ORIGINAL ARTICLE

10.2478/AMB-2025-0075

KOCHIA SCOPARIA SEED INFUSION AMELIORATES BEHAVIORAL IMPAIRMENT IN RATS SUBJECTED TO CALORIE-DENSE DIET

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Abstract. Aim: *The current study aimed to assess the effects of aqueous Kochia scoparia seeds infusions (KSSIs) on the behavioral indices of anxiety, depression, and spatial memory impairment in rats receiving a calorie-dense diet (CDD).* ***Materials and Methods:*** *Five groups (n = 10 each) of male Wistar rats were used. For ten weeks, the control group received a standard laboratory diet, and the other groups – CDD. KSSIs were prepared at increasing strengths by soaking 1.5, 3.0 and 6.0 g Kochia scoparia seeds in 100 ml of boiling water and were given orally ad libitum to groups named CDD+1.5KSSI, CDD+3KSSI and CDD+6KSSI, respectively. The anxiety-like behavior was assessed by the open field test (OFT) and the social interaction test (SIT), the depression-like state – by the forced swim test (FST), and the spatial memory – by the object location test (OLT).* ***Results:*** *KSSI-treated animals spent more time in the central zone in the OFT and demonstrated lower immobility time in the FST compared to the CDD group. As revealed by the OLT, CDD induced the impairment of the spatial memory of the rats and the highest strength of KSSI prevented the changes.* ***Conclusion:*** *Our results suggest that KSSI might exert anxiolytic-like, antidepressant-like and memory-enhancing effects in rats receiving a calorie-dense diet.*

Key words: *Kochia scoparia, cognitive impairment, anxiety, depression, calorie-dense diet, rats*

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Received: *14 February 2025;* ***Accepted:*** *01 April 2025*

INTRODUCTION

The urbanization, technological progress, and easy access to processed food have led to changes in the dietary habits and consumption of calorie-dense foods and beverages. The same factors are considered to be involved in the etiology of mental and cognitive disorders [1]. According to the World Health Organization, since 1990, adult obesity has more than doubled and in 2022, 2.5 billion adults were overweight and over 0.89 billion adults were obese, altogether representing 43% of all adult population globally [2]. At the same time, the number of sufferers from mental disorders is constantly rising – anxiety disorders affect approximately 301 million people (4.05% of the global population) and depressive disorders affect

280 million people [2]. Moreover, cognitive decline and dementia affect 55 million people worldwide, with Alzheimer's disease contributing to 60-70% of the cases [2]. Increased body weight and psychiatric disorders are closely related to each other [3]. Diet plays a crucial role in both maintaining optimal body weight and mental health. Studies support the role of nutrition in the prevention of obesity and psychiatric illnesses [1].

The current pharmacotherapy of mental and cognitive disorders is often associated with undesired side effects, which deteriorate the quality of life of the patients. In addition, the therapeutic results are sometimes unsatisfactory. Therefore, new effective therapeutic strategies with lower incidence of side effects are constantly being explored.

The severity of anxiety and depressive disorders, as well as cognitive decline are associated with a high-calorie dietary pattern. Obesity and neuropsychiatric disorders share a similar pathogenic mechanism, such as oxidative stress and chronic inflammation. Moreover, the level of brain-derived neurotrophic factor (BDNF), involved in the pathogenesis of mood disorders, is nutrient-dependent [1]. These findings indicate the importance of the diet for the development and management of neuropsychiatric diseases.

"Nutritional psychiatry" is a modern branch in science exploring the effects of healthy diet on the mental wellbeing [4]. Plants are valuable sources of nutrients and phytochemicals with possible therapeutic applications in mental disorders.

Kochia scoparia (KS) is an annual herbaceous plant distributed in many Asian, European, African and American countries and its fruits and seeds contain bioactive ingredients such as triterpenoid glycosides (mainly momordin Ic), flavone glycosides, phytoecdysteroids, saponins, and essential nutrients. Pharmacological studies have shown that KS possesses anti-inflammatory, antioxidant, antidiabetic, anti-obesity, analgesic and antimicrobial activities [5]. To our knowledge, the effects of KS seed infusion on the behavior of rats subjected to calorie-dense diet (CDD) have not been studied.

The present work aimed to assess the effect of three different strengths of Kochia scoparia seed aqueous infusion on the behavioral indices of anxiety, depression, and spatial memory impairment in rats receiving CDD diet.

