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EXAMINATION OF THE EFFECTS OF EPIGALLOCATECHIN GALLATE IN EXPERIMENTAL DEPRESSION MODEL OF MICE

FARELERDE OLUŞTURULAN DENEYSEL DEPRESYON MODELİNDE EPİGALLOKATEŞİN GALLATIN ETKİLERİNİN İNCELENMESİ

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Abstract

Depression has a prevalence of approximately 5%. The pathophysiology of depression is reported to involve monoamine deficiency, elevated cortisol levels, Brain-Derived Neurotrophic Factor (BDNF) deficiency, increased glutamate, and inflammation. To date, no effective treatment protocol has been developed for cortisol elevation and inflammatory factors, which are proposed to play a role in the pathophysiology of depression. Epigallocatechin gallate (EGCG) is a flavonoid derivative that occurs naturally in green tea. Numerous studies have shown that the substance possesses both anti-inflammatory and antioxidant properties. It has also been demonstrated to possess anxiolytic properties. The present study was conducted to investigate the potential antidepressant effect of EGCG through anti-inflammatory mechanisms. To this end, the mice were divided into seven groups (n=10) and the "Porsolt's forced swimming test" was administered to compare the effects of EGCG with those of classic antidepressant drugs (paroxetine, venlafaxine, moclobemide). Furthermore, cortisol and IL-6 levels were measured in mice before and after treatment with the effective EGCG dose (100 mg kg^{-1}). In contrast to the effects observed with conventional antidepressants, EGCG doses of 25 mg kg^{-1} and 50 mg kg^{-1} did not demonstrate a significant impact, while the 100 mg/kg dose exhibited a substantial antidepressant effect. A subsequent comparison of corticosterone levels between the control and EGCG 100 mg/kg groups (9387.7 pg mL^{-1} and 6147.0 pg mL^{-1} respectively) revealed a significant ($p<0.05$) decrease in corticosterone levels in the EGCG 100 mg kg^{-1}group. In a similar manner, a comparison of IL-6 levels between the control and EGCG 100 mg kg^{-1} groups (159.0 pg mL^{-1} and 128.3 pg mL^{-1}, respectively) revealed a significant ($p<0.05$) reduction in IL-6 levels in the EGCG 100 mg kg^{-1} group.

In conclusion, the inhibitory effect of EGCG on corticosterone and IL-6 levels in Porsolt's forced swimming test can be interpreted as an antidepressant effect. The potential antidepressant effect may be mediated by anti-inflammatory mechanisms. Further studies in this area are required.

Keywords: Corticosterone, Depression, Epigallocathecin-gallate (EGCG), Forced Swimming Test, IL-6

Öz

Depresyon, yaklaşık %5 prevalans ile yaygın bir hastalıktır. Depresyonun patofizyolojisinde monoamin eksikliği, kortizol düzeylerinde artış, Beyin Kaynaklı Nörotrofik Faktör (BDNF) eksikliği, glutamat artışı ve inflamasyonun rol oynadığı bildirilmektedir. Bugüne kadar, depresyonun patofizyolojisinde rol oynadığı öne sürülen kortizol artışı ve inflamatuar faktörler için etkili bir tedavi protokolü geliştirilmemiştir. Epigallokateşin gallat (EGKG), yeşil çayda doğal olarak bulunan bir flavonoid türevidir. Çok sayıda çalışmanın bulgularında gösterildiği gibi, bu maddenin hem antiinflamatuar hem de antioksidan özelliklere sahip olduğu gösterilmiştir. Ayrıca anksiyolitik özelliklere sahip olduğu da gösterilmiştir. Bu çalışma, EGKG'nin antiinflamatuar mekanizmalar yoluyla potansiyel antidepresan etkisini araştırmak

