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Original Article

Effect of Fenugreek Seed Extract against Induced Cognitive Decline in Experimental Mice

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ABSTRACT

Background: Alzheimer's disease affecting about 18 million people world-wide. The socio-economic burden on world-economies costing more than 172 billion US $ annually for the US alone. **Objectives:** To prepare aqueous extract of *T. foenum graecum* seeds (FSE) to explore the possible treatment for cognitive deficit in experimental animals. **Materials and Methods:** FSE was subjected to preliminary phytochemical evaluation and antioxidant effect using free radical scavenging method (DPPH). All the animal behavior was video recorded with no human intervention during observation and animal groupings were blinded to avoid investigator bias**.** Different doses of FSE (5%, 10% and 20%), control, standard (Piracetam, 200 mg/kg, IP.) were given for male albino mice a period of 15 days followed by cognitive assessment in elevated plus maze and novel object recognition tests. Transfer latencies and time exploring novel and familiar objects were recorded in respective tests. Retention of this learned-task was examined again 24 hr later and Inflexion Ratio (IR) and Discrimination Index (DI) were calculated respectively. Next in the second set of experiment same groups and treatments were continued but scopolamine was administered to all the groups except normal control 1 hr after the last dose and examined similarly. **Results:** FSE showed potential antioxidant effect and a dose dependent increase in transfer latency and improved DI indicating a nootropic effect. FSE at 20% showed significant reversal of scopolamine induced dementia in the second set of experiment. **Conclusion:** FSE improved memory as well as reversed the chemically induced memory deficits in experimental mice.

Keywords: Alzheimer's Disease, Cognitive Disorders, Fenugreek, Herbs, Memory, Nootropic.

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INTRODUCTION

Alzheimer's Disease (AD) is a progressive neurological disorder and the leading cause of dementia in the elderly population. The disease is characterized by a gradual loss of memory and the capacity to perform basic daily activities. This decline in cognitive skills often manifests as behavioral challenges and a loss of personal independence.

The risk factors for AD are understood to be multifaceted, involving both genetic predispositions and environmental influences. At a cellular level, the pathology is linked to elevated oxidative stress, the presence of free radicals, and mitochondrial impairment, all of which contribute to synaptic and neuronal dysfunction and, ultimately, neurodegeneration (NIA, 2020a; Alzheimer's Disease International [ADI], 2019).

The global scale of AD is significant. The National Institute of Health has reported approximately 18 million affected individuals worldwide, with projections suggesting this figure could surge to 65.7 million by 2030 and 115.4 million by 2050 (NIA, 2020b). Data from Alzheimer's Disease International indicates that AD is responsible for 50-80% of all dementia cases globally. The primary risk factor identified is advanced age (65 years and older), though precise prevalence rates are not yet fully documented (NIA, 2020a; Alzheimer's Disease International [ADI], 2019). Current therapeutic strategies, licensed by global pharmaceutical bodies, often involve Acetyl-Cholinesterase (AChE) inhibitors like rivastigmine and donepezil to manage symptoms (Panda *et al.*, 2013).

However, these AChE inhibitors primarily manage symptoms, highlighting a pressing need for novel therapeutic agents. This has spurred research into natural compounds, particularly those with significant antioxidant capabilities and more favorable side-effect profiles. Consequently, there is a growing interest in exploring traditional or herbal medicines as potential treatments for AD.

Acetylcholine is a critical neurotransmitter, and its dysregulation is a well-established component of AD pathology. This understanding is the rationale behind the many clinical trials

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focused on AChE suppressors (Kennedy and Scholey, 2006; Kiefer, 2019; Fu and Li, 2011).

Fenugreek stands out as a plant with notable antioxidant properties. Both its seeds and leaves are utilized in culinary applications and traditional medicine. Research has identified trigonelline, an active compound in fenugreek, as having potential for nerve regeneration and memory enhancement in AD mouse models. The seeds are a rich source of various compounds including steroidal saponins, alkaloids, flavonoids, choline, and polyphenol antioxidants, which collectively contribute to its anti-inflammatory, antioxidant, and neuroprotective effects. Given this background, the current study was designed to investigate the purported cognitive-enhancing efficacy of this herb (Figure 1) (Yadav and Baquer, 2014; Zhou *et al.*, 2012; Al-Asadi, 2014; Zandi *et al.*, 2015; Panda *et al.*, 2013).