MATERIALS AND METHODS

Experimental Protocol

The experiment was carried out in the course of 10 weeks. Fifty male Wistar rats, allocated in five groups (control, CDD, CDD+1.5KSSI, CDD+3KSSI and CDD+6KSSI), were used in the current study. The rodents were housed in plastic cages under standard laboratory conditions – 12-hour light/dark cycle, average room temperature of 23 ± 2°C and free access to food and drinking water/KS infusions.

The animals were fed as follows: the control group received a regular rat chow and tap water, while the remaining groups were given a high-fat, high-fructose (HFHF) diet. The HFHF diet consisted of 17% lard and 17% fructose added to the regular rat chow and 10% fructose in the drinking water or the KS infusions to increase the energy intake. With this diet pattern, control rats received 279 kcal/100 g food, while animals from the other groups – 405 kcal/100 g food and 40 kcal/100 ml fructose solution.

Kochia scoparia seeds infusions (KSSIs) were prepared at increasing strengths by soaking of 1.5, 3.0 and 6.0 g Kochia scoparia seeds, respectively, in 100 ml of boiling water. After cooling to room temperature and filtration, the infusions were given to groups CDD+1.5KSSI, CDD+3KSSI and CDD+6KSSI, respectively, ad libitum instead of drinking water.

All procedures related to animal treatment and the experimental design were carried out in accordance with the relevant national and international legislation and regulations (EU directive 2010/63/EU for animal experiments) and received approval from the Bulgarian Food Safety Agency (Document 177/07.07.2017).

Behavioral Tests for Assessment of Anxiety-like Behavior

Open Field test (OFT)

The OFT is a classic method for the evaluation of locomotor activity and assessment of anxiety-like behavior of rodents. The test was carried out on a wooden arena (100 cm × 100 cm) enclosed by 40 cm high walls. The arena was separated into 25 squares, each measuring 20 cm by 20 cm, by blue lines. Each rat was gently placed in the center of the field and the following behavioral indices were recorded for 5 minutes – time spent in the central zone (the inner 9 squares), number of entries into the central zone, horizontal and vertical activity. The total number of lines crossed by the animal with the four paws was used as a measure of horizontal activity. Vertical activity was evaluated by the number of rearings. The number of entries into the central zone and the time spent in this zone were observed, as they represent a fear-free behavior and can thus be used as reverse indices of anxiety-like behavior.

Social Interaction Test (SIT)

SIT is a method for evaluation of anxiety-like behavior by measuring the duration of a rat's engagement

in social interaction with an unfamiliar test partner. Two rats from different cages were placed in the opposite corners of the open field arena. The animals of each test pair received the same diet and treatment and weighed similarly (difference within a 10% range). The behavior of each animal was monitored for 5 min. The time spent in active social interaction (grooming, sniffing, following, or crawling under/over the partner) was recorded and used as an inverse index of anxiety-like behavior. Passive contact (e.g., reclining or sitting with bodies close to each other) was not considered a social interaction.

Behavioral Tests for Assessment of Depression-like Behavior

Forced Swim Test (FST)

FST was originally designed as a method for evaluation of an antidepressant activity of test substances and is used for detection of depression-like behavior in rats. When a rat is forced to swim with no way out, after an initial phase of vigorous struggle (swimming, climbing), the animal assumes an immobile posture, with minimal movements required to maintain its head above water. The immobility is considered a manifestation of the animal's "despair". The test was performed in a glass cylinder (17 cm in diameter and 50 cm high) filled with water (~24°C) up to 30 cm so that the animal could not touch the cylinder floor with hind paws or tail. The behavior of each rat was monitored for 5 minutes after it was placed in the cylinder. The test was conducted in two sessions, a training and an experimental one, separated by 24 hours. The immobility time during the second session was taken as an index of depression-like behavior.

Behavioral Tests for Assessment of Spatial Memory

Object Location Test (OLT)

OLT is a modified version of the novel object recognition test designed to evaluate rodents' spatial memory. The test was carried out on a wooden arena (60 cm x 40 cm), a separated part of the open field arena. The test was conducted in two sessions, training and experimental, each one lasting 3 min. During the training session, two identical objects were symmetrically placed and securely fastened to the floor, so the test animal could not move them. Each rat was placed in the center of the field and was allowed to freely examine the objects. The experimental session was performed 30 min after the training one. During the experimental session, the location of one of the objects was changed. The animal behavior was monitored and the time spent for exploration of each object (approaching to less than 1 cm, sniffing, climbing on the object) was recorded. A discrimination index was calculated according to the following formula and was used as an indicator of spatial memory:

$$\text{Discrimination index} = B/(A + B),$$

where A was the time of exploration of the object with the original location and B was the time of exploration of the object with the novel location.

