TNF-α and IL-6 are proinflammatory cytokines that are well known to cause inflammatory responses and their levels in the human and rodent brain have been documented to be elevated concerning AD, in contrast, TGF-1β and IL-10 are the anti-inflammatory cytokines that reduce the cellular immune response which provides further anti-inflammatory impacts[27,28]. In the same context, circulating neuro-inflammatory markers such as TNF-α and IL-6 were shown to be elevated in DM patients[29]. Similarly, in another study, anti-inflammatory factors IL-10 and TGF-1β were significantly reduced in a T2DM mouse model. These findings suggested that neuroinflammation is one of the contributing factors in cognitive impairment in diabetic models[30]. In the current study, the anti-inflammatory activity of Ajwa seeds extracts was demonstrated by lowering the levels of pro-inflammatory cytokines TNF-α and IL-6 levels in rat brain homogenate in the type 2 diabetic model. Additionally, the present investigations showed that the treatment with AASE illustrated the anti-inflammatory effects by increasing an anti-inflammatory cytokine IL-10 levels in the rat's brain.

CONCLUSION

Our results indicate that AASE has inhibitory effects on COX-2 activity. It was also concluded that the AASE reduces the development of pro-inflammatory cytokines such as TNF-α and IL-6. Besides, it was noted to increase the production of an anti-inflammatory cytokine such as IL-10. All the above-mentioned observations suggest that AASE extract have anti-inflammatory features that could help to alleviate the inflammatory response associated with diabetic-induced neuronal deficits.

SIGNIFICANCE STATEMENT

Current studies revealed that type 2 diabetes induces neuroinflammation in rat models. Our results revealed that the treatment of diabetic-induced rats with AASE has the potential to revert neuroinflammation by inhibiting COX-2 activity and reducing pro-inflammatory cytokines such as TNF-α and IL-6. Our results also suggest that AASE elevates the production of anti-inflammatory cytokine IL-10. Overall, the AASE have an anti-inflammatory response to diabetes-associated neuronal deficiency.

ACKNOWLEDGMENT

The authors gratefully acknowledge Qassim University, represented by the Deanship of Scientific Research for the financial support for this research under the number (Pharmacy-2019-2-2-I-5643) during the academic year 1440AH/2019AD.

