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THYME HONEY SUPPLEMENTATION IMPROVES MEMORY ABILITY IN HIGH FRUCTOSE TREATED RATS DURING PREPUBERTY AND ADOLESCENCE

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Abstract

Thyme honey is known for its anti-inflammatory, analgesic and antibacterial capacity as well as its ability to promote wound healing. This study aims to evaluate the effect of honey supplementation memory ability in adolescence High Fructose diet (HFD) Wistar rats during prepuberty and adolescence. For this reason, we adopted experimental research carried out on 24 rats divided into 3 groups of 8 rats for each, control group (C): receiving normal diet, group 2: fructose (F), treated with fructose 23% /day for 6 weeks and group 3: Fructose + honey (FH), treating in 6 weeks fructose feeding combined to 2 weeks of thyme honey supplementation (5g/Kg/day). After 8 weeks of experience, working and recognition memory were evaluated using the Object Recognition (OR) Y-maze and Barne maze tests. Honey supplementation increased significantly the recognition index ($p < 0.01$; +67%) as compared with the HFD group, and were able to prevent this effect on the memory induced by the HFD ($p < 0.01$). This may be due to a reduction in the production of factors of attacks and/or an increase in the synthesis of protective factors. Fructose diet alters body and organs weight, Honey supplementation decreased body weight. A fructose rich diet improves memory ability in rats. Honey administration could serve as potential therapeutic agents for memory impairment caused by HFD.

Keywords: Honey Supplementation, Memory, High Fructose Diet, Wistar Rats.

1. INTRODUCTION

Over the past few decades, obesity has emerged as a public health issue, resulting from a combination of genetic and environmental factors [1-3].

The recent progression of this syndrome is related to modifications in lifestyle, mainly immobility and eating habits (fast meals, diet rich in sugars, etc.). Indeed, the increased development of metabolic disorders and mainly obesity are associated with changes in the food table which has become rich in lipids and carbohydrates, and especially fructose [4,5].

Consumption of high amounts of fructose in excess of advised nutritional needs can be responsible of several metabolic diseases in animals and humans. The fructose intake has elevated in last years, particularly in underdeveloped nations. In the visceral adipose tissue, the accumulation of triglycerides resulting from transformation of fructose can lead to hepatic steatosis, obesity, cardiac diseases [6-8].

Fructose high diet constitutes a risk factor for metabolic disorders [9], in addition, it negatively affects the structure and functioning of the nervous system and mainly the brain. Neuropsychiatric symptoms are common in obesity and significantly influence the social functioning and quality of life of people with metabolic disease [10,11]. Although, the undergoing physiological processes of the origin of neuropsychiatric symptoms linked to obesity are still under study and require further study, it involves inflammatory processes.

Numerous studies have identified weight gain as a form of moderate chronic inflammation in obese individuals, characterized by dysregulated production of adipokines and cytokines by adipose tissue. This dysregulation leads to an increased risk of developing and complicating metabolic diseases. In brain cells, disruptions in adipokine synthesis can result in various changes, including neurodegeneration, cognitive and mood disorders, and alterations in blood flow [12].

Diet plays a pivotal role in determining susceptibility to various diseases, but it can also confer significant health benefits. Numerous studies have demonstrated the positive effects of certain foods on overall health and well-being [2].

In last years, considerable attention has been directed towards utilizing various plants for their therapeutic properties, attributed to their potent medicinal benefits, minimal side effects, and relatively affordable cost [13,14]. The therapeutic effects of these plants are associated with secondary metabolites such as flavonoids, polyphenols, saponins, terpenoids, and alkaloids. Phenols derived from plants exhibit therapeutic potential in addressing metabolic disorders such as obesity, brain cell disorders, atherosclerosis, and urolithiasis [15-19].

Honey is described as a natural sweet substance created by bees through the collection and transformation of plant nectar, secretions from living parts of plants, or excretions left by sucking insects. Bees process these materials by mixing them with specific clean substances, then deposit, dehydrate, store, and allow them to ripen in the combs within the hive.

Research endeavors are focused on investigating the hypoglycemic properties of medicinal plants and traditional bee products. The objective is to uncover novel natural remedies that are more potent, less harmful, and have fewer side effects. However, this field remains relatively underexplored in Morocco. In this context, our study aims to assess the impact of honey on weight status and various biological parameters, including glucose levels, lipid profiles, and liver enzyme activity, in rats subjected to high fructose intake during prepuberty and adolescence.

honey is widely used as nutriment and a therapeutic supplement by world population including Moroccan people. Related to its therapeutic properties, mainly its antimicrobial, antioxidant and anti-inflammatory activities [10].