Statistical Analysis

The statistical software GraphPad Prism 7.00 (San Diego, California) was used. To analyze the obtained experimental data, one-way ANOVA was utilized. Unpaired Student's t-test was used to compare two experimental groups. The results are presented as means ± SEM. Values of $p < 0.05$ were considered significant.

RESULTS

Open Field Test

One-way ANOVA revealed a significant difference in the time spent in the central zone between the experimental groups ($p = 0.0487$). HFHF diet decreased the time spent in the central zone of the CDD group compared to the control group with a borderline significance ($p=0.057$ vs. Control group). KSSI increased the time spent in the central zone significantly in all KSSI treated groups, strongest effect being observed with CDD+3KSSI group ($p<0.01$ vs. CDD group) (Fig. 1). There were no significant differences in the vertical and horizontal locomotor activity as well as in the number of entries into the central zone between the groups (Table 1).

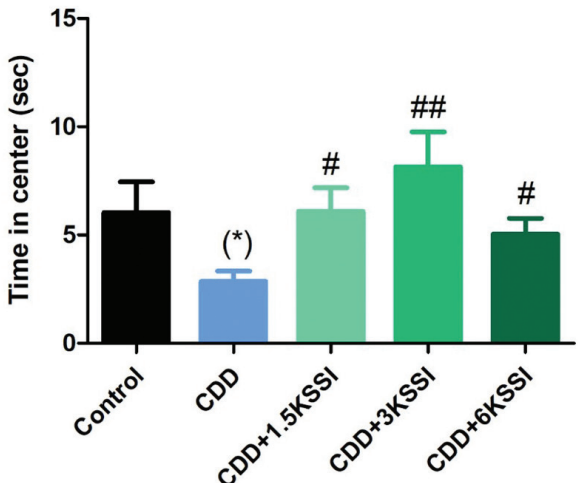

Fig. 1. Time spent in the central zone (sec) of the open field test by rats on calorie-dense diet treated with increasing strengths of KSSI ($p = 0.0487$); (*) $p = 0.057$ vs. control group, # $p < 0.05$ vs. CDD group, ## $p < 0.01$ vs. CDD group

Table 1. Number of horizontal and vertical movements and entries into the central zone in the open field test of rats on calorie-dense diet treated with increasing strengths of KSSI

	Control	CDD	CDD + 1.5KSSI	CDD + 3KSSI	CDD + 6KSSI	p-value (One-way ANOVA)
Horizontal activity	94.1±9.28	106.0±10.23	84.50±8.63	90.40±9.52	85.30±9.01	0.4914
Vertical activity	27.10±3.89	28.40±3.05	28.70±2.32	29.40±3.49	28.20±3.27	0.9916
Entries into the central zone	1.90±0.43	1.00±0.39	1.90±0.64	2.00±0.47	1.00±0.45	0.3614

Social Interaction Test

HFHF diet reduced insignificantly the time of social interaction in CDD group compared to the control one. Although we observed a tendency for improvement of the parameter by KSSI, there were no significant differences between the groups. The results are shown on Table 2.

Forced Swim Test

According to one-way ANOVA, there were significant differences across the groups in the immobility time ($p = 0.0006$). HFHF diet increased insignificantly the immobility time of the rats from the CDD group compared to the control group. Compared to the CDD group, the immobility time was reduced in all KSSI-treated animals and the effect was more pronounced in CDD+3KSSI and CDD+6KSSI groups ($p<0.01$ vs. CDD group) (Fig. 2).

Object Location Test

Administration of HFHF diet significantly reduced the discrimination index in the CDD group compared to the control group ($p<0.05$). KSSI administration increased significantly the index in the experimental group receiving the highest strength of the infusion, CDD+6KSSI ($p<0.05$ vs. CDD group). The overall result of one-way ANOVA was insignificant ($p = 0.1957$). The results are shown on Fig. 3.

DISCUSSION

A large body of evidence has indicated that high calorie intake is associated with increased risk of neuropsychiatric disorders. This idea is supported by data showing that obesity and metabolic syndrome subjects are at a greater risk of development of depressive and/or anxiety disorders and the calorie restriction is associated with symptomatic improvement [6].

