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Antidepressant-like effects of the aqueous lyophilizate of the roots bark of *Capparis sepiaria* (Capparaceae) on an animal's model of depression

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Abstract

Background: Major Depressive Disorder is a common mental illness characterized by persistent low mood, cognitive impairment, anhedonia, weight gain, or loss and several other symptoms, ranging from psychomotor to cognitive impairments. Commonly available antidepressants show side effects and limited efficacy; therefore, an alternative is to be considered. *Capparis sepiaria* (Capparaceae) is a plant used in traditional medicine to treat mental disorders. The aim of this study was to investigate possible antidepressant-like effects of the aqueous lyophilizate of *Capparis sepiaria* in *Wistar* rats.

Methods: Depressive-like behavior was induced using restraint stress for 14 days. The forced swimming test, the open field test, the sucrose preference test, body weight, and the food consumption were done to assess depressive-like behavior. On day 15 animals were sacrificed and the adrenal glands mass and the hippocampi were collected for Hypothalamo-pituitary-axis activity and oxidative stress markers assessment.

Results: The aqueous lyophilizate of the root bark of *Capparis sepiaria* increased swimming time and decreased immobility time ($p<0.001$) in the forced swimming test and, increased sucrose consumption in the sucrose preference test ($p<0.001$). In the open field test, there was no difference in the number of lines crossed between groups. Chronic stress significantly increased adrenal weight ($p<0.05$) which was prevented by the aqueous lyophilizate of *Capparis sepiaria* at the dose 10 mg/kg. Chronic stress decreased food consumption and weight which was prevented by the aqueous lyophilizate of *Capparis sepiaria.* The lyophilizate increased the reduced glutathione (GSH) level ($p<0.001$), and Catalase activity ($p<0.001$), and decreased the malondialdehyde level ($p<0.001$) in the determination of some oxidative stress markers.

Conclusion: These results suggest that the aqueous lyophilizate of the roots bark of *C. sepiaria* possesses antidepressant-like effects.

Keywords: Depression; *Capparis sepiaria;* restraint stress; oxidative stress.

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Background

Major depressive disorder (MDD) or depression is a leading cause of disability worldwide, affecting 4.4% of the population, making it one of the most prevalent health-related causes of human suffering [1-2]. It is a chronic disease threatening human health that is characterized by persistent low mood, slow thinking, cognitive impairment, dysphoria, anhedonia, sleep problems, weight gain or loss, and several other symptoms, ranging from psychomotor to cognitive impairments [3-4]. Depression is also known to be a major risk factor for fatal outcomes such as suicide [5]. It is a disease that can touch both youths and adults and according to WHO more than 800,000 individuals worldwide die from suicide each year [2]. In a recent meta-analysis on the global effect of the COVID-19 pandemic on the general population, Salari *et al.* [6] reported a pooled prevalence of 33.7% for depression, with a predominance in females. Despite tremendous progress in neuroscience research over the past few decades, the pathophysiology of MDD has not been fully elucidated [7]. Many risk factors such as environmental, genetic, and biological are thought to be implicated in the etiology of the pathology [8]. According to the diversity of clinical forms, two depressive subjects may exhibit different symptom profiles [9-11]. The neurobiology main hypothesis of MDD stipulates a strong activity of monoamines oxidase with consequently a decrease of neurotransmitters such as serotonin, dopamine, and noradrenaline [12-13]. Coupled with that, studies revealed that chronic stress or early life stress exposure, and sensitization of deregulation in the HPA axis represent a potent risk factor for depression [8, 14]. Several recent research link the dysregulation of the HPA axis to adrenal gland hypertrophy associated with hypercortisolemia, with the reduction of secretion of neurotransmitters such as serotonin [14]. This deregulation is also thought to cause excessive production of reactive oxygen species [15]. Oxidative stress is caused by an imbalance between ROS production and antioxidant defenses. Excessive production of ROS would lead to the peroxidation of lipids membrane, and DNA damage, leading to altered brain function associated with depression [16-19].

The accidental discovery of the first drugs with antidepressant efficacy in the 1950s, the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs) was followed by an enthusiastic period, when a series of a rationally designed class of psychotropic medications, the selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), were developed and marketed in the late ‘80 and ‘90s [20-21]. Instead, heterogeneity in the pathophysiology of depression makes it resistant because the first-line treatment of depression target only serotonin, dopamine, and noradrenaline secretion [22-23]. More than one-third of those affected with MDD are resistant to conventional pharmacological, psychological, or somatic treatments [24-26] and show some delay in the responses leading to patients with depression being vulnerable within this latent period of action [27]. Indeed, many conventional drugs face restrictions in clinical use because of their side effects [28]. Plants are the major sources of various medicines and are used for treating various illnesses and diseases and have been considered as an alternative to costly synthetic medicine to treat and prevent diseases [29].

Medicinal plants contain various bioactive compounds that either act individually, additively, or synergistically to improve health [30-33]. Several factors encourage the inclusion of herbal regimens in healthcare management in both developed and developing countries, including affordability, availability, and accessibility [34-35]. Early studies have revealed the presence of alkaloids in *Capparis sepiaria*, and *Capparis sepiaria* methanolic extract has reported antibacterial, and anti-inflammatory activities [36]. *C. sepiaria* is traditionally used to alleviate mental health disorders. However, Neuropharmacological activity of *Capparis sepiaria* has not yet been proven. The aim of this study was to assess the antidepressant effects of the aqueous lyophilizate of the root bark of *Capparis sepiaria.*

Methods

Experimental animals

The animals used in our experiments were Wistar rats (Muridae), 2 to 3 months old, of both sexes, weighing between 110 g and 150 g. These animals came from the animal house of the University of Ngaoundéré. The animals were fed with pellets and acclimatized before the start of the experiments. The study was performed at the University of Dschang in Cameroon where animals were treated following the guidelines of Cameroon's Bioethics committee (reg N. FWA IRB00001954) and the NIH-Care and Use of Laboratory Animals manual. Particularly, efforts were made to reduce the number of animals used and to reduce animal suffering.

Plant material

The samples of *Capparis sepiaria (C. sepiaria)* were collected in Lara Kaélé (Mayo-Kani department), a locality located 95 km from Maroua (Far North region of Cameroon) during the rainy season in August and identified by botanists from the Faculty of Science of the University of Ngaoundere. The confirmation of the species was done at the National Herbarium of Yaoundé (Cameroon), where it was identified and listed under the number 14194/SRF Cam in reference to the botanical samples.