MATERIALS AND METHODS

Drugs and chemicals

Piracetam (Nootropil injection, a commercial product) was used as the standard nootropic agent. Commercially available scopolamine hydrobromide was purchased from a local pharmacy. Acetylthiocholine iodide, 5, 5'-dithiobis-2-nitrobenzoic acid, DPPH (2,2-diphenyl-1-picrylhydrazyl radical) was procured from Fluka Chemie (Buchs, Switzerland). All the other chemical agents used were of analytical grade available in our chemistry lab.

Animals

Male Swiss albino mice were procured from the commercial supplier and breeder in Riyadh, Saudi Arabia. Animal studies were performed after obtaining necessary permission from Institutional Animal Ethics Committee (IAEC UCP/18-19/01). After procuring the mice, they were acclimatized for 7 days and housed in groups of six under standard laboratory condition with relative humidity of 45-55% and light/ dark cycle of 12 hr. They were fed with synthetic standard pellet diet available locally and were supplied water *ad libitum*. Male mice weighing between 25-35 g were used in this study and were fasted for 3 hr prior to any administration of vehicle/standard/extract. All the experimental procedures were carried out as per the protocol in a dimly lit room during the light period (8:00 to 16:00 hr).

Experimental design

Preparation of fenugreek seed extract

The fresh *Fenugreek seeds* were purchased locally. The seeds were washed with tap water and dried in the shade at room temperature for 2 days. Then the dried seeds were kept for germination for 1 day in a covered muslin cloth. The germinated seeds were dried, powdered and sieved. Different concentrations (5%, 10% and 20% w/v) were prepared in water and stirred for 2 hr in magnetic stirrer and then centrifuged for 1 hr at 5000 rpm. Supernatant was collected for administration.

Determination of antioxidant activity of FSE

Method followed as per the available references and consists of taking 3 mL of 0.05 mM DPPH in methanol with 30 µL of the different concentrations of the extract in phosphate buffer (pH 7.4), mixed well and kept in the dark for 20 min followed by reading absorbance. Blank reading was taken for DPPH alone without any extract. IC_{50} values for the different concentrations of the extract were calculated, and percentage inhibition was calculated as:

$$\% \text{ inhibition} = \frac{Ab - As}{Ab} \times 100$$

Where Ab is control absorbance, As- sample absorbance. Vitamin C 1mM and 1mM Vitamin E were used as positive control (Ho *et al.*, 2001; Sharma and Bhat, 2009).

Acute toxicity test

Acute toxicity test of fenugreek seed extract was carried as per the method described in OECD Test Guidelines 425 (Up and Down Procedure) (OECD, 2001), wherein a single albino mouse was given 2000 mg/kg p.o. as single dose and observed for first 30 min, then for 4 hr. After survival of treated mouse, 4 additional mice were administered with the same dose under same conditions. Observed for 2 days for any signs of toxicity or death.

Assessment of cognitive performance

For all experimental procedures, all groups of treatments were blinded to the investigators to avoid any bias. The apparatus used for testing were cleaned with 5% alcohol before using each mouse to remove any animal cues. All the experiments were conducted in dim light and were video recorded for offline analysis

Animal groupings

Mice were divided into following groups each containing six, **group I:** Control (Distilled water 10 mL/kg, p.o.), **group II:** Standard (Piracetam, 200 mg/kg, IP.), **group III:** Low dose of FSE (5%), po; **Group IV:** Medium dose of FSE (10%, po), **Group V:** High dose of FSE (20%, p.o). They were fasted for 3 hr prior to the administration but water was supplied *ad libitum*. All the groups of mice were administered respective treatment as shown in the protocol (Figure 2).

