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Effects of Curcuma longa methanolic extract and losartan on anxiety- and depression-like behaviors induced by a high caloric diet in adult female Wistar rats

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Abstract

Obesity is currently a public health problem due to its worryingly increasing prevalence over the last ten years. This disorder affects the behavior. The goal of the current study was to evaluate the effects of Curcuma longa methanolic extract and losartan on anxiety- and depression-like behaviors induced by a high fructose diet (HFD) in adult female Wistar rats. In this study, 2-month-old female Wistar rats aged between 74 and 100g were randomly divided into 6 groups as follows: four groups will be fed the HFD and another 2 groups will receive the standard diet. An evaluation by behavioral tests, depression and anxiety-like, was carried out by using Open field Test (OFT), Elevated Plus Maze test (EPM) and Forced Swim Test (FST). The results show that HFD administration significantly reduced the TCA in female rats when compared with standard diet-treated rats (–85%; $p < 0.001$). However, HFD + Curc administration significantly increased the TCA (+221%; $p < 0.05$), in comparison with the HFD group. The findings show also that HFD induced anxiety-like behavior and that the female rats a spent less TOA, compared with the control animals (–61%; $p < 0.01$). However, following Curc or Los administration, TOA was non significantly elevated in females (+110% and +71%, respectively), in comparison with HFD group ($p > 0.05$). HFD is associated with anxiety-like and depressive behaviors in adult female Wistar rats. Moreover, our results suggest that treatments with Curc and/or Los could serve as potential therapeutic agents for anxiety and depression induced by HFD.

Keywords: Curcuma longa, losartan, anxiety-like, depression-like, high fructose diet, Wistar rats.

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1. Introduction

Obesity is currently a public health problem due to its worryingly increasing prevalence over the last ten years. It is a multifactorial disease resulting from genetic and other environmental factors[1].

The rapid evolution of this pathology is linked to changes in our lifestyles, including a sedentary lifestyle and changes in food habits. Indeed, the increased development of obesity as well as other metabolic disturbances are associated with eating disorders. This imbalance is generally in favor of a diet enriched in lipids and also in favor of an increase in the consumption of carbohydrates, mainly fructose.

Consumption of a quantity of fructose greater than the recommended nutritional requirements can cause metabolic disorders in humans and rats[2]. This consumption has increased in recent decades, especially in industrialized or developing countries. No catabolized energy nutrients are transformed into triglycerides (TG) which will be transported to visceral adipose tissue, the accumulation of which causes obesity, fatty liver, insulin resistance and cardiovascular risk constituting a health problem.

It is well known that obesity leads to an increased risk of developing metabolic disorders[3], and there is growing evidence that obesity negatively affects brain structure and function. Neuropsychiatric symptoms are common in obesity. In addition to their impact on health, these symptoms significantly interfere with the quality of life and social function of obese people. While the pathophysiological mechanisms underlying obesity-related neuropsychiatric symptoms are still under investigation and remain to be clearly identified, there is increasing evidence for a role of inflammatory processes.

Obesity can be characterized as a state of chronic low-grade inflammation. Indeed, adipose tissue is known to produce adipokines, such as the hormones leptin and

adiponectin, and pro-inflammatory cytokines. The production of these adipokines is dysregulated in obesity. Visceral adipose tissue in particular produces more pro-inflammatory cytokines in obesity, which increases the risk of developing metabolic complications. This adipokine imbalance can also lead to changes in brain function, such as impaired cerebral blood flow (CBF), affective and cognitive disorders, and subsequent neurodegeneration[4,5].

Inflammatory adipokines also include angiotensin II (Ang II), a well-known hypertensive hormone generated by the renin angiotensin system (RAS). This system is associated with peripheral fluid homeostasis and cardiovascular function, but recent evidence also suggests a functional role in the brain.

For many years, modulators of the renin-angiotensin system (RAS) have been used primarily for the control of hypertension. These modulators have recently been shown to have other properties independent of their hypotensive effects, such as enhancing cognition. In the brain, different components of the RAS have been widely studied in the context of neuroprotection and cognition.

The diet is a determining factor for health. Several studies support the hypothesis that some food products (food products) can be beneficial for the body. In recent decades, therefore, much effort has been devoted to the use of different plant species due to their potent pharmacological activities, fewer side effects, and relatively low cost[6].

