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*Original Research Article*

# Anti-stress Potential of Ethanol Leaf Extracts of Parquetina and Common Figs in Chronic Forced Swim Stress

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ABSTRACT

Long-term psychological stress causes biological anomalies, especially in the immunological and endocrine systems, which lead to a greater risk of illness, including anxiety and depression. Medicinal plants, such as Parquetina and Fig, have been used locally for centuries to manage various illnesses, including mental health-related conditions, effectively. This study investigated the antistress effects of 250 mg/kg body weight of ethanolic leaf extract of Parquetina (ETEPN) and Fig (ETEFC) in male Wistar rats in a seven-day forced swim stress (FSS) model. Behavioral assessments (open field test (OFT), elevated plus-maze (EPM), and forced swim test (FST)) were performed to estimate the adaptogenic/antistress effects of the extracts. Neurochemical and oxidative stress were determined in the rats' brain homogenates. Compared with the control, FSS elicited an inhibitory effect in the OFT and EPM and a depressogenic effect in the FST. The extracts reversed all these behavioral aberrations. A decrease was detected in the GSH level, whereas the GPx and SOD activities and the MDA and nitrite levels were significantly elevated by FSS. AChE activity and dopamine, serotonin, and cortisol levels were elevated significantly ($p$<0.001), and levels of brain-derived neurotrophic factor were decreased significantly ($p$<0.0001) by FSS. The extracts were able to ameliorate the induced oxidative stress and neurochemical alterations caused by FSS. This study revealed that the two plant extracts demonstrated anti-stress potential by ameliorating the behavioral and neurochemical dysfunction associated with chronic FSS and could be used as drug adjuncts to remedy common day-to-day stress.

***Keywords:*** Stress, Parquetina, Fig, Brain-Derived Neurotrophic Factor, Cortisol, Depression, Neurology

## Introduction

The mental perceptions of a situation as being out of one's control and potentially harmful to one's health are what define stress in an individual. Everyone, in general, experiences stress; notably, certain levels of stress can boost and enhance an individual's performance.[1] The development of behavioral and mental illnesses occurs in people when stress levels exceed their capacity. Stress can be caused by any situation or concept that makes someone feel irritated, furious, or anxious. When a stressor is perceived, circuits and pathways that are activated based on the stressor's classification—physiological or psychological—create a reaction (mediation or modulation) known as the stress response. The changes caused by stress are typically adaptive, self-limiting, and compensating. Examples of early symptoms of stress are anger, sadness, excessive worry, sleep disorders, palpitations, headaches, fatigue, restlessness, increased blood pressure, aches and pains, and many others.[2]Chronic stress is defined as ongoing, persistent stress that negatively affects the cardiovascular, neurological, immunological, and neuroendocrine systems.

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Relationship stress, or tense relationships with friends, coworkers, partners, and family, is one of the main causes of chronic stress. Another is the challenges and expectations of our jobs and work environments.[1] When stressful events exceed certain threshold limits, the resulting changes can sometimes become irreversible, disrupt homeostasis, and lead to fatigue.[3] The effects of chronic stress on the brain include structural changes in different regions, with a reduction in size and mass. These factors ultimately lead to the brain's inability to respond to stress, memory and cognition (learning) impairment, neurogenic disorders, and plasticity incompetence.[2] The risk of neurodevelopmental and psychiatric diseases is significantly increased by prolonged stress. Studies have shown that stress is the root cause of half of anxiety and depression, mostly because of high cortisol levels and disturbances in the hypothalamic-pituitary-adrenal (HPA) axis.[4] Furthermore, there is a strong correlation between stress and infectious diseases, cancer, obesity, emotional overeating, and cardiovascular diseases. As such, stress is a multifaceted factor that contributes significantly to the development of disease and physical harm. It is physiological, mental, and physical.

Modern science continuously updates its parameters to understand the causes and evolve better therapies for stress-induced disease, since stress affects virtually all classes of human beings, from schoolchildren to the elderly. Therapies, such as antidepressants (e.g., selective serotonin reuptake inhibitors) and anxiolytics (e.g., benzodiazepines), which are prescribed for stress management, help to alleviate some of the behavioral symptoms transiently but fail to sustain the elevated cortisol of the HPA axis experienced in chronic stress. To date, no specific drug has been identified as a therapy for stress that can prevent the elevation of cortisol. Herbal drug research is ongoing for the identification and isolation of potent bioactive components that could serve as safe and effective adaptogens, increase individuals' ability to cope with stress, and increase their ability to adapt to changing external

and internal stressors, thereby preventing damage.[5]
Thus, this study was aimed at evaluating the impact of two common herbs ethnobotanically important in the southwestern part of Nigeria on rats subjected to a chronic stress model.