Elevated Plus-Maze

The Elevated Plus Maze (EPM) used was fabricated locally with wood and dimensions meeting the published literature. It had two open arms and two closed arms, crisscrossing each other forming a plus. The closed arms and open arms were 25 cm×10 cm×20 cm and 25 cm×10 cm respectively with a central platform of 10X10

cm area. The entire maze was elevated to a height of 90 cm with a wooden column. All procedures were conducted in a dimly lit dark room (Komada *et al.*, 2008; Dhingra and Kumar, 2012; Journal of Visualized Experiments [JoVE], 2020). All the parameters were recorded using a web cam fixed above EPM to the roof and connected to a computer for recording and offline analysis. On day 15, 1 hr after the dose, each mouse was placed at the end of an open arm, facing away from the central platform. Transfer Latency (TL) i.e. the time taken by mouse with all its four legs to move into one of the enclosed arms was recorded as the initial transfer Latency (L1) on the first day. If the animal does not enter into one of the enclosed arms within 90 sec, it was gently pushed into one of the two enclosed arms and the TL was assigned as 90 sec. The mouse was allowed to explore the maze for next 10 sec and then returned to its home cage. Retention of this learned-task was examined again 24 hr later (L2). The whole apparatus was thoroughly cleaned with 5% alcohol before placing each animal in the maze to avoid animal cues. The Inflexion Ratio (IR) was calculated by the following formula, (IR)= (*L2* – *L1*)/ *L1*, Where *L1* is the initial TL (s) on 1st day and *L2* is the TL (s) on the 2nd day.

Novel object recognition task

The apparatus was made up of wood of a rectangular box measuring 50 cm×50 cm×50 cm. It was placed in dimly lit dark room (Lueptow, 2017; Botton *et al.*, 2010; NeuroReport, 1997). All the parameters were recorded using a video camera. Mice were divided into following groups each containing six. They were fasted for 3 hr prior to the administration but water was supplied *ad libitum*. On day 17, 1 hr after the dose, each mouse was tested in a 30 cm X 30 cm rectangular box. The test consists of 3 phases, 1. Habituation session 2. Training session 3. Test session. All animals were given one habituation session in which they were allowed to explore the apparatus (without objects) for 10 min. For the training session, each mouse was placed into the box with two identical objects (1 and 2) and allowed to explore for 5 min (training). The time spent by the animal exploring each object and also the time spent by the animal exploring both objects and the box were measured. 24 hr after the training, one of the objects was replaced with a novel object (object number 3, novel) and the other object is same as used for training (1, familiar object). Each mouse was individually tested and video-graphed for 5 min. Time spent by mouse exploring objects determined.

Scopolamine induced amnesia in mice using above tests

In the second set of experiment same groups and treatment period were maintained but scopolamine (1 mg/kg, IP) was administered to all the groups 1 hr after last dose on day 19 in the respective tests (EPM and NORT) and then examined to record as above. Retention of this learned-task was examined again 24 hr later and parameters were calculated as per the procedure in above respective methods.

Statistical Analysis

All the results were expressed as mean±standard error. The data were analyzed using ANOVA followed by Dunnett's multiple comparison *post hoc* test. $p<0.05$ were considered as significant. The statistical analysis was done using the SPSS software package for Windows, version 20, Chicago, USA.

RESULTS

Antioxidant activity of FSE

The decrease in DPPH absorption in the presence of varying concentrations of extract was monitored and it was noticed that the extract showed a dose dependent decrease in the absorbance of DPPH radical. IC_{50} value for the extract was found to be 9.93 µg/mL. These results indicated an antioxidant potential of the seed (Table 1).

Effect of FSE on Transfer Latency (TL) in elevated plus maze

Effect of FSE on TL in mice were recorded with elevated plus maze apparatus where piracetam 200 mg/kg and FSE with three different dose levels (w/v) i.e. 5%, 10% and 20%, treated groups have shown a decrease in transfer latencies leading to corresponding increase in inflexion ratios as compared to normal control. But statistically significant effect ($p<0.05$) was observed with high dose 20% of FSE and piracetam ($p<0.05$) (Figure 3A).



Figure 1: Image of leaves and seeds of *Trigonella foenum graecum* and chemical structure of trigonelline.

Table 1: Antioxidant activity of FSE using DPPH free radical scavenging activity.

Sl. No.	Concentration of extract (µg/mL of FSE)	Inhibitory activity (%)
1.	10	50
2.	20	83
3.	30	85
4.	40	86
5.	50	86
6.	60	87
7.	70	89
8.	80	90
9.	90	90
10.	100	90

IC_{50} = 9.93 µg/mL.