Behavior is a way, attitude and conduct of being, acting or reacting of human beings and animals in certain circumstances[7]. If these circumstances are stressful, normal behavior then becomes noticeably or even excessively abnormal. It is a behavioral disorder like depression and anxiety..

Much of the therapeutic effect of medicinal plants has been attributed to plant secondary metabolites such as polyphenols. In particular, natural phenols play an important role in protection against a number of pathological disorders, such as urolithiasis, atherosclerosis, brain dysfunction and obesity[2,8–10].

Turmeric (Curcuma Longa) is one of the most widely used spices across the world, with a rich history as an herbal supplement in ancient China and India.

A polyphenol, curcumin, is the key element responsible for the major therapeutic properties attributed to turmeric, including antioxidant, anti-inflammatory, antimutagenic and antimicrobial activities. The molecular structure of curcumin and its ability to cross the blood-brain barrier provide a promising avenue for neuroprotection[11].

The current study aims to evaluate the effects of Curcuma longa (Rhizome) methanolic extract and losartan as an AT1R antagonist on anxiety- and depression-like behaviors induced by HFD in adult female Wistar rats.

2. Materials and methods

2.1. Study design

The rats used in this manipulation were divided into several groups and had free access to tap water for drinking and a standard diet (provided by the Alf Sahel animal feed marketing company). The animals' food was composed of: 13% crude protein, 2% fat, 0.3% phosphorus, 9% mineral matter, 15% cellulose, 1% calcium, 500 IU of vitamin A, 75 IU Vitamin D, 1 IU of Vitamin E. Other animals were subjected to a standard diet and a high-calorie diet rich in fructose 23% dissolved in water (30ml/Rat) for 2 months [8]. The consumption of the fructose solution for each group of animals was measured daily during the 2 months of the diet.

The group of animals treated with losartan received a dose of 30 mg/kg/day of losartan in their drinking water for one month. The volume needed for each rat is 30ml per day.

2.2. Chemicals

The methanolic extraction of the Curcuma longa was carried out using a Soxhlet apparatus as follows: Turmeric powder, purchased commercially, is placed in a paper sleeve which is contained in a glass container. The hot solvent vapors (Methanol) condense then fall and come into contact with the turmeric powder. By a communicating vessel system, when a drop falls into the container, and another falls into the solvent tank and so on. At the end of extraction, the solvent was evaporated using a rotary evaporator.

The prepared extracts were force-fed to the animals using a 50 mm long metal feeding probe, a daily volume of 0.45 ml of methanolic turmeric extract (100 mg/kg body weight) for 10 days.

2.3. Animals

The experimental protocol is carried out on female rats of the "Wistar" type born and raised in the animal facility of the Laboratory of Biology and Health of the Department of Life Sciences, Faculty of Sciences, IBN TOFAIL University. The animals were subjected to a controlled 12h/12h photoperiod and at a temperature around 23°C. They were regularly followed by body weight gain over the course of their breeding. The cages were regularly cleaned by renewing the composed litter wood chips.

Over a period of 8 weeks, 2-month-old female Wistar rats aged between 74 and 100g were randomly divided into 6 groups as follows: four groups will be fed the high-HFD and another 2 groups will receive the standard diet.

The HFD diet, during these 8 weeks, will induce an obese phenotype. After 8 weeks, the treatment phase will begin where, within each of the diet categories, one group will receive no treatment (Tm and Fr). The 3 groups having received the HFD diet will receive respectively, 100mg/kg/d of turmeric (Fr + CC), 30 mg/Kg/day of Losartan (Fr + L) and 100mg/kg of turmeric + 30mg/kg/d of Losartan (Fr+CC+L). The second group who received a standard diet will also receive 100mg/kg/d of turmeric extract and 30mg/kg/d of Losartan (CC+L).

2.4. Behavioral tests

Anxiety and anxious behaviors were assessed in rats aged 60, 90 and 300 days. All animals were exposed to three tests. Before the application of each assessment, the rats were placed in the testing apparatus under appropriate illumination. All behaviors were then recorded for subsequent analysis.

2.4.1. Open field test

The anxiety was measured by using an open-field test. The field consists of a wooden made apparatus (100 × 100 cm) enclosed by a 40 cm height wall and placed under strong illumination (100 W, 2 m above the apparatus). The area is divided into 25 squares (20 × 20 cm), defined as 9 central and 16 peripheral squares. At the beginning of the test,

each animal is placed in the center of the apparatus and then allowed to freely explore it for 10 min. In between testing, the apparatus is cleaned using 70% ethyl alcohol.