Preparation of the aqueous lyophilizate

The collected *C. sepiaria* roots bark was washed and then shade-dried for one week. They were then crushed and sieved with a 0.5 mm diameter mesh sieve and a fine powder was obtained. A total of 200 g of root bark powder was dissolved in 2 l of distilled water and left to macerate for 5 h. The mixture was vigorously shaken every 1 h. After 5 h, the mixture was filtered through Whatman number 1 filter paper and frozen. Our mixture was subsequently taken to the freeze dryer at 0°C to drive off the solvent. The extraction yield following lyophilization was 24.5%.

Drugs and chemicals

Fluoxetine (Lilly, France) was administered as a positive control. This solution was administered by oral route to rats at a volume of administration of 10 ml/kg, corresponding to an administration dose of 15 mg/kg.

Treatments and depression induction

Treatments

Group, I served as the control receiving distilled water and was not submitted to restraint stress, Group II received distilled water and serve as negative control (10 ml/kg b.w), Group III received fluoxetine (15 mg/kg b.w), Group IV received *C. sepiaria* at the dose 10 mg/kg b.w, Groups V received *C. sepiaria* at the dose 40

mg/kg b.w. Groups II, III, IV, and V were receiving the different treatments one hour before being submitted to the restraint stress.

Induction of chronic depression using restraint stress

Rats underwent chronic restriction-induced stress as described by Ngoupaye et al. [3]. Thus, prior to the induction of chronic stress, the animals were moved into the room, known as the "behavior room" and inserted into a rodent "restrainer." The "restrainer" is a plexiglass cylinder of 6cm diameter, 10 cm height, with a 1cm space for air diffusion, and a siphon at the adjustable top. This cylinder does not present any possibility of mobility for the animal, hence the expression "restriction-induced stress". The animals were introduced into this cylinder every day for two hours for 14 days. To rule out any possibility of habit development in the mice, the following schedule was adopted: Day 1 = 2 h + 0 h, Day 2 = 1 h +1 h, Day 3 = 0 h - 2 h, Day 4 = 2 h + 0 h, Day 5 = 1 h + 1 h, Day 6 = 0 h - 2 h, Day 7 = 2 h + 0 h. A one-hour break between two sessions was maintained where the animals were returned to their cages, in their usual living rooms.

Behavioral tests

Forced Swimming Test (FST)

The forced swim test was conducted on days 14 and 15. It is a well-known paradigm used to assess despair in rats [37]. Briefly, animals were placed in a cylindrical Perspex tank (55 cm height, 20 cm diameter), filled to a depth of 30 cm with water kept at a constant temperature of 22 ± 1°C, and changed between animals. Testing was performed in two phases, the induction phase, and the test phase. The induction phase and test phase were realized as described by Ngpoupaye et al., [37]. The behavioral variable, immobility, was defined as making no movements for at least 2 s or making only those movements that were necessary to keep the nose above water. Rats were allowed to move their forepaws slightly or support themselves by pressing their paws against the wall of the cylinder.

Open Field Test

The open field is a square enclosure with raised edges, illuminated in the center so that the animal cannot hide. The dimensions of the device are 40 cm x 40 cm for the square and 45 cm high [38]. The exploration surface is divided into 16 squares and a central square of equal size [39].

Sucrose preference test

The sucrose preference test is a test used as an indicator of anhedonia, which is the loss of pleasure and interest in things that are usually experienced as pleasant and rewarding. The rats were individually placed in cages; each cage received two bottles for 24 hours: one contained 100 ml of drinking water and the other contained 100 ml of a 5% sugar solution and the bottles were marked to avoid any confusion. 12 hours after the beginning of the test, the bottles were removed: the consumption of the animals was measured and then the bottles were refilled to 100 ml and put back while switching their positions to avoid any kind of habitation. After the last 12 hours, the bottles were removed and the consumption was measured again. The total consumption in 24 hours was then measured [3].

Collection of adrenal gland and hippocampus

After assessment of the level of depression by the various appropriate tests, the animals were sacrificed, and adrenal glands were weighed. The brain was immediately removed from their skeletons and the hippocampi were collected and weighed, then placed in Eppendorf tubes and stored at - 20°C for biochemical assay.

Preparation of homogenates

In a porcelain mortar, the hippocampi were ground (10% w/v). Each of the homogenates was prepared using a 0.1 M phosphate buffer solution containing 1% Triton-100 X (PH 7.4) and was individually centrifuged (3000 rpm) for 15 min [40].

Biochemical assays

Tissue protein assay

Protein determination was done according to the recommendations of the randox kit. Thus, following these recommendations, 10 µL of homogenate was introduced in 500 µL of biuret reagent, the mixture was incubated for 10 minutes at 37°C, then cooled with tap water. The supernatant was pipetted and the absorbance was read at 546 nm on a BIORAD spectrophotometer, SMART SPEC 3000 (USA) against the blank. The amount of protein was determined using the following formula:

Protein Concentration (mg/dl) = (Sample Abs Standard) x Standard Concentration (mg/dl)

Measurement of some oxidative stress parameters

Determination of reduced glutathione (GSH)

Reduced glutathione was measured as previously described by Ellman [41]. Briefly, a volume of 1500 µL of Ellman reagent DTNB was introduced into test tubes containing 100 µL of supernatant. Next, 100 µL of phosphate buffer (PBS) was added and then the mixtures were incubated for one hour at room temperature. The absorbance was read using a BIORAD spectrophotometer SMART SPEC 3000 (USA) at 412nm against the blank, and results were expressed in nmol/mg of wet tissue and the concentration of reduced glutathione was expressed as mmol/ml/mg wet weight.

Determination of malondialdehyde (MDA)

MDA, which is a measure of lipid peroxidation, was spectrophotometrically measured using the thiobarbituric acid assay [42]. Two hundred mL of homogenate was added and briefly mixed with 1 mL of 50% trichloroacetic acid in 0.1 M HCl and 1 mL of 26 mM thiobarbituric acid. After mixing, samples were heated at 100 °C for 20 min. After centrifugation at 4000 rpm for 10 min, the organic layer was separated and absorbance was measured at 532 nm using a spectrophotometer.
The concentration of MDA was expressed as nmol/mg tissue.

Determination of catalase activity

Catalase is an antioxidant enzyme that catalyzes the transformation of hydrogen peroxide (H_2O_2) into water (H_20) and oxygen (O_2). When dichromate is in the presence of acetic acid

and hydrogen peroxide (H_2O_2), it is reduced to chromic acetate, which can be measured calorimetrically [43]. For the assay, 375 µL of PBS was introduced into test tubes and 25 µL of homogenate after. Once the PBS and the homogenate have been introduced into the tube, the stopwatch must be prepared to measure the reaction time of the H_2O_2 with the homogenate. Subsequently, 100 µL of H_2O_2 was introduced into the tube and the stopwatch was immediately started for 60 seconds. When reached, 1000 µL of 5% potassium dichromate + acetic acid solution is immediately introduced into the tube to stop the reaction. The tube is vortexed, sealed with its cap, and then with adhesive tape. It was then incubated in a boiling water bath for 10 min. At the end of the incubation, the tubes were cooled with running water, then the content of each tube (at least 1000 µL) was pipetted and read with a spectrophotometer against the blank. Absorbance is read at 570 nm.