The objective of this study is to ass the therapeutic activity of honey supplementation on memory in model of HFD-induced in Wistar rats during prepuberty and adolescence.

2. MATERIALS AND METHODS

2.1 Animal

The experiments carried out in this work were carried out on male Wistar strain laboratory rats, born and raised in the animal facility of the Department of Biology, Faculty of Sciences, Ibn Tofail University, Kenitra (Morocco). Three groups of male Wistar rats weighing between 350 and 375 grams (g) were used for this study. The animals were separated randomly into one of three pre-established groups and put on a diet upon their arrival. All animals had free access to water and food, subject to a photoperiod of12/12 (12 light/12 dark) and an ambient temperature of 22°C.They were regularly monitored by an increase in body weight during their breeding. The cages were regularly cleaned [20].

2.2 Experimental design

The animals were distributed into 3 groups of eight rats each:

- **Group 1:** control group (C): consisting of 8 rats received normal diet.
- **Group 2:** fructose (F): made up of 8 rats treated with fructose 23% of fructose/day for 6 weeks during prepuberty and adolescence.
- **Group 3:** Fructose + honey (FH): includes 8 rats treating in 6 weeks fructose feeding combined to 2 weeks of thyme honey supplementation (5g/Kg/day).

In current study, the used thyme honey was produced in Drâa Tafilalet area (near Assoul) province of Tinghir in Morocco, known for its therapeutic virtues and its physicochemical properties.

2.3 Memory tests

2.3.1 Object recognition test

The object recognition test in rodents assesses recognition memory and the ability to discern between objects in familiar surroundings. It measures the behavioral reactions of rats upon introducing a new object. Relying on the natural inclination of rats to explore novel objects, the test employs an open field with a square translucent floor and white vertical walls. Over three days, including habituation and training, the test introduces two identical objects and the third is different. Discrimination index parameter reflects the proportion of exploration time of the new object, varying between -100% (familiar object) to 100% (new object). Deficits in short-term recognition memory are expressed by a reduction in the recognition index (% RI), which is calculated according to the following formula: [The total time spent exploring the novel object / (The total time spent exploring the novel object + The total time spent exploring the familiar object)] x 100 [21,22].

2.3.2 Y-Maze test

This Y-maze test examines working memory using three identical aisles arranged in an equilateral triangle. The dimensions of aisle are 13 x 4.5 x 5.5 cm. Known as a "spontaneous alternation" test, the rat freely explores these aisles without external reinforcement. The rat starts in one aisle, facing the intersection, and is allowed 5 minutes of exploration, recording entries when all four legs are inside. Parameters include total visits and alternations, and the percentage of alternation is indicative of working memory capacities, showing an inverse correlation.

The sequence of alternation of entries was analyzed to obtain the % correct alternation which is calculated as follows: % of Spontaneous alternation = [(Number of alternations) / (Total arms entries-2)] × 100 [23,24].

2.3.3 Barne maze assay

Barne maze is a behavioral test using to assess spatial learning and memory that was originally developed by Carol Barnes. A round platform is placed in a room where there are visual clues so that the rodent can find its way. Several holes are present all along the border. Under one of the holes, it is possible to place a box allowing the rodent to escape the maze. This test allows several strategies to be studied: random (the rodent explores all the holes), systematic (it explores all the holes along the same path) or spatial (the rodent makes a straight line to the hole of interest).

2.4 Statistical Analysis

The value differences between experimental and control groups are determined by analysis of variance (ANOVA one way) via GraphPad Prism software (version 9.0). The post-hoc Tukey was performed in the case of significant difference variance. The used significant degrees are significant at $p < 0.05$ (*), very significant at $p < 0.01$ (**) and highly significant at $p < 0.001$ (***).

3. RESULTS

OR test

Recognition performance was tested by OR test and was revealed in Figure 2. In the ORT, our findings show that the object exploration time and the exploration index were increased in FH rats compared to fructose diet and control rats (Figures 1 and 2). Also, the honey supplementation increased significantly the recognition index ($p < 0.01$) as compared with the HFD group (Figure 3). Then, the honey supplementation improves the recognition index when compared to the HFD group ($p > 0.05$).