amacıyla gerçekleştirilmiştir. Bu amaçla, fareler yedi gruba (n=10) ayrılmış ve EGKG'nin klasik antidepresan ilaçlar (paroksetin, venlafaksin, moklobemid) ile etkilerini karşılaştırmak için "Porsolt'un zorlu yüzme testi" uygulanmıştır. Ayrıca, etkili EGKG dozu (100 mg kg^{-1}) ile tedaviden önce ve sonra farelerde kortizol ve IL-6 düzeyleri ölçülmüştür. Geleneksel antidepresanlarla gözlenen etkilerin aksine, 25 mg kg^{-1} ve 50 mg kg^{-1} EGKG dozları önemli bir etki göstermezken, 100 mg kg^{-1} dozunda önemli bir antidepresan etki gözlenmiştir. Kontrol ve EGCG 100 mg kg^{-1} grupları arasında kortikosteron düzeylerinin karşılaştırılması (sırasıyla 9387,7 pg mL^{-1} ve 6147,0 pg mL^{-1}) EGKG 100 grubunda kortikosteron düzeylerinde önemli ($p<0,05$) bir azalma olduğunu ortaya koymuştur. Benzer şekilde, kontrol ve EGKG 100 grupları arasındaki IL-6 düzeylerinin karşılaştırılması (sırasıyla 159,0 pg mL^{-1} ve 128,3 pg mL^{-1}) EGKG 100 mg/kg grubunda IL-6 düzeylerinde önemli ($p<0,05$) bir azalma olduğunu ortaya koymuştur. Sonuç olarak, EGKG'nin Porsolt'un zorla yüzme testinde kortikosteron ve IL-6 düzeyleri üzerindeki inhibe edici etkisi, antidepresan etki olarak yorumlanabilir. Potansiyel antidepresan etki, antiinflamatuar mekanizmalar aracılığıyla ortaya çıkabilir. Bu alanda daha fazla çalışma yapılması gerekmektedir.

Anahtar Kelimeler: Kortikosteron, Depresyon, Epigallokateşin gallat (EGKG), Zorunlu Yüzme Testi, IL-6

1. Introduction

Major depressive disorder (MDD) is regarded as a leading cause of health-related disability and a risk factor for suicidal behaviour (Abdelmeguid et al., 2022). The prevalence of MDD is around 6% yearly, in newly diagnosed patients, and nearly 30% of patients do not remit after numerous treatment attempts. An absence of biomarkers generates an opportunity for a biomarker-based approach to aid clinical diagnostic criteria, and to enhance the understanding of neurobiological mechanisms mediating different MDD endophenotypes. Evidence suggesting that inflammatory disturbances may contribute to psychiatric symptoms has been presented. Circulating pro-inflammatory cytokines are elevated in patients diagnosed with MDD, indicating the importance of inflammatory biomarkers in MDD pathophysiology. Increased levels of interleukin-6 (IL-6) can reduce hippocampal neurogenesis and induce chronic inflammatory diseases and MDD-like characteristics (Sigvardsen et al., 2025). Recent studies observed elevated metabolism and activity within the amygdala, posterior thalamus, and prefrontal cortex among MDD patients. MDD-induced volumetric and functional alterations of these regions, as reported in previous studies, may occur due to reduced expression levels of brain-derived neurotrophic factor (BDNF). BDNF is a neurotrophin that plays roles in the growth and maintenance of neurons. Meanwhile, BDNF shows anti-inflammatory properties. BDNF levels drop in the brain and blood of MDD patients, and pharmacological restoration has beneficial effects on depression-like behaviours. Conventional medications for MDD are mostly tricyclic antidepressants, which inhibit the reuptake of serotonin or noradrenaline transporters, leading to secondary hypersensitivity of adrenergic and serotonergic receptors. The attention in developing new therapeutic medications is increasingly focused on phytomedicine, using plants as a source of new herbal drugs for treating depression with higher potency and lower toxicity (Berk et al., 2023; Hwang et al., 2023; Defar et al., 2023; Greenberg et al., 2023; Balogh et al., 2023).

Epigallocatechin-3-gallate (EGCG) is a polyphenol in powder form from the flavanol group in green tea. Recent studies have suggested several biological activities of EGCG, possibly leading to its use as a therapeutic agent for depression. Thus far, the pharmacological properties of EGCG have been characterized on multiple fronts, indicating its potential as a therapeutic agent for treating various diseases, including cardiovascular, metabolic, and neurodegenerative diseases (Ogłodek, 2022; Harsanyi et al., 2022; García-García et al., 2022).EGCG is hypothesized to ameliorate CUMS-induced depressive-like behaviour and reduce alterations in hypothalamic-pituitary-adrenal (HPA) activity and (perhaps) enhance levels of serotonin and its metabolites in the striatum and prefrontal cortex (Abdelmeguid et al., 2022). Furthermore, chronic unpredictable mild stress (CUMS) has been well documented as a model of choice for researching the etiology of depressive disorders and the mechanisms of antidepressants. Additionally, CUMS is accepted for evaluating the effectiveness of new diagnostic tools for use in preclinical studies. To explore the possible antidepressive effects of EGCG, the study used mice and Porsolt's forced swimming test model. It is hypothesized that the antidepressive effects of EGCG may involve modulation of the levels of IL-6, Corticosterone (CORT), BDNF, and neuronal damage (Zhang et al., 2024; Jia et al., 2024; Zhang et al., 2025; Sharma et al., 2024).