Statistical analysis

The results obtained were analyzed using Graph Pad Prism software version 5.03. They were presented as mean Standard Error or mean (SEM). Statistical analysis of the results was done with the one-way and two-way analysis of variance (ANOVA) test followed by the Newmann keuls and Bonferonni test. Values were considered significant when $P < 0.05$.

Results

Different parameters were considered to statistically evaluate the antidepressant effects of *C. sepiaria*. These were duration of immobility, exploratory activity, sucrose solution intake, sucrose discrimination index, water and food intake, adrenal gland weight, reduced glutathione, malondialdehyde, and catalase activity.

Antidepressant effects of aqueous lyophilizate of C. sepiaria on depression assessed in the forced swimming test

Figure 1 depicts the effect of the aqueous lyophilizate of *C. sepiaria* on three parameters related to depression-like phenotype, immobility time, swimming, and climbing times assessed on the forced swimming test. Analysis of the forced swimming test revealed that the immobility time of rats of the control group was 11.13 ± 2.75 s. This time was significantly increased in the negative control group when compared to animals of control groups, which moved from 11.13 ± 2.75 s in the control group to 73.63 ± 12.73 s in the negative control [F (2, 20) = 22.78; p<0.0001]. Animals receiving fluoxetine prior to the restraint stress showed a significant decrease in the immobility time compared to the negative control. This time moved from 73.63 ± 12.73 s for the negative control to 33.6 ± 38.83 s in animals receiving fluoxetine [F (2, 20) = 5.927; p=0.0105]. Animals treated with aqueous lyophilizate of *C. sepiara* spent less time immobile compared to the negative control group. Their Immobility times varied from 73.63 ± 12.73 s for the negative control to 33.6 ± 38.83 s, at the dose 10 mg/kg [F (2, 20) = 23.48; p<0.0001] and 4.88 ± 1.77 s, 2.5 ± 0.56 s at the dose 40 mg/kg [F (2, 20) = 25.25; p<0.0001] of the aqueous lyophilizate of *C. sepiara* (Figure 1a).

Figure 1b shows that animals from the control group displayed 175.75 ± 15 s swimming time. This time was significantly decreased in the negative control as it moved from 175.75 ± 15 s in the control group to 124.38 ± 9.52 s in the negative control [F (2, 20) = 3.792; p=0.0422]. Treatment with fluoxetine showed a tendency to increase swimming time from 124.38 ± 9.52 s in the negative control to 157.13 ± 11.00 s [F (2, 20) = 2.762; p=0.0899]. Treatment with the aqueous lyophilizate of *C. sepiaria* root increased the swimming time from 124.38 ± 9.52 s in the negative control to 186.25 ± 6.53 s at the dose 10 mg/kg [F (2, 20) = 13.61; p=0.0003] and 197.63 ± 10.22 s at the dose 40 mg/kg [F (2, 20) = 12.07; p=0.0005]

There was no climbing effect after treatments when compared to the negative group [F (2, 20) = 0.3680; p=0.8295] (Figure 1c).

Antidepressant effects of the aqueous lyophilizate of C. sepiaria bark in chronic treatment in the Sucrose Preference Test

The two-way analysis of sucrose consumption showed a significantly high consumption of the sucrose solution compared to water consumption in animals treated with *C. sepiaria* at the dose of 10 mg/kg [F (1, 24) = 7.632; p=0.0108] (Figure 2a). The sucrose preference index shows that animals from the negative control showed a significant decrease in sucrose preference index compared to the control [F (2, 20) = 6.658; p=0.0068]. Animals treated with fluoxetine significantly increased this index compared to the negative control [F (2, 20) = 4.381; p=0.0282]. Treatment with the aqueous lyophilizate of *C. sepiaria* significantly increased this index respectively at the dose 10 mg/kg [F (2, 20) = 6.249; p=0.0087] and 40 mg/kg [F (2, 20) = 5.332; p=0.0152] (Figure 2b)

Effects of aqueous lyophilizate of C. sepiaria on locomotor activity assessed in the Open Field Test

Figure 3 shows the number of lines crossed during the locomotor activity in the Open Field Test. The analysis of the locomotor activity in the open field test following the different treatments shows that there was no significant alteration of the locomotor activity between groups [F (2, 20) = 1.262; p=0.3066].

Effect of the aqueous lyophilizate of C. sepiaria on food intake and weight evolution

The food intake was significantly higher in the control compared to the negative control on Day 0 [F (1, 42) = 29.23; p<0.0001]. This intake significantly decreased at day 7 [F (2, 42) = 22.33; p<0.05] and day 14 [F (2, 42) = 22.33; p<0.05] (Table 1).

Table 2 depicts the evolution of the weight of rats during the14-Days of treatment. The consumption of the negative control group significantly decreased throughout the weeks when compared to those of the negative group [F (1, 42) = 39.65; p<0.0001]. This weight significantly decreases at day 0 [F (1, 42) = 4.651; p<=0.0489]; day 7 [F (1, 42) = 22.10; p=0.0013], and day 14 [F (1, 42) = 10.06; p<0.0001].

Effect of aqueous lyophilizate of C. sepiaria on adrenal gland mass

Figure 4 shows the effects of *C. sepiaria* on the relative mass of the adrenal glands collected after the dissection of the animals. The mass of the Rats' adrenal glands of the negative control was significantly higher than animals from the control group [F (2, 20) = 6.299; p=0.0084]. Animals treated with *C. sepiaria* (10 mg/kg) showed a significant decrease in this weight compared to the negative control [F (2, 20) = 5.320; p=0.0153].

Effects of aqueous lyophilizate of C. sepiaria on some parameters of oxidative stress

The analysis of the concentration of reduced glutathione represented by Figure 5a reveals a significant decrease of the concentration observed in the Control compared to the negative control [F (2, 11) = 8.219; p=0.0093]. Fluoxetine treatment significantly increased this concentration [F (2, 11) = 6.772; p=0.0160]. The aqueous lyophilizate of *C. sepiaria* (10 mg/kg) increased significantly this concentration compared to the negative control [F (2, 11) = 4.336; p=0.0456]. Figure 5b shows that there was a significant decrease in the catalase activity in the negative control compared to the control [F (2, 11) = 7.795; p=0.0109]. Fluoxetine treatment significantly increased this concentration [F (2, 11) = 48.75; p<0.0001]. The aqueous lyophilizate of *C. sepiaria* (10 mg/kg) significantly increases the catalase activity [F (2, 11) = 8.070; p=0.0098], as well as (40 mg/kg) activity [F (2, 11) = 10.84; p=0.0040]. Figure 5c shows that animals receiving fluoxetine as a treatment showed a significant decrease in MDA concentration [F (2, 11) = 9.643; p=0.0058]. This concentration also decreased when animals receiving the aqueous lyophilizate of *C. sepiaria* at the dose 10 mg/kg [F (2, 11) = 36.71; p<0.0001] and 40 mg/kg [F (2, 11) = 26.96; p=0.0002].