Table 2. Time spent in social interaction (sec) in the social interaction test of rats on calorie-dense diet treated with increasing strengths of KSSI

	Control	CDD	CDD+1.5KSSI	CDD+3KSSI	CDD+6KSSI	p-value (One-way ANOVA)
Time of social interaction (sec)	26.43±3.82	17.74±2.68	18.75±3.63	24.77±.260	22.74±3.68	0.2923

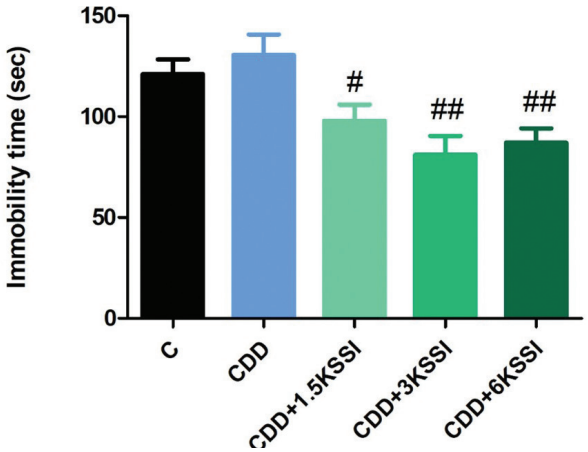

Fig. 2. Immobility time (sec) in the forced swim test of rats on calorie-dense diet treated with increasing strengths of KSSI; # $p < 0.05$ vs. CDD group, ## $p < 0.01$ vs. CDD group

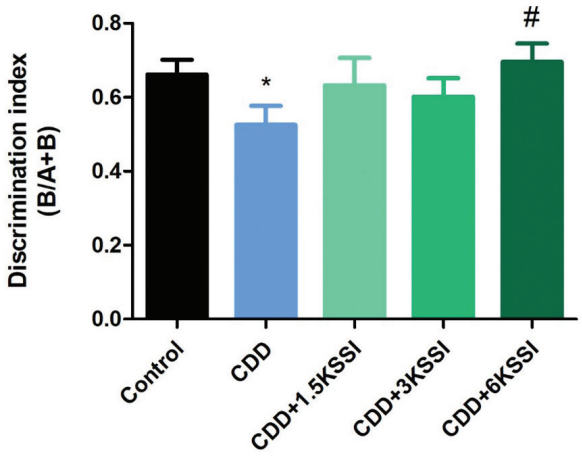

Fig. 3. Discrimination index, B/(A+B), in the object location test of rats on calorie-dense diet treated with increasing strengths of KSSI; *$p < 0.05$ vs. control group, # $p<0.05$ vs. CDD group

Furthermore, mild cognitive decline and Alzheimer's disease are more frequently observed in obese subjects than in those receiving calorie-restricted diet [7].

Oxidative stress (OxS) is involved in the development of obesity as well as mental and neurocognitive diseases [1]. Clinical studies support the role of the endogenous antioxidant system in ameliorating neuropsychiatric conditions, as antioxidant levels were observed to be reduced and parameters of OxS increased in these patients: for instance, patients with major depressive disorder had higher levels of the OxS by-pass product malondialdehyde, and lower level of antioxidants such as uric acid, paraoxanase and zinc. It has also been suggested that treatment aiming to improve the oxidative status could alleviate the symptoms of the primary condition [8]. Therefore, stimulation of the antioxidant system of the body by nutrients from food appears to be a reasonable preventive and therapeutic strategy for both overweight/obesity and mental disorders.

Another essential link between obesity and neuropsychiatric diseases is the presence of low-grade chronic inflammation. In visceral obesity, the white adipose tissue becomes the primary organ releasing pro-inflammatory substances such as hormones (resistin, visfatin), interleukins (IL-1, IL-6, IL-7, IL-18), chemokines (angiopoietin, macrophage inflammatory proteins-1α and -1β), growth factors (transforming growth factor-β) and components of the complement system (factors C2, C3, C4, C7, B and D). Moreover, macrophages infiltrate the adipose tissue and maintain the low-grade inflammatory state [9]. On the other hand, studies have indicated that similar inflammatory status exists in patients with cognitive decline [10], anxiety and depressive disorders [11]. Consumption of high-calorie foods triggers postprandial inflammation. Moreover, weight loss and implementation of a healthy dietary pattern with high intake of antioxidants are associated with lower circulating levels of inflammatory markers [9].

As previously mentioned, BDNF level is affected by the calorie content of the food [1]. Reduced circulating BDNF level, which is typical for obese subjects, has been associated with decreased cognitive performance [12]. It appears that agents with proven BDNF-elevating activities could be promising therapeutic options in cognitive decline.

In the current study, we aimed to test the effects of three different strengths of KSSI on anxiety- and depression-like states and spatial memory impairment in rats receiving high-calorie diet. We detected a borderline anxiety-inducing effect of the diet in the OFT where KSSI treatment exerted an anxiolytic-like effect. In the second test for anxiety assessment – SIT, we did not demonstrate significant differences between the experimental groups, although a clear drop in the time of social interaction was produced by the CDD, with a trend of counteracting this effect by KSSI. Similarly, in the FST, a prolongation tendency in the immobility time was found in the CDD group compared to the control one, with the KSSI administration in all three strengths significantly decreasing that time, indicating an antidepressant-like effect. The OLT revealed an impairment of the spatial memory of the animals fed the CDD, where the highest strength of KSSI significantly counteracted the memory deficit.