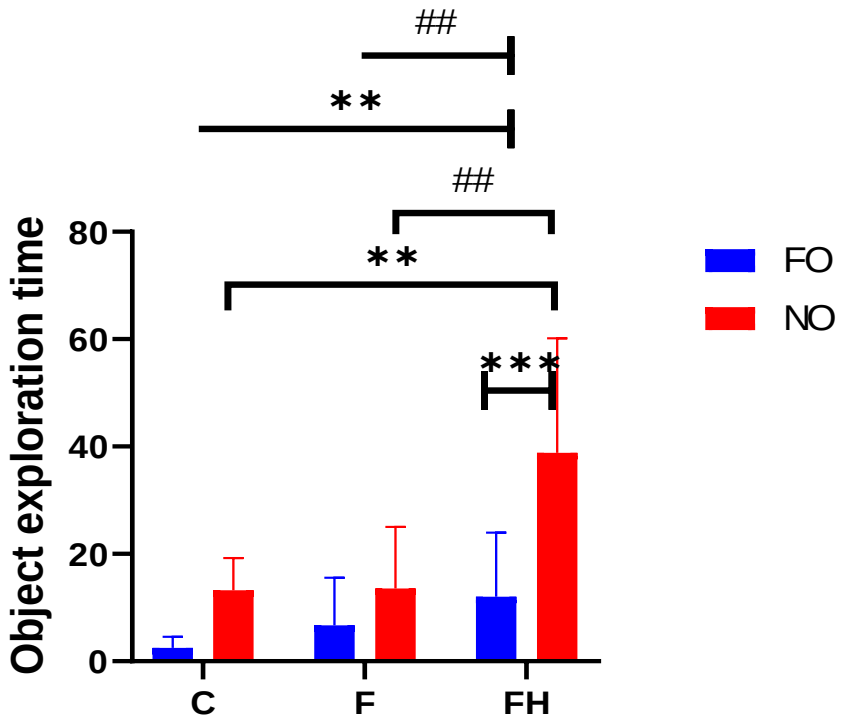

Figure 1: Effects of 6 weeks fructose feeding combined or not to 2 weeks of thyme honey supplementation on memory activity expressed in exploration time expressed in sec using One-Way ANOVA followed by Sidak's multiple comparisons test. * p < .05, ** p < .01, *** p < .001. Values are mean ± SEM of eight rats per group (Control (C), Fructose (F) and fructose + honey (FH), familiar object (FO), novel object (NO)). **P < 0.01 vs C and ## P < 0.01 vs F. For NO, **P < 0.01 vs C and ## P < 0.01 vs F. For FH, P < 0.001 vs FO

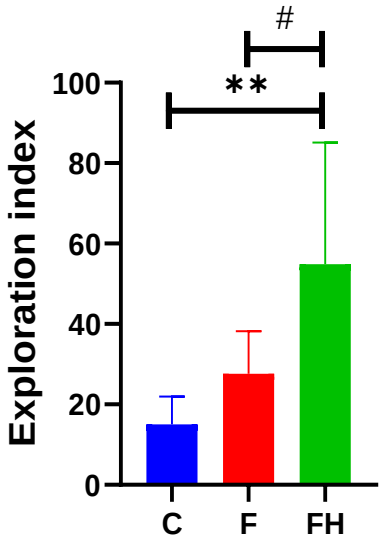

Figure 2: Effects of 6 weeks fructose feeding combined or not to 2 weeks of thyme honey supplementation on memory activity expressed in exploration index using One-Way ANOVA followed by Tukey's multiple comparisons test. * p < .05, ** p < .01, *** p < .001. Values are mean ± SEM of eight rats per group (Control (C), Fructose (F) and fructose + honey (FH), familiar object (FO), novel object (NO)). **P < 0.01 vs C, ## P < 0.01 vs F