Discussion

It is well known that major depressive disorder is caused by several factors among which the dysfunction of the hypothalamic-pituitary-adrenal axis leading to hypercortisolemia which impacts the regulation of neurotransmitters release such as serotonin, dopamine, and noradrenaline. The Forced Swimming Test (FST), the Open Field Test (OFT), and the Sucrose Preference Test (SPT) represent appropriate paradigms for the evaluation of depressive-like behaviors in animals in preclinical studies according to the drug development process for both improved and conventional drugs [44-45].

Recent research on different sources of stress applied to animal models has demonstrated damage to brain structures and functions leading to depressive-like behaviors [45-47]. Despair and loss of pleasure are major symptoms of depressive states that can be mimicked in the Forced swimming and sucrose preference tests respectively in preclinical research [45]. Rats were more immobile in the forced swimming test, signifying the helplessness to get out of an aversive environment, which is water. These despair-like behaviors have been associated with a depressive-like phenotype [45]. The aqueous lyophilizate of *C. sepiaria* successfully prevents this behavior response by reducing the immobility time, suggesting antidepressant effects. Animals' models for depression have typically been used to produce behavioral phenotypes suitable to predict the response of depressive symptoms to therapeutic interventions. Indeed, some antidepressants have specific effects on swimming and climbing [48-50]. To evaluate the specific involvement of the serotonin or adrenergic pathways, behavioral observation of the swimming or climbing time was done. Indeed, serotonin selective reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), and catecholaminergic antidepressants decrease total immobility duration [44]. However, SSRI antidepressants increase swimming frequency, whereas TCA and catecholaminergic drugs increase climbing frequency [51-53]. The results observed show that animals spent more time swimming than climbing, suggesting the involvement of the serotonergic pathway [37,53]. To check whether activities observed in the forced swimming test were not due to muscle stimulation, the open field test was done to assess locomotor activity. The results obtained show that there was no difference between the different groups. These results correlate with previous studies done by Ngoupaye et al. [37] showing that *Gladiolus dalenii* did not alter the locomotor activities in mice assessed in the open field after displaying a significant reduction of the immobility time. These results suggest antidepressant effects.

Chronic stress is a major contributor to the development of depression [54]. To mimic chronic stress, the stress induced by chronic restriction [40] has been used. The Sucrose preference test (SPT) is a test that shows the preference of animals for sweet substances that produce pleasure. Reduction in sucrose preference ratio assessed during the sucrose preference test, relative to a control group is defined as anhedonia and healthy animals usually show a preference for the sugary solution while anhedonic animals tend to consume less [40, 55-56].

This study shows that *C. sepiaria* was able to prevent anhedonia in groups pretreated with the lyophilizate like fluoxetine (10mg/kg). Indeed, anhedonia, is characterized by the loss of positive emotions or pleasure during activities normally considered pleasurable to the individual suffering from it [57], and underpinned by a decrease in dopaminergic transmission in the nucleus accumbens [58]. These results suggest that chronic administration of *C. sepiaria* shows antidepressant effects with the involvement of the serotoninergic and dopaminergic signaling pathways.

Stress (physical, chemical, psychological), lead to an increase in oxidative compounds that result in biochemical disorders and act as a trigger for certain diseases, or as a cause of their aggravation [59]. High levels of cortisol in plasma or urine, as well as hypertrophy of the pituitary and adrenal glands, have been observed in cases of chronic stress leading to depression [60]. In this study, we observed a significant increase of the adrenal gland weight in animals with depressive-like phenotype. Treatment with *C. sepiaria* (dose 10mg/kg) significantly prevented the increase of the adrenal gland mass. The plant may have acted by blocking hyperactivation of the HPA axis and contributed to a drop in cortisol secretion, resulting in less stimulation of the glands and a consequent reduction in their mass. The brain is constantly subjected to oxidative and nitrosative stress owing to its high demand for oxygen and its rich lipid environment. In the case of a failure in endogenous antioxidant defense, high levels of free radicals may promote lipid peroxidation, and neuronal cells may suffer damage [61]. Immobilization stress leads to oxidative stress, which is thought to be the cause of depressive disorders [62].

The attack of lipids, an important component of the cell membrane by ROS, results in a chain reaction called lipid peroxidation that leads to increased production of ROS and radicals that can damage other cellular components and compromise the integrity of the cell. Unsaturated fatty acids are particularly sensitive to oxidation and the oxidative lipid damage caused can be measured using, among others, malondialdehydes (MDA) [63-65], establishing malondialdehyde as an excellent pro-oxidant marker [66-67]. The concentration of MDA resulting from oxidative damage of lipids evaluated in this study reveals an increased level in the negative control group when compared to the control. The administration of fluoxetine and the plant prevented the increase of this concentration.

Evaluation of the markers of the antioxidant activity in this study shows an increase in the concentration of GSH in groups treated with Fluoxetine and *C. sepiaria* (dose 10mg/kg) in the same way, significantly elevated activity of catalase is marked in the animals treated with Fluoxetine and *C. sepiaria* in a dose-dependent manner (10m g/kg; 40 mg/kg). GSH a nonenzymic antioxidant and catalase antioxidant enzymes are good normalizers of the levels of

reactive oxygen species (ROS) and antioxidant activity after successful antidepressant therapy [68] suggests that oxidative stress mechanisms can be especially important in the study of pathophysiology and prognosis of depression [17], and that *C. sepiaria* has successfully prevented oxidative stress induced by depression. The phytochemical compounds of the plant such as the polyphenols and flavonoids [69] act as antidepressants because, as revealed in the literature, they have been considered as health-promoting agents with proven in vitro and in vivo biological effects which include antioxidative activity and thus antidepressant effects [70].