REFERENCES

1. Petersmann, A., D. Müller-Wieland, U.A. Müller, R. Landgraf and M. Nauck *et al*., 2019. Definition, classification and diagnosis of diabetes mellitus. Exp. Clin. Endocrinol. Diabetes, 127: S1-S7.
2. Latha, S. and R. Vijayakumar, 2019. The facts about diabetes mellitus-A review. Galore Int. J. Health Sci. Res., 4: 64-75.
3. Saeedi, P., I. Petersohn, P. Salpea, B. Malanda and S. Karuranga *et al*., 2019. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the international diabetes federation diabetes atlas, 9th edition. Diabetes Res. Clin. Pract., Vol. 157. 10.1016/j.diabres.2019.107843.
4. Fowler, M.J., 2008. Microvascular and macrovascular complications of diabetes. Clin. Diabetes, 26: 77-82.
5. Leszek, J., E. Trypka, V.V. Tarasov, G.M. Ashraf, G. Aliev, 2017. Type 3 diabetes mellitus: A novel implication of Alzheimers disease. Curr. Topics Med. Chem., 17: 1331-1335.
6. Infante-Garcia, C. and M. Garcia-Alloza, 2019. Review of the effect of natural compounds and extracts on neurodegeneration in animal models of diabetes mellitus. Int. J. Mol. Sci., Vol. 20. 10.3390/ijms20102533.
7. Dyken, P.V. and B. Lacoste, 2018. Impact of metabolic syndrome on neuroinflammation and the blood-brain barrier. Front. Neurosci., Vol. 12. 10.3389/fnins.2018.00930.
8. Guo, T., D. Zhang, Y. Zeng, T.Y. Huang, H. Xu and Y. Zhao, 2020. Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. Mol. Neurodegener., Vol. 15. 10.1186/s13024-020-00391-7.
9. McCrimmon, R.J., C.M. Ryan and B.M. Frier, 2012. Diabetes and cognitive dysfunction. Lancet, 379: 2291-2299.
10. Sheikh, B.Y., S.M.N.K. Zihad, N. Sifat, S.J. Uddin and J.A. Shilpi *et al*., 2016. Comparative study of neuropharmacological, analgesic properties and phenolic profile of Ajwah, Safawy and Sukkari cultivars of date palm (*Phoenix dactylifera*). Orient. Pharm. Exp. Med., 16: 175-183.
11. Hamad, I., H. AbdElgawad, S. Al Jaouni, G. Zinta and H. Asard *et al*., 2015. Metabolic analysis of various date palm fruit (*Phoenix dactylifera* L.) cultivars from Saudi Arabia to assess their nutritional quality. Molecules, 20: 13620-13641.
12. Khalid, S., N. Khalid, R.S. Khan, H. Ahmed and A. Ahmad, 2017. A review on chemistry and pharmacology of Ajwa date fruit and pit. Trend Food Sci. Technol., 63: 60-69.
13. Hasan, M. and A. Mohieldein, 2016. *In vivo* evaluation of anti diabetic, hypolipidemic, antioxidative activities of saudi date seed extract on streptozotocin induced diabetic rats. J. Clinic. Diagn. Res., Vol. 10. 10.7860/jcdr/2016/16879.7419.
14. Sarfraz, M., T. Khaliq, J.A. Khan and B. Aslam, 2017. Effect of aqueous extract of black pepper and ajwa seed on liver enzymes in alloxan-induced diabetic Wister albino rats. Saudi Pharm. J., 25: 449-452.
15. Ahmad, A., K. Ramasamy, A.B.A. Majeed and V. Mani, 2015. Enhancement of β-secretase inhibition and antioxidant activities of *tempeh*, a fermented soybean cake through enrichment of bioactive aglycones. Pharm. Biol., 53: 758-766.
16. Mani, V., S. Sajid, S.I. Rabbani, A.S. Alqasir, H.A. Alharbi and A. Alshumaym, 2021. Anxiolytic-like and antidepressant-like effects of ethanol extract of *Terminalia chebula* in mice. J. Trad. Compl. Med., Vol. 11. 10.1016/j.jtcme.2021.04.003.
17. Aboonabi, A., A. Rahmat and F. Othman, 2014. Antioxidant effect of pomegranate against streptozotocin-nicotinamide generated oxidative stress induced diabetic rats. Toxicol. Rep., 1: 915-922.
18. Lin, X., Y. Xu, X. Pan, J. Xu and Y. Ding *et al*., 2020. Global, regional and national burden and trend of diabetes in 195 countries and territories: An analysis from 1990 to 2025. Sci. Rep., Vol. 10. 10.1038/s41598-020-71908-9.
19. Kodl, C.T. and E.R. Seaquist, 2008. Cognitive dysfunction and diabetes mellitus. Endocr. Rev., 29: 494-511.
20. Srikanth, V., A.J. Sinclair, F. Hill-Briggs, C. Moran and G.J. Biessels, 2020. Type 2 diabetes and cognitive dysfunction-towards effective management of both comorbidities. Lancet Diabetes Endocrinol., 8: 535-545.
21. Wang, K., F. Song, K. Xu, Z. Liu, S. Han, F. Li and Y. Sun, 2019. Irisin attenuates neuroinflammation and prevents the memory and cognitive deterioration in streptozotocin-induced diabetic mice. Mediators Inflammation, Vol. 2019. 10.1155/2019/1567179.
22. Pasqualetti, G., D.J. Brooks and P. Edison, 2015. The role of neuroinflammation in dementias. Curr. Neurol. Neurosci. Rep., Vol. 15. 10.1007/s11910-015-0531-7.
23. Khare, P., A.K. Datusalia and S.S. Sharma, 2017. Parthenolide, an NF-κB inhibitor ameliorates diabetes-induced behavioural deficit, neurotransmitter imbalance and neuroinflammation in type 2 diabetes rat model. NeuroMol. Med., 19: 101-112.
24. Liu, Y.W., X. Zhu, L. Zhang, Q. Lu, F. Zhang, H. Guo and X.X. Yin, 2014. Cerebroprotective effects of ibuprofen on diabetic encephalopathy in rats. Pharmacol. Biochem. Behav., 117: 128-136.
25. Font-Nieves, M., M.G. Sans-Fons, R. Gorina, E. Bonfill-Teixidor and A. Salas-Pérdomo *et al*., 2012. Induction of COX-2 enzyme and down-regulation of COX-1 expression by lipopolysaccharide (LPS) control prostaglandin E_2 production in astrocytes. J. Biol. Chem., 287: 6454-6468.

26. Yang, Y. and L. Gao, 2017. Celecoxib alleviates memory deficits by downregulation of COX-2 expression and upregulation of the BDNF-TrkB signaling pathway in a diabetic rat model. J. Mol. Neurosci., 62: 188-198.
27. Mani, V., S.M. Jaafar, N.S.M. Azahan, K. Ramasamy, S.M. Lim, L.C. Ming and A.B.A. Majeed, 2017. Ciproxifan improves cholinergic transmission, attenuates neuroinflammation and oxidative stress but does not reduce amyloid level in transgenic mice. Life Sci., 180: 23-35.
28. Shen, X.N., L.D. Niu, Y.J. Wang, X.P. Cao and Q. Liu *et al*., 2019. Inflammatory markers in Alzheimer's disease and mild cognitive impairment: A meta-analysis and systematic review of 170 studies. J. Neurol., Neurosurg. Psychiatry, 90: 590-598.
29. Rom, S., V. Zuluaga-Ramirez, S. Gajghate, A. Seliga and M. Winfield *et al*., 2019. Hyperglycemia-driven neuroinflammation compromises BBB leading to memory loss in both diabetes mellitus (DM) type 1 and type 2 mouse models. Mol. Neurobiol., 56: 1883-1896.
30. Lang, X., N. Zhao, Q. He, X. Li, X. Li, C. Sun and X. Zhang, 2020. Treadmill exercise mitigates neuroinflammation and increases BDNF via activation of SIRT1 signaling in a mouse model of T2DM. Brain Res. Bull., 165: 30-39.