MDD is a chronic disorder of the central nervous system (CNS) that is characterized by feelings of sadness and hopelessness, loss of interest or pleasure in everyday activities, fatigue, sleep problems, feelings of worthlessness, and suicidal

thoughts. A biomarker-based approach has been proposed to support the clinic's diagnostic criteria. Such a methodology also aids in the identification of previously unknown neurobiological mechanisms that could mediate various endophenotypes of MDD (Abdelmeguid et al., 2022). Growing evidence supports the involvement of inflammatory disturbances in the mediation of some psychiatric symptoms. For example, MDD patients display higher circulating levels of proinflammatory cytokines, particularly IL-6. Increased levels of IL-6 impair cellular electrophysiology and hippocampal neurogenesis, indicating that this cytokine significantly contributes to the induction of MDD. Thus, IL-6 can serve as a therapeutic target for the treatment of MDD (Cutler et al., 2022; Cui et al., 2024; Nierenberg et al., 2023).

Studies on patients diagnosed with depression using magnetic resonance imaging (MRI) have revealed changes in the anatomy as well as the function of various brain regions, for example, the amygdala, the thalamus, the hippocampus, and the prefrontal cortex (PFC). Exposure to chronic stress could result in alterations induced by MDD in these regions, due to reduced expression levels of brain-derived neurotrophic factor (BDNF). BDNF, which has a variety of roles associated with neurogenesis, neuronal development, and plasticity, is implicated in several learning and memory functions. BDNF, along with its trophic function, has also been implicated in the pathogenesis of MDD. New-generation antidepressants, including selective serotonin reuptake inhibitors (SSRIs), selective serotonin/noradrenaline reuptake inhibitors, norepinephrine/dopamine reuptake inhibitors, and tricyclic antidepressants, are prescribed in clinical settings to MDD patients (Rong et al., 2025; Zhang et al., 2024).

1.1. Overview of depression

The area of research on depression is vast and covers numerous specific topics. However, in our thesis, we try to narrow to pinpoint the effects of dietary supplements, particularly EGCG, a green tea-derived flavonoid, on the depression-enhancing mechanism induced by chronic corticosterone treatment. EGCG is one of the main polyphenol components of green tea, and it has beneficial effects, attracting researchers' attention. The tea plant has been used for centuries in various cultures for its health-related effects. EGCG is a substance with a short half-life and many health benefits, including anti-inflammatory, anti-cancer, antioxidant, and anti-diabetic properties. It is a potent neuroprotectant and a major bioactive component of green tea. However, given the vastness of the research area, this section sheds light on depression, which is the main theme of the study, and some general mechanisms contributing to depression (Abdelmeguid et al., 2022; Zhou et al., 2025; Stoeva et al., 2025).

It is common to feel sad or depressed at times. When this feeling is prolonged for more than two or three weeks and leads to impairment in daily functioning, it is defined as MDD. Depression affects how people think, feel, and carry out their daily activities. Clinical symptoms include universal sadness, hopelessness, worthlessness, and helplessness, causing depressed individuals to perceive the surrounding world as negative no matter how positive it is. They can also develop different abnormal behaviours or conditions, such as insomnia, loss of appetite, impaired concentration, and suicidal ideation. This breadth of clinical manifestations makes MDD one of the most complicated and heterogeneous human diseases in the world. Despite years of extensive research, the molecular and cellular mechanisms underlying depression remain poorly understood, which constitutes a major roadblock in the quest for more effective therapies (Marx et al., 2023; Skosnik et al., 2023).

1.2. Role of antioxidants in mental health

Oxidative stress and inflammation affect mental health and have been implicated in the pathophysiology of depression and bipolar disorder. Antioxidant activity can protect against oxidative damage by free radicals, inflammation, lipid peroxidation, and receptor-mediated excitotoxicity. By reducing oxidative stress, flavonoids are effective as neuroprotective agents in model systems of depression (Vanhee et al., 2025; Yang et al., 2025; Rezaeezade_Roukerd et al., 2025).