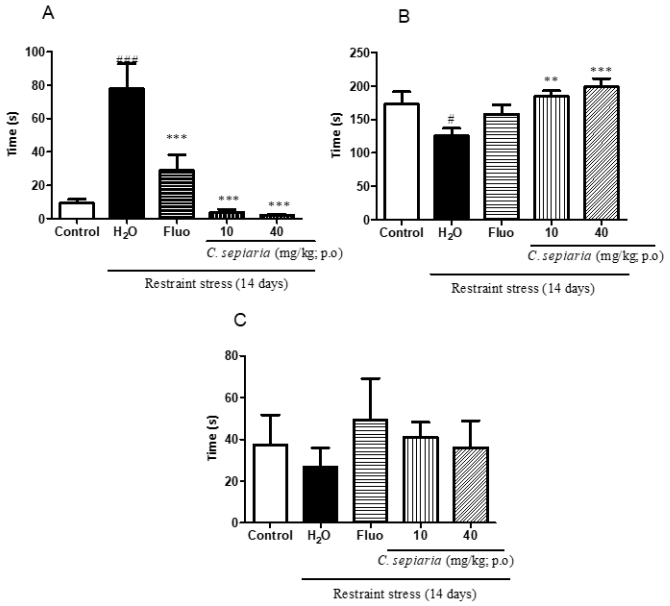

Figure 1. Effect of *C. sepiaria* on chronic depression in forced swimming.
A: Immobility, B: Swimming C: Climbing. Each bar represents means ± SEM. N = 7 **p< 0.01; ***p< 0.001 compared to H2O. # < 0.05; ###p < 0.001 compared to control; two-way ANOVA followed by Newman-keuls test. Control: distilled water; H_2O: negative control; Fluo: Fluoxetine 15 mg/kg; 10: *C. sepiaria* 10 mg/kg b.w.; 40: *C. sepiaria* 40 mg/kg b.w.

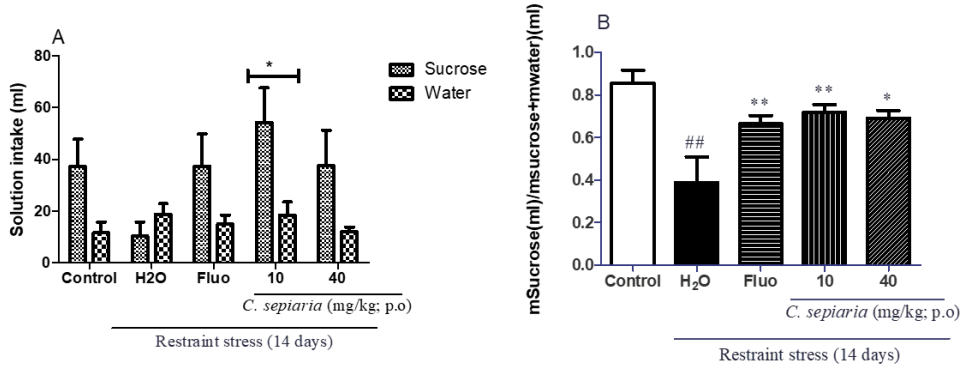

Figure 2. Effects of *C. sepiaria* in the Sucrose Preference Test.
A: sugar solution intake; B: sucrose preference index. Each bar represents the means ± SEM. N= 7 *p<0.05 **p<0.01 compared to H_2O; ##p<0.01 compared to Control. ANOVA followed by Newman Keuls test and Bonferonni test. Control: distilled water; H_2O: negative control; FLUO: Fluoxetine 15 mg/kg b.w.; 10: *C. sepiaria* 10 mg/kg b.w.; 40: *C. sepiaria* 40 mg/kg b.w.

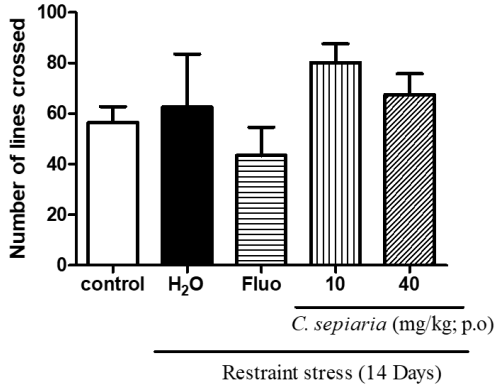

Figure 3. Effect of *C. sepiara* on chronic depression assessed in the Open Field Test.

Each bar represents the means ± SEM. N=7. ANOVA followed by Newman Keuls test. Control: distilled water; H_2O: negative control; FLUO: Fluoxetine 15 mg/kg b.w.; 10: *C. sepiaria* 10 mg/kg b.w.; 40: *C. sepiaria* 40 mg/kg b.w..

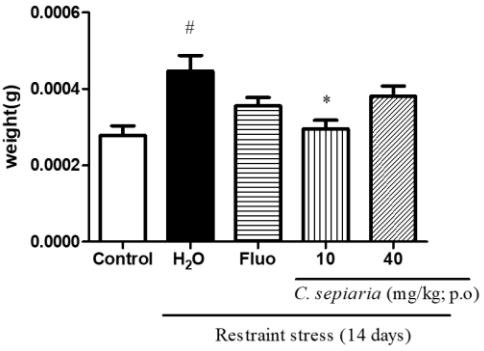

Figure 4. Effects of *C. sepiaria* on adrenal gland mass.

Each bar represents the means ± SEM. N= 7 *p<0.05 compared with H_2O; #p<0.05 compared to Control. ANOVA followed by Newman Keuls test. Control: distilled water; H_2O: Negative control; FLUO: Fluoxetine 15 mg/kg b.w.; 10: *C. sepiaria* 10 mg/kg b.w.; 40: *C. sepiaria* 40 mg/kg b.w.

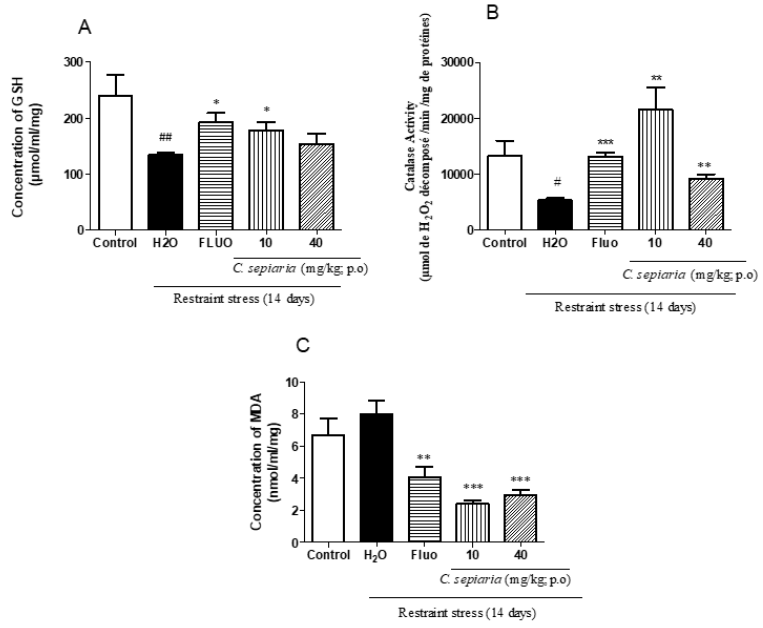

Figure 5. Effects of *C. sepiaria* on oxidative stress

A: glutathione concentration; B: Catalase activity; C: malondialdehyde level. Each bar represents means ± SEM N=4 *p<0.05, **p<0.01 ***p<0.001 compared to H_2O. #p<0.05, ##p<0.01 compared to Control. ANOVA followed by Newman Keuls test. Control: distilled water; H_2O: Negative control; FLUO: Fluoxetine (15 mg/kg b.w.); 10: *C. sepiaria* 10 mg/kg b.w.; 40: *C. sepiaria* 40 mg/kg b.w.