## Materials and Methods

*Animals*
The study employed healthy adult male Wistar rats weighing 160 ± 20 g. The rodents were kept in the Department of Biochemistry animal facility at the Federal University of Technology, Akure, under standard living conditions, with a temperature of 27 ± 3°C and a 12-hour light-dark cycle. They received enough water and were fed normal rat chow from Vita Feeds Nigeria Limited. Seven days before the commencement of the experiments, the rats were acclimated. The experiments were conducted using standard guidelines for animal care and use. Ethical permission was obtained from the Research Ethics Committee, Federal University of Technology, Akure (FUTA/ETH/21/24).

*Plant collection and identification*
Fresh leaves of Parquetina (*Parquetina nigrescens*) and fig (*Ficus capensis*) were procured from farms in Igoba, Akure (7.31° N, 5.26° E), southwestern Nigeria in August 2017. Mr. Omomoh Bernard E. at the Department of Crop, Soil, and Pest Management, Federal University of Technology, Akure (FUTA), conducted identification and authentication. Voucher specimens (FUTA 0242 and 0241, respectively) were deposited at the Herbarium (FUTA Centre for Research and Development (CERAD)). After being cleaned, the leaves were allowed to air dry for three weeks at room temperature (27 ± 3°C) before being pulverized into a powder using an electric grinder.

*Extraction of plant materials*
Two hundred grams of each powdered sample was soaked in 1 L of ethanol (80% v/v) for 24 hours. The suspension was filtered using a muslin cloth, concentrated at a lower pressure in a rotary evaporator, and then freeze-dried. The extracts were hereafter designated ETEPN for Parquetina leaf extract and ETEFC for fig leaf extract.

*Pharmacological study*
*Forced swim stress procedure*
Forced swim stress (FSS) was performed according to the methods of Kaur and Kulkarni.[6] The animals were made to swim in groups of six for one hour every day for seven days in a clear plastic container of 25 cm in diameter and 48 cm in height. The container was filled with water that was two-thirds full and maintained at a temperature of 25 ± 2 °C. The animals were not allowed to cling to the container's walls or one another.
The animals were split into 5 groups (n=6); Group 1 was not stressed but was handled as often as the stressed rats and served as a control; Groups 2-5 animals underwent FSS; and Groups 3, 4, and 5 animals were orally administered 250 mg/kg body weight ETEPN, ETEFC, and imipramine (30 mg/kg), respectively, daily 1 h before FSS.

*Behavioral study*
The animals were evaluated via the open field test (OFT) and elevated plus maze (EPM) on the final day and via the forced swim test (FST) twenty-four hours later.

*Measurement of locomotor activity*
*Open field test (OFT)*
The device was a 72 x 72 x 36 cm wooden box having its floor divided into 16 squares. The box had a central square drawn in the middle, while the remaining squares next to the walls were referred to as the periphery. A 200-W white bulb provided illumination. The open field test was utilized to measure behavioral responses, including hyperactivity, locomotor activity, and exploratory behavior. To evaluate the locomotory and exploratory activities of the rats as indicators of stress, a digital clock and a video camera positioned above the open-field equipment were used to track and record each rat's behavior for five minutes after it was carefully placed in the middle of the field. The number of rearing instances and assisted rearing (defined as when the forepaws are placed on a wall of the open field apparatus), as well as center square crossings and square crossings (which occur when all four paws move from one square to another), were recorded.[7] The more time the rat spends in the center space and the more square crossings (ambulation) it makes, the lower the stress level is perceived to be. After each session, ethanol was used to clean the floor of the open field to eliminate any smell cues.