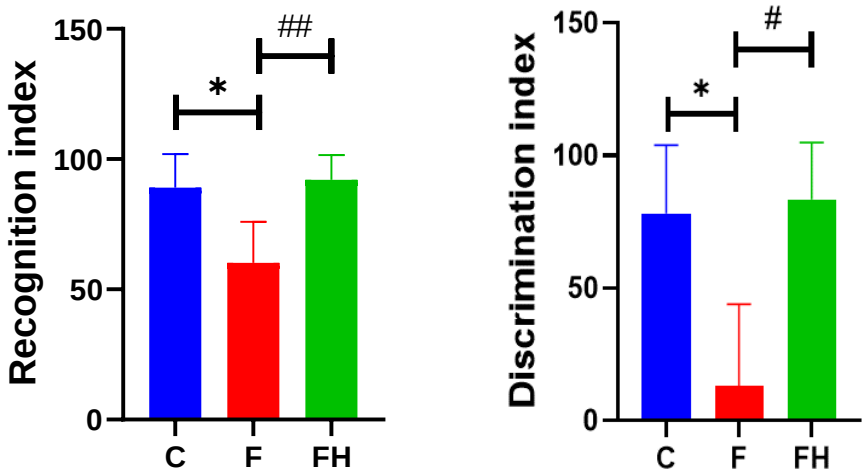

Figure 3: Effects of 6 weeks fructose feeding combined or not to 2 weeks of thyme honey supplementation on memory activity expressed in recognition and discrimination indexes using One-Way ANOVA followed by Tukey's multiple comparisons test. * p < .05, ** p < .01, *** p < .001. Values are mean ± SEM of eight rats per group (Control (C), Fructose (F) and fructose + honey (FH), familiar object (FO), novel object (NO)). *P < 0.05 vs C, # P < 0.05 vs F, ## P < 0.01 vs F

Y-maze test

The results recorded for the state of working memory of adult rats are shown in Figure 4. HFD-treated group had a lower % of alternation in rats in comparison with standard diet-treated rats ($p < 0.001$). In addition, honey supplementation elevated the percentage of spontaneous alternation significantly (+35% and +59%, respectively; $p > 0.001$), in comparison with the HFD group.

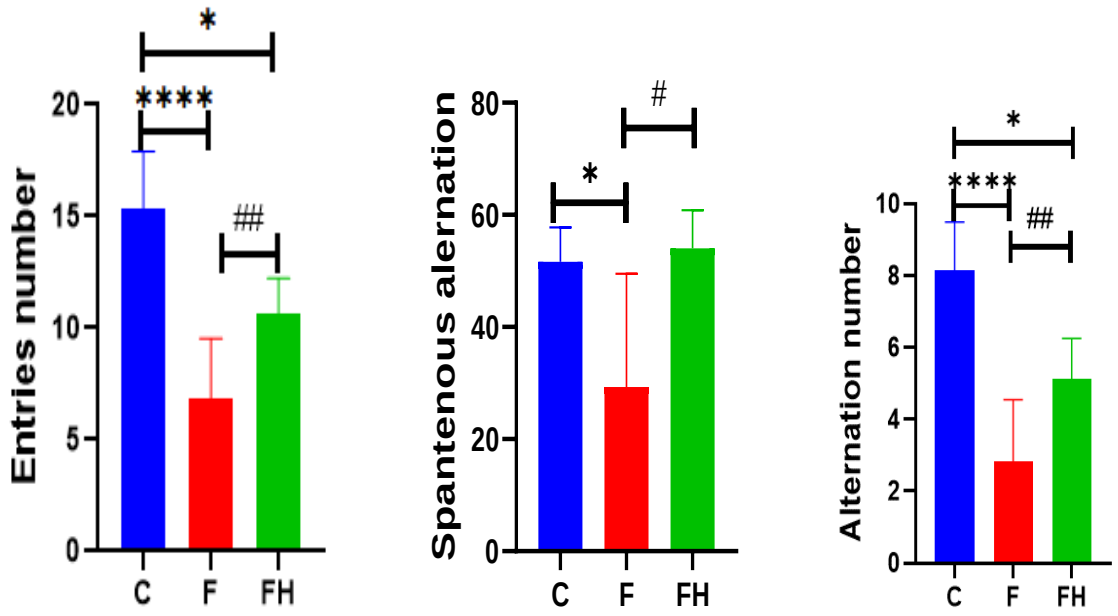

Figure 4: Effects of 6 weeks fructose feeding combined or not to 2 weeks of thyme honey supplementation on memory activity expressed in entries number and alternation number and spontaneous alternation using One-Way ANOVA followed by Tukey's multiple comparisons test. * p < .05, ** p < .01, *** p < .001. Values are mean ± SEM of eight rats per group (Control (C), Fructose (F) and fructose + honey (FH)). *P < 0.05 vs C, ****P < 0.0001 vs C, # P < 0.05 vs F, ## P < 0.01 vs F

Barne maze test

The Barne maze test was used to examine the influence of different treatments on the spatial learning and memory performance of rats. Figures 5 and 6 show that fructose intake lengthened escape latency in adult female rats, in comparison with standard diet-treated rats ($p > 0.05$). Furthermore, honey supplementation was able to prevent this HFD-induced rise in latency ($p < 0.01$) (Figure 5).