Tableau 1. Effects of the aqueous lyophilizate of *C. sepiaria* on food consumption

Period	Control	Treatments			
		H_2O	Fluo	10	40
Day 1	36.48±13.21	25,51±8.35$^{###}$	19.50±6.62	25.31±5.62	21.74±7.94
Day 7	31.49±5.09	23.19±0.92$^{\#}$	15.89±3.07*	24.41±2.14	23.54±4.68
Day 14	29.03±4.72	21.15±1.70$^{\#}$	15.22±2.57	20.69±2.82	20.91±5.10

Data represented as means ± SEM N=7 *p<0.05 compared to H2O. #p<0.05. ###p<0.001 compared to Control. ANOVA followed by Newman Keuls test. Control: distilled water; H_2O: negative control; FLUO: Fluoxetine (15 mg/kg b.w.); 10: *C. sepiaria* 10 mg/kg b.w.; 40: *C. sepiaria* 40 mg/kg b.w.

Tableau 2. Effects of the aqueous lyophilizate of *C. sepiaria* on weight evolution

Period	Treatment				
	Control	H_2O	FLUO	10	40
Day1	184.88±32.48	144.13±29.50$^{\#}$	155.5±37.86	151.00±31.37	159.75±29.28
Day7	191.73±32.25	145.04±23.79$^{\#\#}$	148.48±33.40	155.91±24.11	161.82±21.35
Day14	202.95±36.03	152.11±16.69$^{###}$	143.95±20.19	158.48±21.18	166.47±19.44

Data represented as means ± SEM N=7. #p<0.05. ##p<0.01 compared to Control. ANOVA followed by Newman Keuls test. Control: distilled water; H_2O: negative control; FLUO: Fluoxetine (15 mg/kg b.w.); 10: *C. sepiaria* 10 mg/kg b.w.; 40: *C. sepiaria* 40 mg/kg b.w.

Conclusion

The aqueous lyophilisate of *C. sepiaria* possess anti-depressant properties in an animal model of major depressive disorders. *C. sepiaria* can mediate its properties through modulation of reactive oxygen species homeostasis by impairing the MDA levels and enhancing GSH levels and Catalase activity. The plant may also produce its effect through serotoninergic, dopaminergic neurotransmissions, and HPA modulation. However, further studies are needed to confirm its actions on monoamines and HPA axis.

Abbreviations

C. sepiaria: Capparis sepiaria
GSH: reduced glutathione
MDA: Malondialdehyde
H_2O_2: Hydrogen peroxide
PBS: Phosphate Buffer solution

Authors' Contribution

FBY co-designed the experiments, conducted the laboratory trials, data analysis and manuscript writing as part of its PhD's thesis; GTN designed the work and supervised the experiments, data analysis and manuscript writing; SJKN, TDK, MBA, and AFF gave support for behavioral and biochemical tests; ENB supervised the work, manuscript writing and gave general advices.

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Conflict of interest

The authors declare no conflict of interest.

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References

1. Gutierrez-Rojas L, Porras-Segovia A, Dunne H, Andrade-Gonzalez N, and Cervilla JA 2020. Prevalence and correlates of major depressive disorder: a systematic review. *Braz J Psychiatry.* 42, 657–672.
2. World Health Organization. 2021**.** Depression. Available online: https://www.who.int/news room/fact-sheets/detail/depression (accessed on 29 July 2021). WHO. *Suicide Worldwide in 2019: Global Health Estimates*; Licence: CC BY-NC-SA 3.0 IGO; World Health Organization: Geneva, Switzerland, 2021.
3. Ngoupaye GT, Yassi FB, Bahane DAN. et al. 2020. Antidepressant and anti-amnesic effects of the aqueous lyophilisate of the leaves of Leptadenia Arborea on an animal model of cognitive deficit associated depression. *Biomed Pharmacother*. 130 :110603
4. Kandola A, Lewis G, Osborn DPJ, Stubbs B, Hayes JF. 2020. Depressive symptoms and objectively measured physical activity and sedentary behaviour throughout adolescence: a prospective cohort study. Lancet Psychiatry.7(3):262 71.
5. Moitra M, Santomauro D, Degenhardt L, Collins L, Whiteford H, Vos T, et al. 2021. Estimating the risk of suicide associated with mental disorders : a systematic review and meta-regression analysis. *J Psychiatr Res* 137: 242–9.
6. Salari N, Hosseinian-Far A, Jalali R et al (2020) Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. *Glob Health* 16:e1–e11.
7. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, *et al*. 2018. Genome-wide association analyses identify 44 risk variants and refne the genetic architecture of majordepression. *Nat Genet.* 50: 668–68
8. Eliwa, H., Brizard, B., Le Guisquet, A.M., Hen, R., Belzung, C. and Surget, A., 2021. Adult neurogenesis augmentation attenuates anhedonia and HPA axis dysregulation in a mouse model of chronic stress and depression. *Psychoneuroendocrinology*, 124: 105097.
9. Ballard ED, Henter ID, Zarate CAJ. 2019**.** The Classification of Depression: Embracing Phenotypic Heterogeneity in the Era of the RDoC, in: Quevedo, J., Carvalho, A.F., Zarate, C.A. (Eds.), Neurobiology of Depression: Roads to Novel Therapeutics. Elsevier, London, pp. 1–6.
10. Dantzer R. 2001. Cytokine-Induced Sickness Behavior: Where Do We Stand? Brain. *Behav. Immun.* 15: 7–24.
11. Fried EI. 2017. Expert Review of Neurotherapeutics Moving forward: how depression heterogeneity hinders progress in treatment and research EI Fried Moving forward: how depression heterogeneity hinders progress in treatment and research. https://doi.org/10.1080/14737175.2017.1307737.
12. Czéh B, Fuchs E, Wiborg O, et al. 2016. Animal models of major depression and their clinical implications. *Prog Neuropsychopharmacol Biol Psychiatry.* 64:293– 310.