Our data provides some experimental evidence that KSSI could be a potentially beneficial phytotherapeutic agent in mental and cognitive disorders. KS seeds are known to contain bioactive compounds such as oleanolic acid, phytosteroids (20-hydroxyecdysone) and polyphenols (3-hydroxytyrosol, morin hydrate) [13]. An important pharmacokinetic feature of the aforementioned active ingredients is their ability to cross the blood-brain barrier [14-17].

A number of in vitro and in vivo animal studies indicate that oleanolic acid exerts anti-inflammatory effect by suppressing the nuclear factor/kappa beta (NF-kB) pro-inflammatory pathway, thus reducing the production of IL-1β, IL-6 and tumor necrosis factor-alpha (TNF-α). Moreover, oleanolic acid has been found to down-regulate the NLRP3 inflammasome. Its antioxidant activity is attributed to the stimulation of the antioxidant Nrf2/Keap1 signaling, thus boosting the expression of numerous antioxidant genes [18]. Interestingly, oleanolic acid has been reported to elevate BDNF and prevent cognitive dysfunction [19].

The phytoexdysteroid 20-hydroxyecdysone has been found to suppress both early and late pro-inflammatory responses, as demonstrated in a model of muscle injury in mice, and to protect the neurons, as demonstrated in animal models of cerebral ischemia and subarachnoidal hemorrhage [15, 20].

3-hydroxytyrosol is known for its anti-inflammatory properties mediated by inhibition of the IL-1/6 and TNF-α synthesis and blockade of the cyclooxygenase-2/prostaglandin E2 as well as the nitric oxide synthase/nitric oxide pathways. At low concentrations, it possesses strong antioxidant capacity and exerts radical-scavenging and antioxidant enzymes-stimulating effects through Nrf2 activation. Moreover, 3-hydroxytyrosol has been found to exert neuroprotective effects by blocking the enzyme monoamino-oxidase which leads to a dose-dependent elevation of the brain serotonin levels [21]. According to a study

of Calahorra and co-workers [22], this polyphenol is capable of stimulating the brain expression of BDNF.

The bioflavonoid morin hydrate has been shown to produce neuroprotective effects documented in in vitro studies on murine microglial cells, primary rat neurons and astrocytes, as well as in experimental models of Alzheimer's disease and sleep deprivation-induced memory impairment. These effects have been attributed to its anti-inflammatory properties via modulation of NF-κB, mitogen-activated protein kinase, phosphoinositide 3-kinase/AKT, and protein kinase A/hemeoxigenase-1 pathways, effects on the matrix metalloproteinase activity, antioxidant effects through Nrf2 activation, BDNF boost in the brain and anti-apoptotic effects on hippocampal neurons [23].

In our previous studies, we have reported on the antioxidant and anti-inflammatory effects of KSSI administered to rats subjected to a diet-induced model of metabolic syndrome. It was shown that KSSI antagonized the paw swelling triggered by carrageenan in rats with metabolic syndrome in a dose-dependent manner at an early time point (on the 30th minute after induction) [24]. KSSI was able to alleviate the OxS in the same experimental model. Furthermore, the infusion of KS exerted antiobesity, anti-dyslipidemic and hepatoprotective effects [25]. We could speculate that the observed behavioral effects of the KSSI in the current study are likely due to the biologically active compounds in the seeds with their antioxidant, anti-inflammatory and potentially additional central pharmacological activities.

CONCLUSION

In summary, the results of our study indicated that Kochia scoparia seed infusion is capable of exerting anxiolytic-like, antidepressant-like and memory-enhancing effects, which are most likely related to the antioxidant and anti-inflammatory activities of the seeds' bioactive compounds. The present experimental data warrant further research for clinical confirmation of the beneficial effects of this phytotherapeutic agent in patients with cognitive decline and mood disorders.

Funding: *The study was supported by the Science Fund of Medical University – Varna, project No. 16011.*

Conflict of Interest Statement: *The authors declare no conflicts of interest related to this work.*

Ethical statement: *All procedures related to animal treatment and the experimental design were carried out in accordance with the relevant national and international legislation and regulations (EU directive 2010/63/EU for animal experiments) and received approval from the Bulgarian Food Safety Agency (Document 177/07.07.2017).*

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