In the probe test, the % of time spent in previous hole quadrant time on the 11day in rats was significantly reduced in fructose diet group in comparison with to control rats ($p < 0.01$). Importantly, Figure 6 shows also that honey supplementation was able to prevent this effect on the memory induced by the HFD ($p < 0.01$), by increasing the % of time spent in the correct hole quadrant.

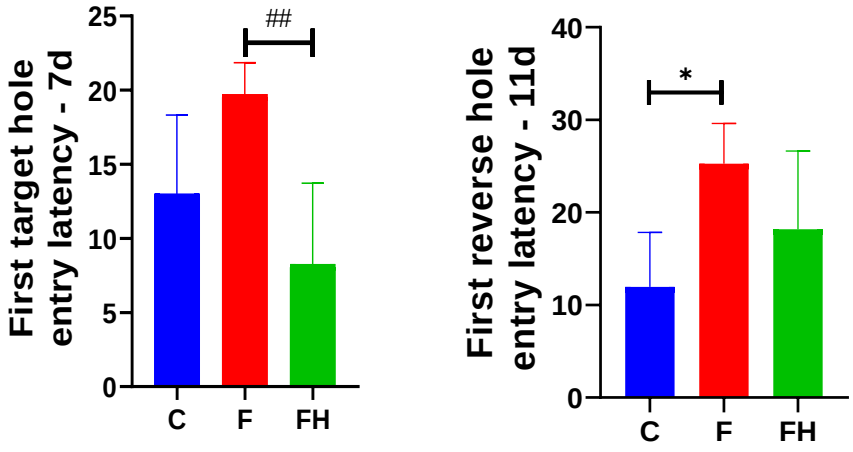

Figure 5: Effects of 6 weeks fructose feeding combined or not to 2 weeks of thyme honey supplementation on memory activity expressed in latency time for the first hole entry on the 7day and 11 expressed in sec using One-Way ANOVA followed by Tukey's multiple comparisons test and Dunn's multiple comparisons test. * p < .05, ** p < .01, *** p < .001. Values are mean ± SEM of s eight rats per group (Control (C), Fructose (F) and fructose + honey (FH)). # # P < 0.01 vs F, *P < 0.05 vs C

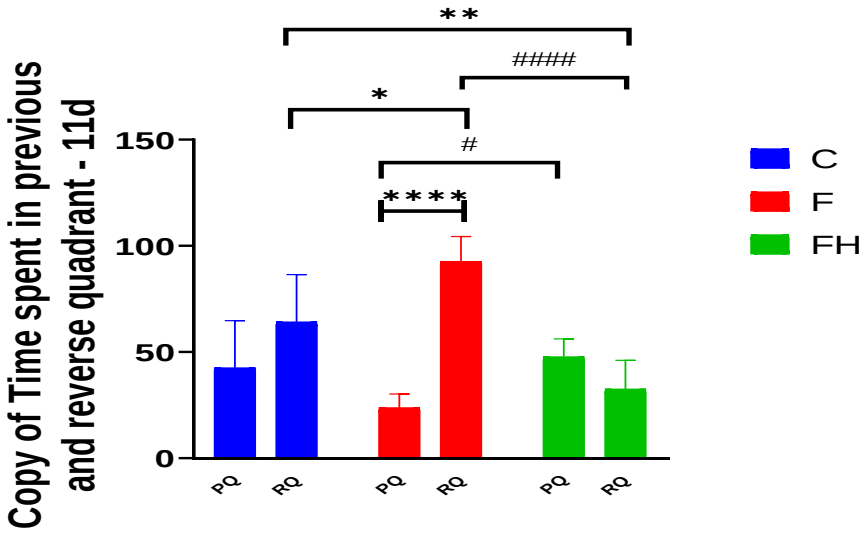

Figure 6: Effects of 6 weeks fructose feeding combined or not to 2 weeks of thyme honey supplementation on memory activity expressed in time spent in previous hole quadrant time on the 11day expressed in sec using Two-Way ANOVA and Sidak's multiple comparisons test. * p < .05, ** p < .01, *** p < .001. Values are mean ± SEM of eight rats per group (Control (C), Fructose (F) and fructose + honey (FH)). *P < 0.05 vs RQ, *P < 0.01 vs RQ, ****P < 0.0001 vs PQ, # P < 0.05 vs PQ, #### P < 0.0001 vs RQ