13. Liu Z, Liu X, Luo S, et al. 2018. Extract of sesame cake and sesamol alleviate chronic unpredictable mild stress-induced depressive-like behaviors and memory defcits. *J Funct Foods.* 42:237–247.
14. Ngoupaye, G.T., Ngo Bum, E. and Daniels, W.M.U., 2013. Antidepressant-like effects of the aqueous macerate of the bulb of Gladiolus dalenii Van Geel (Iridaceae) in a rat model of epilepsy-associated depression. *BMC Complement Altern Med. 13*(1), pp.1-8.
15. Lindqvist D, Dhabhar FS, James SJ, Hough CM, Jain FA, Bersani FS, et al. 2017. Oxidative stress, inflammation and treatment response in major depression. *Psychoneuroendocrinology* 76: 197–205
16. Bakunina N, Pariante CM, and Zunszain, PA., 2015. Immune mechanisms linked to depression via oxidative stress and neuroprogression. *Immunol. 144* (3): 365-373.
17. Adifbair A, Saleem M, Lanctôt K, Herrmann N. 2016**.** Potential biomarkers for depression associated with coronary artery disease: A critical review. *Curr. Mol. Med.,* 16, 137–164.
18. Dhama K, Latheef SK, Dadar M, Samad HA, Munjal A, Khandia R, Karthik K, Tiwari R, Yatoo MI, Bhatt P, Chakraborty S, Singh K P, Iqbal H, Chaicumpa W, Joshi S K. 2019. Biomarkers in stress related diseases/disorders: Diagnostic, prognostic, and therapeutic values. *Front Mol. Biosci.* 6: 91.
19. Bhatt S, Nagappa AN, Patil CR. **2020**. Role of oxidative stress in depression. *Drug Discov. Today. 25:* 1270–1276.
20. Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR. 2007. The STAR*D Project results: a comprehensive review of findings. *Curr Psychiatry Rep.* 9:449—59.
21. Pereira V, & Hiroaki-Sato V. 2018. A brief history of antidepressant drug development: From tricyclics to beyond ketamine. *Acta Neuropsychiatrica,* 1-16. doi:10.1017/neu.2017.3
22. Al-Harbi K. 2012. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Prefer Adherence.;6:369–388. Available from: https://doi.org/10.2147/PPA.S29716.
23. Kraus C, Kadriu B, Lanzenberger R, Zarate CA Jr, Kasper S. 2019. Prognosis and improved outcomes in major depression: A review. *Transl Psychiatry* 9: 127
24. Akil H. *et al.* 2018. Treatment resistant depression: A multi-scale, systems biology approach. *Neurosci.Biobehav.Rev.* 84: 272–288.
25. Dudek KA. *et al. 2019.* Neurobiology of resilience in depression: immune and vascular insights from human and animal studies. *Eur. J. Neurosci.* 00: 1–39
26. Berlim MT, Fleck MP, Turecki G. 2008. Current trends in the assessment and somatic treatment of resistant/refractory major depression: an overview. *Ann Med.* 40(2):149-59.
27. Harmer CJ, Duman RS, Cowen PJ. 2017. How do antidepressants work? New perspectives for refining future treatment approaches. *Lancet Psychiatry.* 4:409-18.
28. Haque, E., Ahmed, F., Chaurasiya, P., Yadav, N., Dhiman, N. and Maity, M.K., 2023. A review on antidepressant effect of herbal drugs. *J Pharm Negat*. 14(2): 2716-2723.
29. Alkahtani, J., Elshikh, M.S., Dwiningsih, Y., Rathi, M.A., Sathya, R. and Vijayaraghavan, P., 2022. *In-vitro* antidepressant property of methanol extract of Bacopa monnieri. *J King Saud Univ Sci.* 34(8):102299.
30. Govender L, Pillay K, Siwela M, Modi A, Mabhaudhi T. 2017 Food and nutrition insecurity in selected rural communities of KwaZulu-Natal, South Africa—Linking human nutrition and Agriculture. *Int J Environ Res Public Health.* 14:17.
31. Kamal Z, Bairage JJ, Moniruzzaman DP, Islam MT, Faruque MO, Islam MR, Paul PK, Islam MA, Rahmatullah M. 2014 Ethnomedicinal practices of a folk of medicinal practitioner in Pabna district, Bangladesh. *World J Pharm Sci.* 3:73–85.
32. Maseko I, Mabhaudhi T, Tesfay S, Araya HT, Fezzehazion M, Du Plooy C P. 2017. African Leafy Vegetables: A review of status, production and utilization in South Africa. *Sustainability.* 10:16.
33. Oguntibeju OO, Aboua YG, Kachepe P. 2020. Possible therapeutic effects of vindoline on testicular and epididymal function in diabetes-induced oxidative stress male Wistar rats. *Heliyon.* 6: e03817.
34. Devadas RP, Saroja S. 1980**.** Availability of Fe and â-carotene from Amaranthus to children. In: Emmaus P., editor. *Proceeding of the 2nd Amaranthus Conference.* Rodala Press Inc.; Emmaus, PA, USA. pp. 15–21.
35. Ejoh AR, Mbiapo FT, Fokou E. 1996. Nutrient composition of the leaves and flowers of *Colocasia esculenta* and the fruits of *Solanum melongena*. *Plant Foods Hum Nutr.* 49:107–112.
36. Lemmens RHMJ. 2013. Capparis sepiaria L. In: Schmelzer, G.H. & Gurib-Fakim, A. (Editeurs). Prota 11(2): Medicinal plants/Plantes médicinales 2. PROTA, Wageningen, Pays Bas.
37. Ngoupaye GT, Bum EN, Taiwe GS, Moto FC, Talla E. 2014. Antidepressant properties of aqueous macerate from Gladiolus Dalenii corms. AJTCAM 11(1):53–61
38. Lister RG. 1990. Ethologically, based animal models of anxiety disorders. *Pharmacol. Ther.* 46 321–340.
39. Jenck F, Moreau JL, James RM, Gavin JK, Rainer KR, Monsma FJJr, Nothaker HP, Civelli O. 1997. Orphanin FQ acts as an anxiolytic to attenuation behavioural responses to stress, Proceedings of the National Academy of Sciences of the United States of America, Neurobiology 94 14854–14858, https://doi.org/ 10.1073/pnas.94.26.14854 14854-14858 PNAS. 94.
40. Ngoupaye, G.T., Yassi, F.B., Bahane, D.A.N. and Bum, E.N., 2018. Combined corticosterone treatment and chronic restraint stress lead to depression associated with early cognitive deficits in mice. *Metab Brain Dis.* 33: 421-431.
41. Ellman GL. 1959. Tissue sulfhydryl groups. *Arch Biochem Biophys.* 82 :70–77.