The quantified parameters were the number of total squares visited (a measure of locomotor activity), the time spent in the central area (a measure of anxiety) [12], and the number of returns to the 9 central squares (a measure of anxiety) [13]. The central area of a novel environment is anxiogenic and aversive; therefore, the behavioral inhibition appears as an avoidance towards the central zone of the open field.

2.4.2 The Elevated Plus Maze (EPM)

The maze used in this study was manufactured in the laboratory and consists of a wooden maze made up of four arms raised 60 centimeters from the ground with a length of 50 cm and a width of 10 cm . The arms are arranged in a cross with two closed opposite arms, enclosed by edges 50cm high, the ceiling being open, and two open opposite arms of the same dimensions but the edges have a height of 1 cm to prevent rats from falling from the labyrinth. The intersection of the four arms is a square with a side of 10 cm and gives access to the different arms. All platforms were white.

The rats are placed in the central square facing an open arm and their behavior is monitored for 5 minutes using a camera linked to a PC, which allows the recording of the animal's behavior without the presence of a computer. the experimenter in the room. The maze is cleaned after each trial.

The parameters measured are:

- The number of entries into the open arms (NEBO).
- The number of entries into closed arms (NEBF).
- The total number of arm entries (EBT), (locomotor activity indicator).
- Time spent in open arms (TPBO).
- Time spent in closed arms (TPBF).

Entries in open arms and the time spent there correlate inversely with the level of anxiety [12]. The total number of arm entries reflects general locomotor activity[13].

2.4.2 Forced Swim Test (FST)

To assess depressive behavior in animals, we use the Forced Swim Test or Porsolt test [14]. The rats were placed individually in a cylinder (height = 50 cm, diameter = 30 cm) containing 27 cm of water (22 °C) from which they could not escape. The rats were placed in water for 5 minutes during which time of immobility, swimming and flapping were measured.

2.5. Statistical analysis

All statistical processing was carried out using GraphPad software, analyzes of variance were carried out using one-way ANOVA.

The probability of significance of the variances is considered significant (*) if $p< 0.05$, very significant (**) if $p< 0.01$, and highly significant (***) if $p< 0.001$.

3. Results and Discussions

Effects on the Anxiety-Like behavior determined in the OFT

The data recorded for the levels of anxiety of rats are shown in Figure 1. HFD administration significantly reduced the TCA in female rats when compared with standard diet-treated rats (–85%; $p < 0.001$). In addition, HFD + Curc administration significantly increased the TCA (+221%; $p < 0.05$), in comparison with the HFD group. Importantly, the association between HFD, Cur and Los increased significantly the TCA when compared with HFD group (+450%; $p < 0.001$) (Figure 1A).

Also, the NRC was significantly reduced in HFD group in comparison with to control rats (–72%; $p < 0.01$). Additionally, the administration of Curc or Los no significantly ($p > 0.05$) increased the NRC (+83% and (+58% respectively) as compared with the HFD group. However, the association between HFD, Cur and Los increased significantly the NRC in comparison with HFD group (+208%; $p < 0.01$) (Figure 1B). Besides, the NTS was unaffected by any treatment ($p > 0.05$) (Figure 1C).

Effects on the Anxiety-Like behavior determined in the EPM

In the EPM, our findings show that HFD induced anxiety-like behavior and that the female rats a spent less TOA, compared with the control animals (–61%; $p < 0.01$). However, following Curc or Los administration, TOA was non significantly elevated in females (+110% and +71%, respectively), in comparison with HFD group ($p > 0.05$). While their association (HFD + Cur + Los) significantly increased the TOA by 146% as compared to HFD group ($p < 0.05$) (Figure 2A).

Similarly, the results revealed also that HFD administration produced a significant anxiogenic effect in EPM, characterized by a significant decrease of EOA, when compared to standard diet-treated rats (–56%; $p < 0.01$). Also, the EOA was significantly reduced in HFD + Curc and HFD + Los groups in comparison with to control rats (–47% and –42%, respectively; $p < 0.01$), and their association (HFD + Cur + Los) reduced this anxiogenic effects by increasing the EOA by 85% as compared with the HFD group ($p > 0.05$) (Figure 2B)

Effects on Depressive-Like behavior

Measurements in the FST showed that the mean duration of TIM in HFD group dramatically exceeded the respective values in control groups (+527%; $p < 0.001$). This fact was indicative of the development of strong depression-like behavior in fructose-fed rats. Figure 3 shows also that HFD + Cur, HFD + Los or HFD + Cur + Los administration was able to prevent this depressogenic effect induced by the HFD ($p < 0.001$), by decreasing the TIM by 75%, 68% and 77%, respectively).