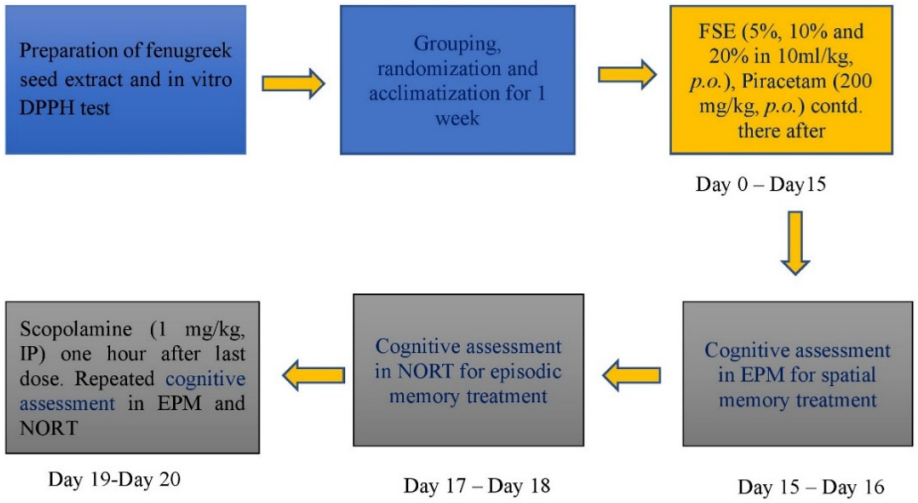


Figure 2: Detailed protocol for the experimental design for normal and scopolamine induced cognitive deficit in mice.

Effect of FSE on transfer latency in scopolamine induced amnesic mice in EPM

The effect of the vehicle, scopolamine (1 mg/kg), FSE (5%, 10% and 20%) and piracetam (200 mg/kg) are shown in Figure 3B. The scopolamine alone treated group showed a significant (p<0.01) increase in TL values on the acquisition as well as on the retention days (decrease in inflexion ratio) as compared to vehicle control mice, indicating an impairment in learning and memory. Whereas in the acquisition as well as retention trial FSE demonstrated dose dependent decrease in the TL (increase in inflexion ratio) when compared to the scopolamine alone treated group (p<0.01). Piracetam (200 mg/kg IP) exhibited marked decrease (p<0.01) in TL in comparison with the scopolamine. However, FSE at the dose levels 20% and 10% showed a comparable decrease in the TL (p<0.05).

Effect of FSE for object exploration in mice using novel object recognition test

Effect of FSE on discrimination indices in mice was recorded using the novel object recognition test. Piracetam (200 mg/kg) and FSE at three dose levels — 5%, 10% and 20% (w/v) — showed a decrease in exploration time toward the familiar object, leading to an increase in discrimination index compared with control. A statistically significant effect (p < 0.05) was observed with the high doses (10% and 20%) of FSE, indicating a dose-dependent nootropic-like effect, while piracetam also increased the discrimination index very significantly (p < 0.01) (Figure 4A).

Effect of FSE on time spent exploring in scopolamine induced dementia in mice using NORT

The effect of the vehicle, scopolamine (1 mg/kg, IP), FSE (5%, 10% and 20%) and piracetam (200 mg/kg) were evaluated at the

end of treatment period. The scopolamine (1 mg/kg) control group showed a significant (p<0.01) increase in exploration time for novel object on the acquisition as well as on the retention days (decrease in discrimination index) as compared to vehicle control mice, indicating an impairment in learning and memory. In the acquisition as well as retention trial, FSE demonstrated dose dependent decrease in the exploration time (increase in DI) as compared to the scopolamine control group. Piracetam (200 mg/kg IP) exhibited marked decrease (p<0.01) in exploration time in comparison with the scopolamine control group (Figure 4B).

DISCUSSION

Alzheimer's disease remains a major neurodegenerative condition defined by declining cognitive function. Despite its high prevalence and severe impact, conventional allopathic medicine has not yet produced a definitive cure (Schneider *et al.*, 2005). This therapeutic gap motivated the present study, which focused on evaluating the potential memory-enhancing effects of Fenugreek Seed Extract (FSE) within chemically-induced amnesia models.