42. Hritcu L, Foyet HS, Stefan M, Mihasan M, Asongalem AE, Kamtchouing P. 2011 Neuroprotective effect of the methanolic extract of Hibiscus asper leaves in 6-hydroxydopamine-lesioned rat model of Parkinson's disease. *J. Intercult.Ethnopharmacol.* 137: 585–591.
43. Dimo T, Ngueguim TF, Kamtchouing P, Dongo E, Tan PV. 2006. Glucose lowering efficacy of the aqueous stem bark extract of Trema orientalis Linn Blume in normal and streptozotocin rats. *Die pharmazie.* 61: 233-236.
44. Cryan JF, Markou A, and Lucki I. 2002. Assessing antidepressant activity in rodents: recent developments and future needs. *Trends Pharmacol Sci.* 23: 238–245.
45. Planchez B, Surget A, Belzung C. 2019. Animal models of major depression: drawbacks and challenges. *J Neural Transm.* 126(11):1383–408.
46.Nandam LS, Brazel M, Zhou M, Jhaveri DJ. 2020. Cortisol and major depressive disorder–translating findings from humans to animal models and back. Front Psychiatry 10:974(10). doi: 10.3389/fpsyt.2019.00974 30.
47. Becker M, Pinhasov A, Ornoy A. 2021. Animal models of depression: what can they teach us about the human disease? Diagnostics 11(1):123. doi: 10.3390/ diagnostics 11010123
48. Kelliher P, Kelly JP, Leonard BE, and Sánchez C. 2003. Effects of acute and chronic administration of selective monoamine re-uptake inhibitors in the rat forced swim test. *Psychoneuroendocrinology.* 28: 332–347.
49. Kokras N, Polissidis A, Antoniou K, and Dalla C. 2017. Head shaking in the forced swim test: a robust but unexplored sex difference. *Pharmacol Biochem Behav.* 152, 90–96.
50. Biselli T, Lange SS, Sablottny L, Steffen J, and Walther A. 2021. Optogenetic and chemogenetic insights into the neurocircuitry of depression-like behaviour: A systematic review. *Eur J Neurosci.* 53, 9–38.
51. Lucki I. 1997. The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. *Behav Pharmacol.* 8, 523–532.
52. Cryan JF, and Lucki I. 2000. Antidepressant-like behavioral effects mediated by 5-Hydroxytryptamine (2C) receptors. *J Pharmacol Exp Ther.* 295, 1120–1126.
[53] Belovicova K, Bogi E, Csatlosova K, and Dubovicky M. 2017. Animal tests for anxiety-like and depression-like behavior in rats. *Interdiscip Toxicol.* 10, 40–43.
54. Youssef MMM. *et al.* 2022. TOB is an effector of the hippocampus-mediated acute stress response. *Translational Psychiatry.* doi.org/10.1038/s41398-022-02078-7.
55. Klein DF. 1974. Endogenomorphic depression. A conceptual and terminological revision. *Arch Gen Psychiatry.* 31: 447-454
56. Cryan, J.F., Hoyer, D. and Markou, A., 2003. Withdrawal from chronic amphetamine induces depressive-like behavioral effects in rodents. *Biol Psychiatry*. 54(1): 49-58.
57. American Psychiatric Association [APA] (ed.) 2013. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*, 5th Edn. Washington, D.C: American Psychiatric Association
58. Bewernick, Bettina H, René Hurlemann, Andreas Matusch, Sarah Kayser, Christiane Grubert, Barbara Hadrysiewicz, Nikolai Axmacher et al. 2010. « Nucleus Accumbens Deep Brain Stimulation Decreases Ratings of Depression and Anxiety in Treatment-resistant Depression ». *Biol Psychiatry.* 67(2):110-6
59. Ursini F, Maiorino M, Forman HJ Redox homeostasis: 2016 The Golden Mean of healthy living. *Redox Biol.* 8:205–215.
60. Juruena MF, 2014. Early-life stress and HPA axis trigger recurrent adulthood depression. *Epilepsy Behav.* 38: 148-159.
61. Patel, M., 2016. Targeting oxidative stress in central nervous system disorders. *Trends Pharmacol Sci. 37*(9): 768-778.
62. Budni J, Zomkowski AD, Engel D, et al. 2013. Folic acid prevents depressive-like behavior and hippocampal antioxidant imbalance induced by restraint stress in mice. *Exp Neurol.* 240:112– 121.
63. Temdie RJG, Fotio, Lambou A, Dimo T. 2012. Acute and Chronic Anti-Inflammatory effects of the Methanol Leaf Extract of Markhamia Tomentosa (Benth.) K. Schum. (Bignoniaceae) *J Scientific Res Pharm* 1(4): 12-18.
64. Ngueguim TF, Mbatchou A, Donfack JH, Dzeufiet Djomeni PD, Gounoue Kamkumo R, Djouwoug Noussi C, Kamtchouing P, Dimo T. 2016. *Dichrocephala integrifolia* (Linn. f.) O. Kuntze (Asteraceae) leaves aqueous extract prevents ethanol-induced liver damage in rats. *Pharmacologia.* 7(6-7): 337-343.
65. Kouemou NE, Taiwe GS, Moto FCO, Pale S, Ngoupaye GT, Njapdounke JSK, Nkantchoua GCN, Pahaye DB, and Bum EN. 2017. Nootropic and Neuroprotective Effects of Dichrocephala integrifolia on Scopolamine Mouse Model of Alzheimer's Disease. *Front Pharmacol.* 8: 847.
66. Del Rio D, Stewart AJ, Pellegrini N. 2005. A review of recent studies on malonaldehyde as toxic molecule and biological marker of oxidative stress. *Nutr Metab Cardiovasc Dis.* 15 (4): 316–328
67. Mazereeuw G, Herrmann N, Andreazza AC, Scola G, Ma D, Oh PI, Lanctôt KL. 2017. Oxidative stress predicts depressive symptom changes with omega-3 fatty acid treatment in coronary artery disease patients. *Brain Behav. Immun.* 60: 136–141.
68. Cumurcu BE, Ozyurt H, Etikan I, Demir S, Karlidag R. 2009. Total antioxidant capacity and total oxidant status in patients with major depression: Impact of antidepressant treatment. *Psychiatry Clin. Neurosci.* 63 (5): 639–645.
69. Rajesh P, Latha S, Selvamani P, Kannan VR. 2009. Phytochemical Screening and Toxicity Studies on the Leaves of Capparis sepiaria Linn. (Capparidaceae). J Basic Clin Pharm. 1(1): 001.
70. Guan LP, Liu BY. 2016. Antidepressant-like effects and mechanisms of flavonoids and related analogues. *Eur J Med Chem.* 121: 47 –57.