*Measurement of anxiety*
The plus maze is 50 cm high and has two open arms and two closed arms, each measuring 50 × 10 × 40 cm.[8,9] When animals are exposed to a new maze alley, they experience an approach-avoidance conflict that is more intense in an open arm than in a closed arm. Rodents, such as mice and rats, tend to prefer enclosed spaces over high, open areas, leading them to spend more time in enclosed environments. Animals that encounter an open arm freeze, become motionless, urinate, and exhibit fear-like behaviors. The maze was set up in a room with good lighting and soundproofing. The rats were positioned in the middle of the maze, facing one of the open arms, one after the other. A digital clock and a video camera positioned above the maze were used to record, for five minutes, the total amount of time each rat spent in the maze's open and closed arms, the number of times they entered the arms, and the total number of times they entered both arms. Considerations were taken to ensure that no external stimulation evoked anxious reactions in the rats.

*Measurement of immobility time*
*Forced swim test (FST)*
Each rat was made to swim alone in a cylindrical, open container from which it was unable to escape.[10] Animal behavior was recorded using a digital clock and a video camera mounted above the cylinder. The sum of the immobility time and the delay or latency to immobility over 5 min was computed.

*Biochemical analyses*
On the eighth day, the animals were sacrificed via cervical dislocation. Blood samples were obtained via cardiac puncture into plain bottles to clot. Blood serum was obtained by centrifuging the blood for 10 minutes at 3000 rpm at 4°C, and the supernatant was aspirated for use in biochemical investigations. The removed brains were blotted with filter paper, washed in a cold 1.15% (w/v) potassium chloride solution, and weighed. A 10% (w/v) 0.1 M saline phosphate buffer (pH 7.4) was then used to homogenize the samples. The supernatant, which was utilized for biochemical studies, was obtained by centrifuging the resulting homogenate at 10,000 x g for 25 minutes at 40°C.[11]

*Estimation of lipid peroxidation and antioxidant parameters*
Reduced glutathione (GSH) levels were assessed via the methods of Beutler et al.[12] The method of Haque et al.[13] was used to determine the activity of glutathione peroxidase (GPx). Kakkar et al.'s method[14] was used to estimate the activity of superoxide dismutase (SOD), and lipid peroxidation was estimated via the methods of Varshney and Kale.[15] Estimates of nitrite and nitrate in biological materials are frequently employed as indicators of the generation of nitric oxide (NO). The Griess reaction was used to assess the nitrite levels in the brain homogenates.[16]

*Assessment of neurotransmitter levels*
The level of dopamine was estimated according to Guo et al.[17] The activity of acetylcholinesterase was determined using the method of Ellman et al.[18] ELISA kits were used for the determination of the serotonin, cortisol, and brain-derived neurotrophic factor (BDNF) levels according to the manufacturers' instructions.

*Statistical analysis*
The results are presented as the means ± standard deviations (SDs). Microsoft Excel and GraphPad Prism 8.0 (GraphPad Software Inc., CA, USA) were used to analyze the data. One-way analysis of variance (ANOVA) and Tukey's multiple comparison tests were used for the

statistical studies. $p<0.05$ was used as the threshold for statistical significance in each test.

## Results and Discussion

Stress, anxiety, and mental disorders can result from the complexities of modern civilization, growing challenges, and changes in lifestyles. These issues have emerged as the most significant issues in contemporary communities.[19] Exposure to excessive or chronic stress disrupts a person's homeostasis and elicits various physical, behavioral, biochemical, and neurochemical responses, leading to conditions such as depression and anxiety. Cardiovascular disorders, cognitive dysfunction, high blood pressure, and ulcerative colitis are also linked to such stress-related situations.

In this study, subjecting rats to forced swimming for an hour daily over seven days induced a state of chronic stress and fatigue, as demonstrated by the reduced locomotion (43.00 ± 7.07) and central crossing (3.67 ± 1.53) of the stressed rats in comparison with those of the control rats (58.40 ± 3.06 and 7.00 ± 1.73) in the OFT (Table 1). This finding highlights the anxiogenic effect of chronic swim stress on the animals. Conversely, the extracts significantly mitigated this effect, evidenced by increased ambulation (ETEPN 62.80 ± 2.89, ETEFC 71.60 ± 5.12), increased rearing (ETEPN 16.00 ± 0.71, ETEFC 16.75 ± 2.22), and increased central crossing (ETEPN 7.33 ± 1.58, ETEFC 8.25 ± 0.96), which were comparable to the values observed in the IMIPRAMINE group (67.33 ± 5.00, 17.00 ± 2.53, and 6.00 ± 0.89). Notably, ETEFC exhibited a greater anxiolytic capacity in this test, surpassing even the standard drug.