We employed an exteroceptive model, the Elevated Plus Maze (EPM), to assess the nootropic (memory-enhancing) activity of FSE. In this model, cognitive improvement was measured by a decreased Transfer Latency (TL) and a corresponding increased Inflexion Ratio (IR). For the interoceptive model, we used scopolamine-induced amnesia, where the protective effect of FSE was demonstrated by its ability to prevent the expected decrease in TL and IR observed in the EPM task (Komada *et al.*, 2008; Dhingra and Kumar, 2012).

The findings from the EPM test, specifically the observed decrease in transfer latency and increase in inflexion ratio, suggest that FSE possesses memory-enhancing properties. This indicates a pronounced nootropic effect from the FSE, which was shown to be comparable to the standard drug, piracetam (Nootropil), used in this study.

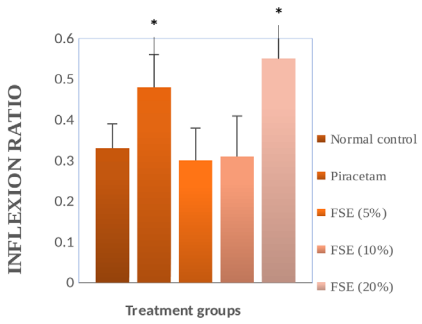
FSE demonstrated a clear facilitatory effect on memory retention, even in mice with scopolamine-induced amnesia. This was further corroborated in the Novel Object Recognition Task (NORT), where scopolamine-treated control animals showed a significant increase in exploration time, confirming cognitive impairment. In contrast, pretreatment with FSE significantly improved the mice's ability to discriminate and identify the novel object.

Across both the EPM and NORT assessments, FSE administration improved memory indices in both normal mice and those with scopolamine-induced memory deficits. The cholinergic system's role in cognitive deficits related to AD and aging is well-established (Parsons *et al.*, 2013; Anjaneyulu *et al.*, 2018). The fact that FSE was able to reverse the amnesia induced by scopolamine strongly suggests that FSE may exert its effects through the activation of this cholinergic system.

A contributing mechanism to this cognitive enhancement is the extract's antioxidant capability. This was demonstrated in the DPPH free radical scavenging assay, which showed FSE has the potential to scavenge oxidative radicals and prevent associated tissue damage. This antioxidant activity is likely due to the presence of phenolic and flavonoid compounds in the FSE, which are known antioxidants. This aligns with other studies confirming the antioxidant capacity of fenugreek seeds, suggesting this property aids in preventing chemically-mediated memory deficits (Bafadam *et al.*, 2019; Moin and Kassaee, 2017; Khalili *et al.*, 2018).

In conclusion, these findings suggest FSE may offer a significant advantage in ameliorating memory loss, such as that seen in Alzheimer's disease. This potential likely stems from a dual mechanism: the activation of the cholinergic system and a

3A. Inflexion ratio in normal mice in the elevated plus maze



3B. Inflexion ratio in scopolamine-induced amnesic mice in the elevated plus maze

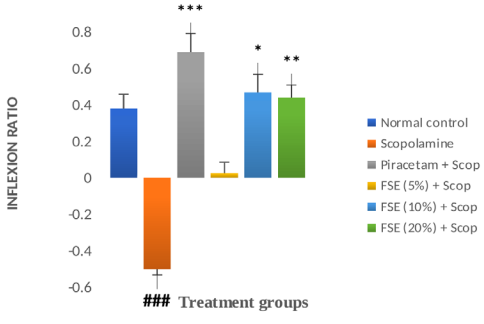
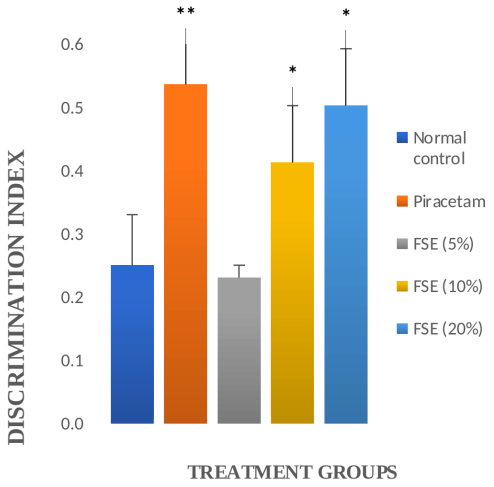


Figure 3: Effect of FSE on inflexion ratio in mice in the elevated plus maze. 3A. Inflexion ratio in normal mice in the elevated plus maze. 3B. Inflexion ratio in scopolamine-induced amnesic mice in the elevated plus maze. Statistical analysis by one-way ANOVA followed by Dunnett's test. Values are expressed as mean±S.E.M (n=6). *p<0.05, **p<0.01, ***p<0.001 compared with normal control group; ###p<0.001 compared with the scopolamine control group.