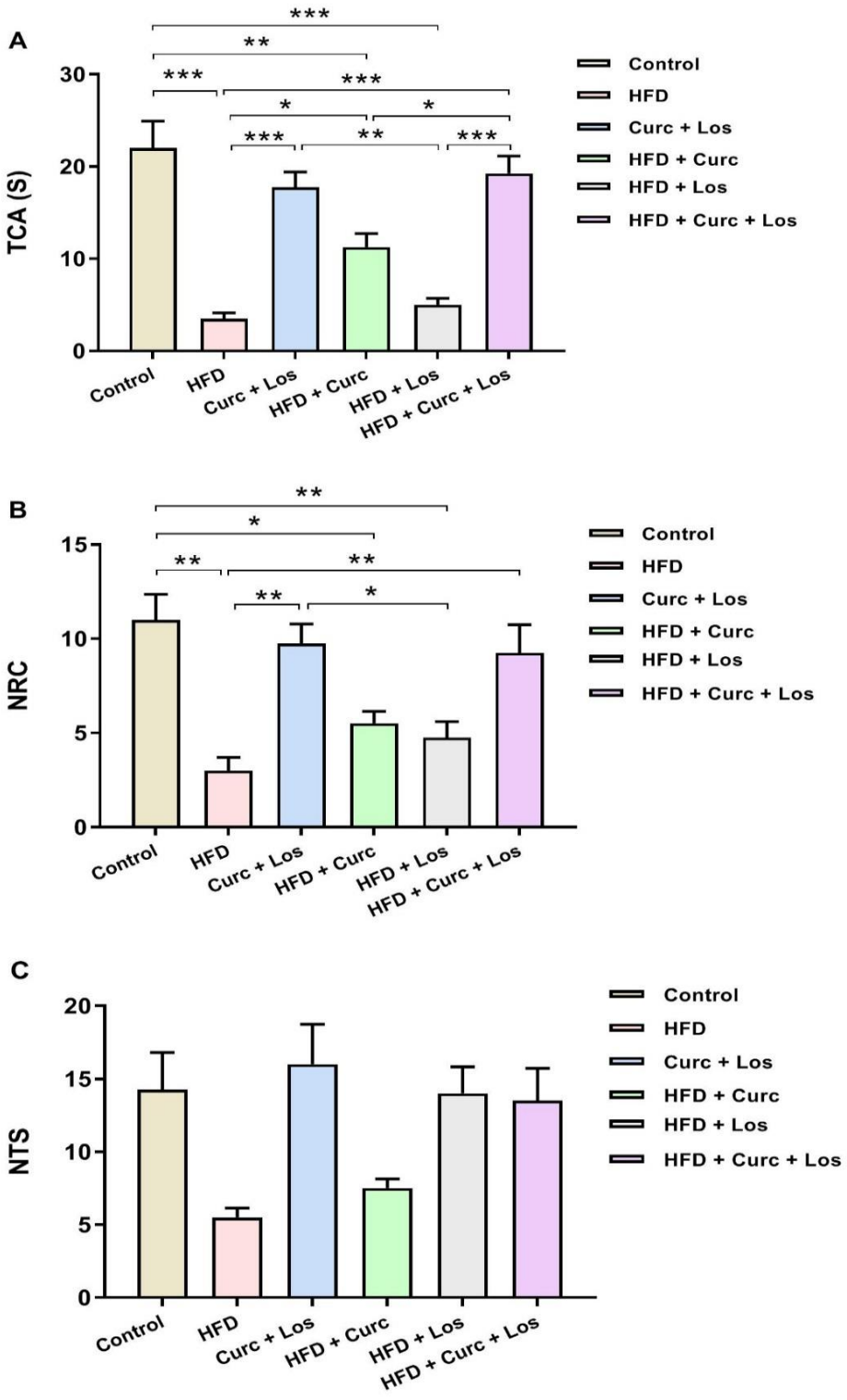

Figure 1: Behavioral performances of adult female rats in the open field test. A – Total amount time spent in the center (TCA); B – Number of return into center area (NRC), C – Number of total squares crossed (NTS). The significance level is 0.05 with * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