**Table 1:** Impact of extracts on behavioral metrics of rats in the open field test

| TREATMENT GROUP | AMBULATION | REARING | CENTER CROSSING |
|---|---|---|---|
| **CONTROL** | 58.40 ± 3.06 | 15.20 ± 3.11 | 7.00 ± 1.73 |
| **STRESSED** | 43.00 ± 7.07$^{c}$ | 12.00 ± 2.65 | 3.67 ± 1.53$^{b}$ |
| **ETEPN+ STRESSED** | 62.80 ± 2.89$^{z}$ | 16.00 ± 0.71 | 7.33 ± 1.58$^{y}$ |
| **ETEFC+ STRESSED** | 71.60 ± 5.12$^{z}$ | 16.75 ± 2.22$^{w}$ | 8.25 ± 0.96$^{z}$ |
| **IMIPRAMINE+ STRESSED** | 67.33 ± 5.00$^{z}$ | 17.00 ± 2.53$^{w}$ | 6.00 ± 0.89 |

Results are presented as the means ± SDs (n=6). $^{c}p<0.001$, $^{b}p<0.01$ vs. CONTROL. $^{z}p<0.0001$, $^{y}p<0.001$, $^{w}p<0.05$ vs. STRESSED. Abbreviations: CONTROL: naive rats; STRESSED: 7 days of forced swim stress for 1 h (FSS); ETEPN+STRESSED: FSS with 250 mg/kg *Parquetina nigrescens* leaf extract 1 h before stress; ETEFC+STRESSED: FSS with 250 mg/kg *Ficus capensis* leaf extract 1 h before stress; IMIPRAMINE+STRESSED: FSS with 30mg/kg imipramine 1 h before stress.

Aversion to the exposed arm of the elevated plus maze is innate in rodents and serves as an indicator of fear or anxiety. Substances that alter this aversive trait are known to be anxiolytic and can help reduce stress levels in the animals. Compared with the control, chronic swimming stress significantly ($p < 0.0001$) reduced open arm entry (23.19 ± 2.96) and open arm time (4.79 ± 4.14) relative to those of the control (35.73 ± 2.15 and 27.30 ± 4.15, respectively), with a commensurate increase in entries into both the closed and open arms (Table 2). This further proves the anxiogenic effect of this activity on the rat. When compared to the stressed group, the extracts were able to considerably increase both open arm entry and open arm time. This finding indicates an enhancement of the exploratory activity in the rats, thus attenuating the anxiogenic effect of the chronic stress and open arm exposure on the rats. The total number of entries into both the open and closed arms (TE), an indicator of locomotor activity in the EPM test, was also lower in the stressed rats than in the control rats. The extracts increased this parameter, similar to the effect of the standard drug. Compared with ETEPN-treated rats, ETEFC-treated rats presented greater locomotor activity, which was consistent with observations in the open field test.

**Table 2:** Impact of extracts on behavioral metrics of rats in the elevated plus maze test

| TREATMENT GROUP | TE | OAE (%) | CAE (%) | OAT (%) | CAT (%) |
|---|---|---|---|---|---|
| **CONTROL** | 8.75 ± 1.71 | 35.73 ± 2.15 | 64.27 ± 2.15 | 27.30 ± 4.15 | 72.70 ± 4.15 |
| **STRESSED** | 5.67 ± 1.53 | 23.19 ± 2.96$^{d}$ | 76.81 ± 2.96$^{d}$ | 4.79 ± 4.14$^{d}$ | 95.22 ± 4.14$^{d}$ |
| **ETEPN + STRESSED** | 9.00 ± 2.24$^{w}$ | 34.33 ± 3.20$^{z}$ | 64.28 ± 5.55$^{z}$ | 13.79 ± 0.70$^{w}$ | 86.31 ± 0.70$^{x}$ |
| **ETEFC + STRESSED** | 12.20± 2.39$^{z}$ | 35.35 ± 2 .65$^{z}$ | 64.65 ± 2.65$^{z}$ | 14.96 ± 1.32$^{y}$ | 85.05 ± 1.32$^{y}$ |
| **IMIPRAMINE+ STRESSED** | 9.00 ± 1.22$^{w}$ | 42.96 ± 2.57$^{z}$ | 57.04 ± 2.57$^{z}$ | 28.05 ± 5.18$^{z}$ | 71.95 ± 5.18$^{z}$ |