4. DISCUSSION

This experiment aimed to assess the effects of honey supplementation on memory impairment induced by a high-caloric diet (HFD) in Wistar rats during prepuberty and adolescence. Our study results show that HFD impaired working memory, as evaluated in the Y maze, recognition memory assessed in the object recognition test (ORT), and spatial learning and memory evaluated in the Barnes maze test in Wistar rats. This observation is consistent with previous research indicating memory dysfunction resulting from hypercaloric diets. For instance, studies by Underwood and Thompson also demonstrated the detrimental effects of HFD on memory and spatial learning, as evidenced by decreases in the percentage of alternation and object recognition index in rats of both genders [25]. Also, Sangüesa et al. reported that the hypercaloric-fed group showed a decreased short-term memory in comparison with their controls [26]. Additionally, as assessed by the Barne maze test, the hypercaloric-fed rats showed an altered spatial learning and memory (decreased long-term memory) [27-29].

The adverse effects of high-caloric diets on memory function can be attributed to several mechanisms, including reduced neurogenesis and alterations in the Hypothalamic-Pituitary-Adrenal (HPA) axis [12], and changes in the gut microbiota composition [16]. Interestingly, oxidative stress (OS) is considered key factors in the causality of memory impairments. It is therefore possible that the altered memory in HFD-treated rats could be assigned to increased OS in the hippocampus, a brain structure well known for regulating cognition [13]. In this context, a number of studies have revealed high levels of OS in people suffering from memory dysfunction. High oxygen metabolism can produce the overproduction of free radicals, which, in excess, could be damaging many essential biomolecules vital to the normal activity of neuronal cells [30-34]. Contributing to this view, our work showed that a diet rich in fructose affected the memory functioning, which was associated with increased OS in the hippocampus, reflected by increased levels of reactional species in the hippocampus of female rats [35,36]. Previous research has indicated that honey exhibits antioxidant properties and free radical scavenging activity, which can counteract the oxidation of LDL cholesterol. Furthermore, honey's anti-lipid effects have been shown to potentially delay or prevent the progression of atherosclerosis [37]. The presence of antioxidants in honey also plays a role in controlling blood sugar levels, benefiting tissues or organs susceptible to oxidative stress associated with diabetes. Consequently, this may lead to a reduction in diabetic complications such as nephropathy, retinopathy, neuropathy, and cardiomyopathy [38].

Furthermore, an interaction between treatment effects and diet was observed. In rats fed a high fructose diet, supplementation with honey notably enhanced memory function, as assessed by Y-Maze, ORT, and Barnes maze tests. The neuroprotective properties of honey on memory deficits have been demonstrated in various animal models through a range of behavioral assessments. Many studies have indicated improvements in both short and long-term memory. Additionally, honey administration is suggested for managing kidney failure induced by stones [39,41]. The mechanisms behind the positive enhancement of memory deficits remain to be elucidated. Importantly, these effects of honey on memory are accompanied by a decrease in reactional species levels. In this regard, honey could serve as a potential therapeutic agent for cognitive disorders induced by HFD as observed in our study. Our experiment's findings also suggest that honey plays a role in improving memory

deficits induced by a high-fat diet (HFD). This aligns with several prior rodent studies indicating that honey possesses cognitive protective properties. [40]. Its therapeutic proprieties are related to the improvement of morphology-related brain structures, the enhancement of the cholinergic system, and inhibition of neuroinflammatory and microglial activation [40]. In agreement, our study demonstrates honey intake prevents against HFD complications and protect the memory [41]. Pre-treatment with honey have beneficial effects in the body, particularly in the brain.

5. CONCLUSION

In summary, the findings of this research demonstrated that the continuous consumption of a HFD impaired working memory, recognition memory and spatial learning and memory in female Wistar rats. Moreover, our results suggest that honey supplementation could serve as potential therapeutic agents for memory impairment caused by HFD. It is clear, however, that additional works will be required to reveal the nature of the actual mechanisms behind such an association.

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