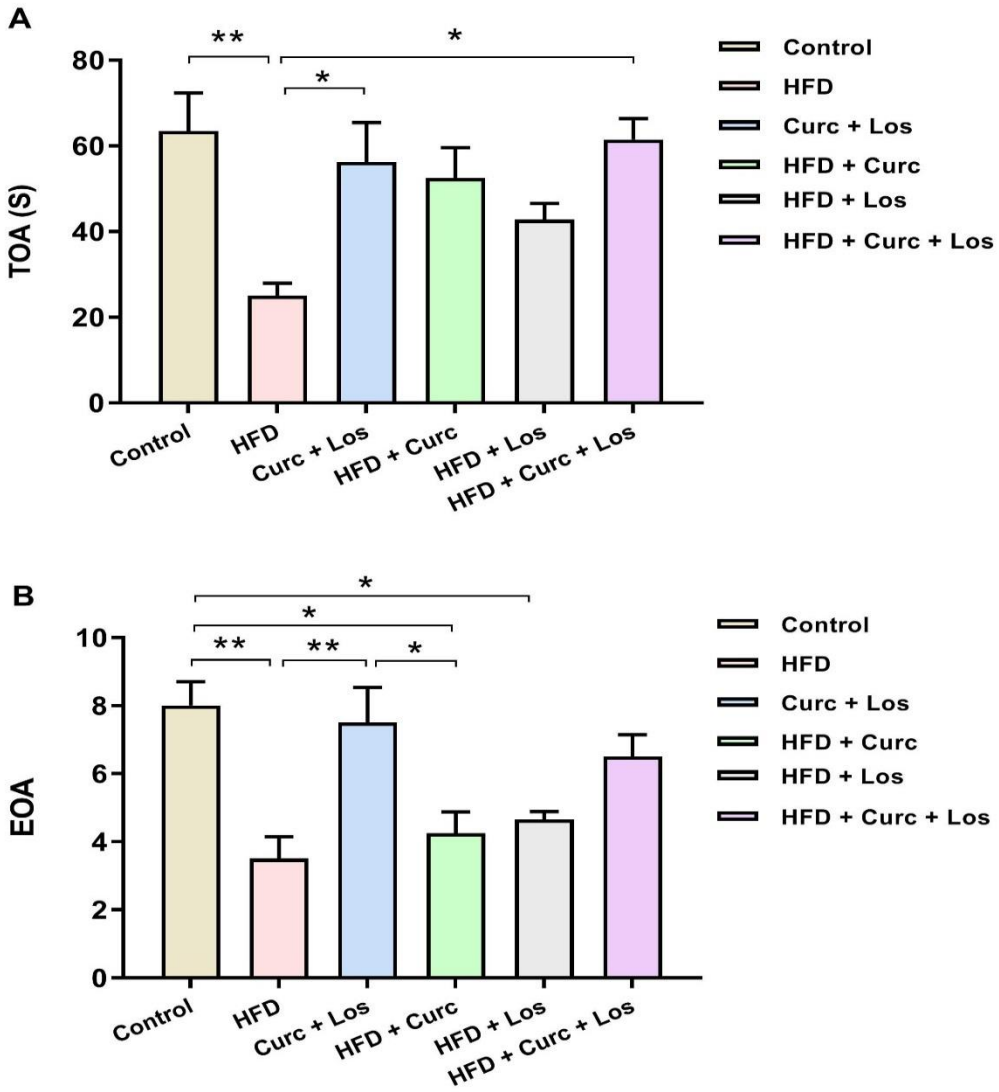

Figure 2: Behavioral performances of adult female rats in to the elevated plus maze. A – Time spent on the Open Arms (TOA); B – Entries into Open Arms (EOA). The significance level is 0.05 with * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