Results are presented as the means ± SDs (n=6). $^{d}p<0.0001$ vs. CONTROL. $^{z}p<0.0001$, $^{y}p<0.001$, $^{x}p<0.01$, $^{w}p<0.05$ vs. STRESSED. Abbreviations: CONTROL: naive rats; STRESSED: 7 days of forced swim stress for 1 h (FSS); ETEPN+STRESSED: FSS with 250 mg/kg *Parquetina nigrescens* leaf extract 1 h before stress; ETEFC+STRESSED: FSS with 250 mg/kg *Ficus capensis* leaf extract 1 h before stress; IMIPRAMINE+STRESSED: FSS with 30 mg/kg imipramine 1 h before stress; TE: total number of entries into open and closed arms; %OAE: percentage of open arm entries; %CAE: percentage of closed arm entries; %OAT: percentage of time spent in open arms; %CAT: percentage of time spent in closed arms.

The depressogenic effect of chronic swimming stress was also confirmed through the forced swim test, where the stressed rats exhibited a greater tendency toward immobility and quicker surrender in the water. A significant ($p < 0.0001$) increase in the time of immobility (81.56 ± 3.24) and a decrease in the latency to immobility (29.00 ± 4.36) compared with those of the unstressed control (69.72 ± 1.95 and 43.40 ± 5.77) were recorded (Table 3). This depicts a state of depression or an inability of the animals to cope with the rigors of the chronic stress, likely due to fatigue. Both extracts showed adaptogenic/antidepressant effects in the forced swim test by reducing the locomotor impairment, as demonstrated by a significant ($p < 0.0001$) decrease in the time of immobility (ETEPN 56.17 ± 1.19, ETEFC 51.61 ± 5.19), along with increased latency to immobility (ETEPN 58.75 ± 7.62, ETEFC 97.50 ± 10.61).

**Table 3:** Impact of extracts on behavioral metrics of rats in the forced swim test

| TREATMENT GROUP | TIME IMMOBILE (%) | LATENCY TO IMMOBILITY (s) |
|---|---|---|
| **CONTROL** | 69.72 ± 1.95 | 43.40 ± 5.77 |
| **STRESSED** | 81.56 ± 3.24$^{d}$ | 29.00 ± 4.36$^{a}$ |
| **ETEPN + STRESSED** | 56.17 ± 1.19$^{z}$ | 58.75 ± 7.62$^{z}$ |
| **ETEFC + STRESSED** | 51.61 ± 5.19$^{z}$ | 97.50 ± 10.61$^{z}$ |
| **IMIPRAMINE STRESSED** | 38.58 ± 4.24$^{z}$ | 119.00 ± 7.07$^{z}$ |

Results are presented as the means ± SDs (n=6). $^{d}p<0.0001$, $^{a}p<0.05$ vs. CONTROL. $^{z}p<0.0001$ vs. STRESSED. Abbreviations: CONTROL: naive rats; STRESSED: 7 days of forced swim stress for 1 h (FSS); ETEPN+STRESSED: FSS with 250 mg/kg *Parquetina nigrescens* leaf extract 1 h before stress; ETEFC+STRESSED: FSS with 250 mg/kg *Ficus capensis* leaf extract 1 h before stress; IMIPRAMINE+STRESSED: FSS with 30 mg/kg imipramine 1 h before stress.

Prolonged stress is well known to result in depression, decreased motor activity, and anxiety-like behavior. As a general adaptive response triggered by shocks that disrupt homeostasis, stress releases the body's energy reserves needed to overcome this homeostatic disrupting influence.[20] However, when stress becomes chronic, it can lead to detrimental effects on both physical and mental health, often exacerbating existing conditions. Addressing stress through effective coping mechanisms and support systems is essential for restoring balance and promoting overall well-being. Depending on how the stressor is interpreted, the amount of stimulation or the nature of the fear it evokes can cause several metabolic changes that can disrupt

physiological and psychological equilibrium.[21,22] The stressed group presented a significant ($p < 0.01$) reduction in the GSH level, and a significant ($p < 0.0001$) increase in the SOD and GPx activities, in comparison with the control. Lipid peroxidation was also elevated in the stressed animals, as revealed by the elevated MDA level. The extracts and standard drug ameliorated these effects. Compared with those in the stress group, the nitrite levels in the brain were also significantly lower ($p < 0.05$) in the treatment groups (Figure 1).