4A. Discrimination index in normal mice in the novel object recognition test



4B. Discrimination index in scopolamine-induced amnesic mice in the novel object recognition test

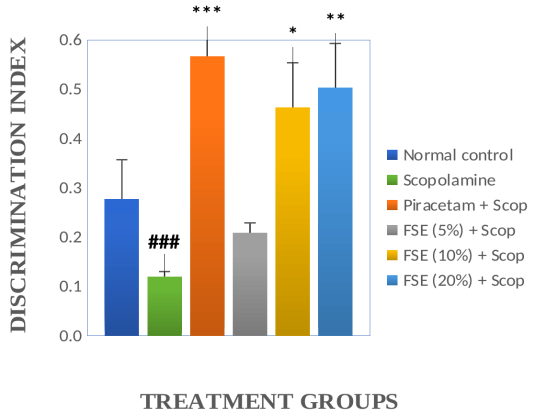


Figure 4: Effect of FSE on discrimination index in mice. 4A. Discrimination index in normal mice in the novel object recognition test. 4B. Discrimination index in scopolamine-induced amnesic mice in the novel object recognition test. Statistical analysis by one-way ANOVA followed by Dunnett's test. Values are expressed as mean±S.E.M (*n*=6). **p*<0.05, ***p*<0.01 compared with normal control group.

neuroprotective effect provided by its free-radical scavenging capabilities, both of which are critical in the management or prevention of AD.

The results observed with FSE are consistent with previous publications that have demonstrated the cognitive benefits of both fenugreek extract and its primary constituent, trigonelline, in various chemical-induced deficit models (Anjaneyulu *et al.*, 2018; Moin and Kassaee, 2017; Chowdhury *et al.*, 2018; Fahanik-Babaei *et al.*, 2019; Prema *et al.*, 2016). While this study provides proof for our initial hypothesis, it is not an exhaustive investigation. Further research is necessary to explore the specific effects of FSE on brain AChE levels, its impact on amyloid-beta plaques, and its interaction with other key neurotransmitter systems, including glutamate, GABA, and catecholamines.

CONCLUSION

In this study, we concentrated on exploring FSE's ability to improve memory in laboratory mice as well as reversing chemically induced memory deficits in experimental mice. The results of the *in vitro* studies have shown that FSE is an antioxidant and the results of the *in vivo* analysis have concluded that FSE has nootropic function in the absence of cognitive deficits and has also been effective in preventing chemically induced memory deficits in experimental mice. The mechanism by which FSE has shown these properties can be related to its antioxidant, neuroprotective properties, its choline content or activation of acetylcholine system in brain. In the light of above, it may be worthwhile to explore the potential of these seeds in the management of AD patients

ABBREVIATIONS

AD: Alzheimer's disease; **FSE:** Fenugreek Seed Extract; **DPPH:** 2, 2, diphenyl-1-picryl hydrazyl radical; **IR:** Inflexion ratio; **DI:** Discrimination index; **AChE:** Acetyl-cholinesterase; **EPM:** Elevated Plus Maze; **TL:** Transfer latency; **NORT:** Novel object recognition task; **IP:** Intraperitoneal; **p.o.:** Per os; **ANOVA:** Analysis of variance; **IC_{50}:** Half maximal inhibitory concentration; **w/v:** weight/volume.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Shalam M. Hussain conceived the idea, experiments and designed the write up, carried the data analysis and finalized the manuscript. Nayef Almutairi, Fahad Alrakaf, Mohammed Aljameli, carried the experiments, collected data, reviewed the initial manuscript and participated in the preparation of manuscript. All the authors reviewed the initial manuscript and provided feedback. Final manuscript was rechecked by Shalam M. Hussain. All authors read the manuscript and approved it for submission.

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