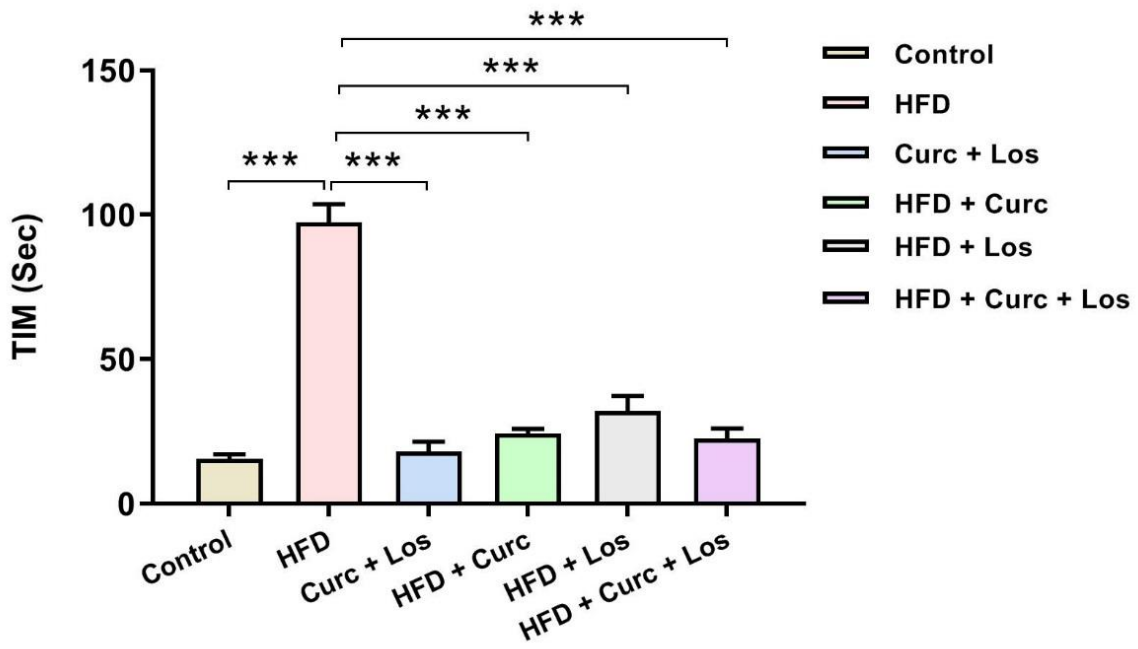

Figure 3: Effect of High fructose diet on depression-related behavior of female rats in the forced swim test. TIM: immobility time. The significance level is 0.05 with * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

One of the main observations of this research is that adult female Wistar rats show more anxious behavior in OF and EPM tests following HFD administration. These findings corroborate a previous study showing the anxiogenic impact of a high-caloric diet in rodents [15,16]. In addition, in the experiment of Mota et al., (2023), anxiety-like behavior was revealed in High-Sugar-fed rats, as they spent less time in the open arms of the EPM in comparison with control group. Confirming this anxiety-like behavior, it was also showed that High-sugar diet significantly increased the time spent in the closed arm of the apparatus [17]. However, it should be borne in mind that these findings and the behavioral anxiety tests employed reflect only a small part of the emotional state tested, and do not reflect the entire emotional prism of the animals. On the other hand, contrary to the results of our study, O'Flaherty's study showed no effects of fructose intake on affective behavior tested in the OFT, in male Sprague-Dawley rats [18]. This is perhaps due to methodological differences related to housing conditions, the type of rats, or even the test procedures used [19]. Another point raised in our research is the duration of treatment. Numerous dietary studies have been focused on short-term treatments. To complement this knowledge, our study used a chronic treatment model that better mimicked the consumption of high-caloric diets in modern societies.

Relative to depression, we observed that, in the FST, a validated measurement of depressive-like behavior [20], fructose-fed female rats exhibited increased immobility time when compared to control group, reflecting a depressive-like phenotype. In line with our results, many recent works have also demonstrated that HFD consumption leads to changes in depression related behaviors [16,21], and there is a high co-morbidity between anxiety and depression. In human, consuming a diet rich in fructose can severely impair emotional well-being [22]. Furthermore, obese children have increased levels depression and anxiety than normal weight children.