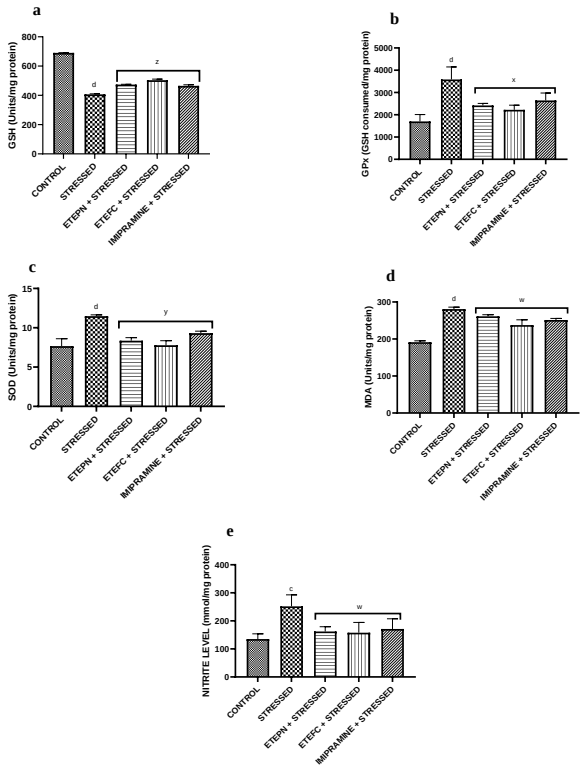


**Figure 1:** Effects of *Parquetina nigrescens* and *Ficus capensis* on the following antioxidant parameters in the cerebral homogenates of rats: (a) GSH level, (b) GPx activity, (c) SOD activity, (d) MDA level, and (e) nitrite level. The results are presented as the means ± SDs (n=6). $^{d}p<0.0001$ vs. CONTROL. $^{z}p<0.0001$, $^{y}p<0.001$, $^{x}p<0.01$, $^{w}p<0.05$ vs. STRESSED. Abbreviations: CONTROL: naive rats; STRESSED: 7 days of forced swim stress for 1 h (FSS); ETEPN+STRESSED: FSS with 250 mg/kg *Parquetina nigrescens* leaf extract 1 h before stress; ETEFC+STRESSED: FSS with 250 mg/kg *Ficus capensis* leaf extract 1 h before stress; IMIPRAMINE+STRESSED: FSS with 30 mg/kg imipramine 1 h before stress.

Oxidative stress is a key contributor to the pathology and symptoms of chronic fatigue and the resulting mental situations of anxiety, depression, and insomnia. In this study, seven days of forced swimming stress in rats resulted in alteration/impairment of the antioxidant defense system, which is indicated by a reduction in the GSH level and elevation of the activity of the antioxidant enzymes, which are indices of the oxidative stress status of the rats. Daily stress can impair the body's antioxidant defenses, potentially leading to oxidative damage due to an alteration in the balance between oxidant and antioxidant components. The amplified production of free oxygen radicals may result in excessive generation of antioxidant defense enzymes, such as SOD and GPx, as demonstrated in this study, to counteract the overwhelming amount of free radicals.[23] The elevated glucocorticoid concentration under stress may be the cause of the elevated reactive oxygen species levels. These hormones have been shown to escalate the production of reactive oxygen species.[24] The stressed rats presented increased levels of SOD and GPx enzymatic activity, consequent to the body's antioxidant defense system being mobilized in response to the increase in oxidative stress. The extracts demonstrated protective effects, as shown by the decrease in enzymatic acticity in treated rats.

One major effect of oxidative stress is lipid peroxidation, which eventually has a number of detrimental enzymatic effects.[25] By primarily peroxidizing polyunsaturated fatty acids and phospholipids, excessive lipid peroxidation has been demonstrated to cause membrane disarray. This alters the ratio of polyunsaturated fatty acids to other fatty acids, which ultimately compromises or changes cell integrity and function. Lipid peroxidation is thus considered a severe consequence of free radical toxicity, resulting in significant alterations to the structure and function of membranes that lead to cell death.[26,27]

In addition to increased oxidative stress, the nitric oxide (NO) pathway is involved in the pathogenesis of chronic stress or fatigue syndromes. As a crucial neurotransmitter in the neurological system, NO controls a wide range of emotional, cognitive, and behavioral functions, including depression. Nitrite is the stable byproduct of nitric oxide in biological systems. Mice under stress presented markedly elevated plasma nitrite levels. The inducible nitric oxide synthase (iNOS) enzyme is upregulated in patients with stress–induced symptoms and associated illnesses, according to several studies.[28,29] Increased iNOS expression enhances nitric oxide production, which may trigger the body's inflammatory response. Therefore, nitrosative stress appears to play a significant role in stress-induced depression. The rats subjected to the FSS in this study demonstrated greater lipid peroxidation and greater NO. Treatment of the rats with leaf extracts of Parquetina and Ficus restored the levels of nitrite and lipid peroxidation, indicating that these plants directly protect against extremely harmful free and hydroxyl radicals that damage the majority of biological targets, such as proteins, lipids, and DNA. These findings further suggest that the mechanism of neuroprotection of these plant extracts involves the nitric oxide pathway. Imipramine's neuroprotective effects via the nitric oxide pathway have been proposed.[30]

The results of the assessment of neurological parameters are as shown in Figure 2. In the stressed group, dopamine, serotonin, and cortisol levels were significantly ($p < 0.001$) raised; however, the extracts in the treated groups reduced these levels. In addition, the stressed animals presented increased acetylcholinesterase inhibitory activity, which was attenuated by the extracts. The extracts also reduced the stress-induced decrease in the BDNF level.

Genetic predisposition, anomalies of the HPA axis, endocrine dysregulation, and psychosocial factors are also culpable in the development of stress-induced pathologies. The hypothalamic-pituitary-adrenal (HPA) axis system is activated by stress, allowing the bloodstream to release glucocorticoids, β-endorphin, and adrenocorticotropic hormone (ACTH). As a neuromodulator in the brain, corticotropin-releasing factor (CRF) acts on the HPA axis to raise serum cortisol levels. Many behavioral, neuroendocrine, and autonomic reactions to environmental stimuli are known to be modulated by this action inside the central nervous system. Increased cortisol levels in humans are linked to decreased motor reactivity and anxiety-like behavior. These physiological responses underscore the intricate relationship between stress and behavior, highlighting how prolonged activation of the HPA axis can lead to various mental health issues. Understanding these mechanisms is crucial for developing effective interventions to mitigate the negative effects of chronic stress on well-being. This was confirmed to be the effect of seven days of FSS in the current study, and the administration of the leaf extracts ameliorated this HPA abnormality by reducing the cortisol levels in the rats. The optimal antistress supplement or adaptogen should effectively target and lower the increase in cortisol caused by psychological stress, which is a recognized indicator of stress-induced disorders. The ability of Parquetina and Ficus extracts to function as adaptogens is evident in their effectiveness at reducing cortisol levels in stressed rats. These findings suggest that these extracts may have potential therapeutic applications in managing stress-related conditions.