These deleterious effects of high-caloric diets on mood functioning can be explained by several mechanisms, including, reduced neurogenesis [23], alteration of the Hypothalamic Adrenal Pituitary [21], and changes in the gut microbiota composition [24]. Interestingly, oxidative stress (OS) and neuroinflammation are considered key factors in the causality of psychiatric impairments [25–27]. It is therefore possible that the increased levels of anxiety and depression in HFD-treated rats could be assigned to increased OS and neuroinflammation in the hippocampus, a brain structure well known for regulating mood and anxiety [28,29]. In this context, a number of studies have revealed high levels of OS and cytokines such as interleukin IL-1, IL-6, and TNF-α in people suffering from anxiety and/or depression [30]. Naturally, because of its high oxygen requirement, the brain is highly vulnerable to oxidizing species [31]. 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 (e.g. proteins, DNA and membrane lipids) [32], and triggering the overexpression of pro-inflammatory cytokines causing neuroinflammation [33]. On the other hand, inflammation can also intensify OS by recruiting leukocytes and generating free radicals. Contributing to this view, many works showed that a diet rich in fructose increased anxiety-like behavior, which was associated with increased OS and neuroinflammation in the hippocampus, reflected by increased levels of free radicals, TNFα, IL6 and IL1 [34,35]. Subsequently, these pro-inflammatory cytokines affect

neuronal cells via their specific receptors, thus contributing to the emergence of neuropsychiatric disturbances by altering the metabolism of monoamines involved in mood regulation, such as serotonin and dopamine [29].

An interaction between treatments effects and diet was also detected. In female rats fed high fructose diet, Curc exhibited an anxiolytic and antidepressant effects. The efficacy of Curc in the regulation of mood behavior in various animal models has been demonstrated in a variety of behavioral investigations. Most of the studies have pointed to a reduction in anxiety in the EPM test [36,37] and an improvement in performance in the FST [38,39]. Only one study found no improvements in anxiety, nor in "depressive-like" states, as evaluated by the FST [40]. In addition, Curc is considered to have anti-obesity properties which, given the close relationship between obesity and psychiatric disturbances, could result in the amelioration of psychiatric disorders. The mechanisms behind curcumin's anxiolytic and antidepressant properties remain to be elucidated. Curc was found to mitigates OS and neuroinflammation, by down-regulating the activity of lipoxygenase, cyclooxygenase-2 (COX-2), and inducible NOS (iNOS) enzymes, and inhibiting the production of inflammatory cytokines such as TNF-α and interleukins 1, 2, 6, 8 and 12 [41–43], and modulating the levels of antioxidant markers [44]. In addition to Curc's recognized role as an antioxidant and anti-inflammatory agent, the positive enhancement of depressive deficits could be effected by the regulation of serotonin levels in the hippocampus, prefrontal cortex and/or striatum, which may be caused by the interaction found between Curc and 5-HT/cAMP/PKA/CREB/BDNF-signaling pathway or 5-$HT_{1A/1B}$ and 5-HT_{2C} receptors [45], an inhibition of Ca^{+2} channels [46], or an increased level of corticosterol and cortisone in plasma [47]. With respect to the above properties, Curc could serve as a potential therapeutic agent for anxiety and depression induced by HFD as observed in our study.

Several data sources have documented Los' neuroprotective effects and its therapeutic action against a series of neurological and psychological problems [48]. The findings of our experiment also revealed that Los is implicated in decreasing anxious and depressogenic behaviors that are provoked by HFD. This is in line with numerous previous rodent studies reporting Los' anxiolytic and antidepressant effects [49,50]. One of the mechanisms of action proposed to explain losartan's anxiolytic and antidepressant actions is blockade of the AT1 receptor in the amygdala, which improves responses to anxiety. In addition, Los have been shown to reduce OS and inflammation in the brain via a number of parallel mechanisms including but not limited to the reduction of AP-1, and NF-κB activation and nuclear translocation in target areas, and inhibition of pro-inflammatory mediators such as IL-1β, IL-6, TNF-α, iNOS, COX-2, NO, and PGE2.

Interestingly, we observed that co-administration of methanolic extract of Curcuma longa (rhizome) and losartan improved fructose-induced behavioral disturbances compared to treatment with losartan or turmeric extract only. This may be explained by the possible interaction between Curc extract and Los. A study on the interactions between medicinal plants and synthetic antihypertensives showed that Curcuma Longa is one of the plants with a beneficial effect on the pharmacokinetics of antihypertensives such as Los [51]. Pre-treatment with Curc improves plasma concentrations of Los and its metabolite in Wistar rats, thereby increasing Los bioavailability [51], and subsequently enhancing its beneficial effects in the body, particularly in the brain.

4. Conclusions

In summary, the findings of this research support the idea that a subchronic HFD is associated with anxiety-like and depressive behaviors in adult female Wistar rats. Moreover, our results suggest that treatments with Curc and/or Los could serve as potential therapeutic agents for anxiety and depression induced 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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