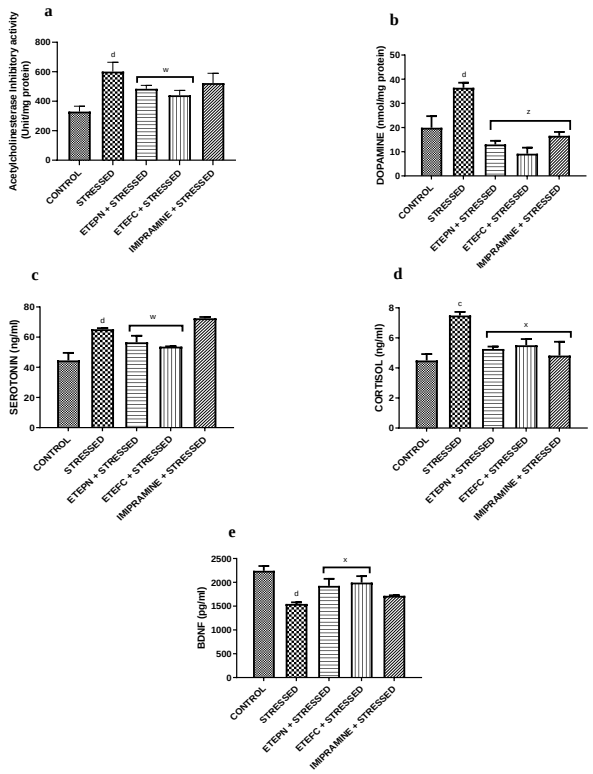


**Figure 2**: Effects of *Parquetina nigrescens* and *Ficus capensis* on the following neurological parameters of rats: (a) acetylcholinesterase activity, (b) dopamine level, (c) serotonin level, (d) cortisol level, and (e) brain-derived neurotrophic factor (BDNF) level. The results are presented as the means ± SDs (n=6). $^{d}p<0.0001$, $^{c}p<0.001$ vs. CONTROL. $^{z}p<0.0001$, $^{x}p<0.01$, $^{w}p<0.05$ vs. STRESSED. Abbreviations: CONTROL: naive rats; STRESSED: 7 days of forced swim stress for 1 h (FSS); ETEPN+STRESSED: FSS with 250 mg/kg *Parquetina nigrescens* leaf extract 1 h before stress; ETEFC+STRESSED: FSS with 250 mg/kg *Ficus capensis* leaf extract 1 h before stress; IMIPRAMINE+STRESSED: FSS with 30 mg/kg imipramine 1 h before stress.

Further research is needed to explore the mechanisms behind their adaptogenic properties and to evaluate their efficacy in human subjects. Changes in monoamines, such as serotonin and dopamine, under stressful conditions are closely associated with behavioral abnormalities in learning, memory, and other mood disorders. Dysregulation of monoamine function is a major cause of memory impairment under stressful circumstances.[31] The growth and survival of monoamine neurons are improved by brain-derived neurotrophic factor (BDNF), which is stimulated by antidepressants that raise the levels of neurotransmitters like 5-HT. Serotonin is one of the neurological markers examined in this study. It is known to be a key modulator of stress effects, and its level is increased in the brain by stress. The raphe nuclei' ascending serotonergic neurons innervate limbic and hypothalamic regions and have a general role in controlling adrenocorticotropic hormone (ACTH) production during stressful situations.[32] Consequently, long-term stress exposure can modify serotonin neurotransmission at these postsynaptic sites, resulting in functional impairments in these brain areas and aberrant behavioral output.

The stressed experimental rats in this study showed increased dopamine output in their brains, which could be related to a decrease in GABA-A receptor-mediated transmission. Stressful conditions and some other treatments decrease GABAergic transmission and enhance dopamine production in the cerebral cortex and nucleus accumbens of rats,[33] and this dopaminergic innervation has been demonstrated to be inhibited or decreased by benzodiazepines (e.g., diazepam), which are standard anxiolytics. In this study, swim-stressed rats presented elevated dopamine levels, confirming the anxiogenic effect of this treatment. *Ficus capensis* demonstrated a strong ability to attenuate this anxiogenic effect.

BDNF, in association with its receptors, is widely spread in regions of the brain that are associated with mental illnesses, including the prefrontal cortex, amygdala, and hippocampus, and is intricately connected to cellular processes like synapse formation, cell growth and survival, and neurogenesis. As a signaling protein in the hippocampus, its level and protective cell signaling cascades are depleted in chronic stress conditions, and this has been observed in situations of depression. Herbal antidepressant plants, like saffron, have been suggested to elevate BDNF expression in the brains of treated rats.[34,35] Similarly, the plant extracts in this study elevated the levels of BDNF in the stressed rats, which could ultimately lead to improved neuronal plasticity and neurogenesis, which are typical of antidepressant treatments in depressed patients.

To improve neurotransmission in the brain, acetylcholinesterase inhibitors are employed to slow the breakdown of acetylcholine (ACh). This study revealed that the extracts had a significant inhibitory effect on acetylcholinesterase, indicating that the mechanism of neuroprotection might involve inhibition of the cholinergic system and neuronal damage caused by oxidative stress.

The extracts from this study demonstrated neuroprotective potential by improving the behavioral deficits observed in the chronic forced swim stress-induced rats, reducing oxidative stress, and modulating neurochemical dysfunction via their antioxidant, neurochemical, and neurotransmitter modulatory ability.

## Conclusion

This study revealed that rats exposed to seven days of chronic forced swim stress exhibited an anxiogenic and depressogenic phenotypic behavioral pattern, which was accompanied by altered neurochemical states and oxidative stress. The ethanolic leaf extracts of Parquetina and fig, employed in this study, demonstrated the ability to ameliorate the stress-induced behavioral, neurological, and oxidative imbalances, thus acting as potent adaptogens to combat of stress-induced alterations in daily life. Further research is needed to explore the mechanisms behind their adaptogenic properties and to evaluate their efficacy in human subjects.

## Conflict of Interest

The author`s declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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