1.3. Epigallocatechin gallate: sources and properties

Polyphenols are categorised into two distinct groups: phenolic acids and flavonoids. Flavanols and flavonols represent the predominant flavonoids present in tea. Green tea is characterised by its high flavonoid content, with catechins and catechin derivatives accounting for approximately 30% of its dry weight. The main catechins found in green tea are EGCG, epigallocatechin (EGC), epicatechin (EC) and epicatechin gallate (ECG). EGCG is the most important catechin in green tea (Figure 1).

Catechins, accompanied by galloyl moiety, catechins, inhibit proliferation and induce apoptosis in cancer cells through antioxidant properties and the modulation of several transcription factors. They might be considered a suitable alternative for the treatment of MDD and stress-induced memory dysfunctions.

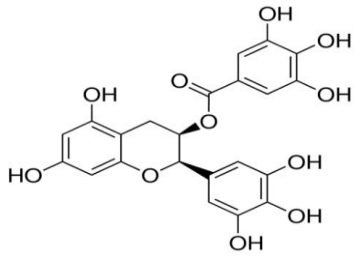

Figure 1. Chemical structure of epigallocatechin gallate

Four main pathways are considered to mediate the antidepressant activity of EGCG. The up regulation of NTRK2 expression in dentate gyrus cells promotes neurogenesis and cerebrovascular growth, increases the expression of SIRT1 and SIRT2 (Sirtuin 1 and Sirtuin 2), decreases QR/Aβ peptides, inhibits the growth of the gut bacteria Proanaerobacteroides, and inhibits both creatine kinases and GLUT4 translocation to plasma membranes (Ferland et al., 2013).

Tea is produced from the leaves of the Camellia sinensis plant, which is cultivated in many regions of the world. Its popularity is due to its flavour, low cost, local availability, and health benefits. It was reported that around 65% of the population in developing countries are already tea drinkers. It is estimated that black tea comprises about 96% of tea consumption worldwide, while green tea makes up about 3%. Per person, black tea consumption is estimated to be about a cup (300 ml) per day and green tea consumption about 0.3 cups (100 ml) daily. Regular consumption of tea daily provides a sufficient catechin intake for medicinal and health prevention. It has been suggested that dry tea amounted to about 2 g per individual per day (Abdelmeguid et al., 2022; Stoeva et al., 2025; Nakadate et al., 2023).

Tea polyphenols make up 25% to 35% of tea's dry weight. These polyphenols are catechins and flavonoids: benzopyran-4-one derivatives consisting of two aromatic rings and a heterocyclic ring (Afzal et al., 2022). EGCG accounts for approximately 50% of the total catechins in green tea. Tea catechins are known to have anti-carcinogenic, antioxidant, and antithrombotic effects. In recent years, tea catechins have also been found to have a multitude of health-promoting functions, including anti-diabetic, neuroprotective, anti-obesity, anti-inflammatory, and cardioprotective effects observed in humans, pigs, mice, rats, dogs, and monkeys. Among tea catechins, EGCG is the most studied and strongly favoured for its health-promoting functions (Assad et al., 2023; Shi et al., 2023).

2. Material and Methods

2.1. Ethical aspects of the study

This study was conducted with the approval of the Local Ethics Committee for Animal Experiments at Karadeniz Technical University, dated February 8, 2017, and numbered 53488718-162.

2.2. Experimental animals

In the present study, a total of 70 male and female mice of the Swiss Albino strain, with a body mass range of 25–39 g and aged between 2 and 5 months, were used. These mice were produced at the Laboratory of Animal Production and Surgical Research Centre of the Faculty of Medicine, Karadeniz Technical University.

2.3. Environmental conditions

The mice were maintained under standard laboratory conditions, which comprised a 12-hour light/12-hour dark cycle, at a constant temperature of 22±2 °C, and a relative humidity of 45–55%. Water and food were provided ad libitum. To mitigate the stress caused by handling, the mice were acclimated to handling prior to the experiment.

2.4. Experimental groups

Following a seven-day acclimatisation period, the experimental animals were randomly divided into seven groups (Table 1).

Table 1. Experimental Groups and Procedures Applied to the Groups

Group Name (n=10)	Drug administered	Dosage and route of administration	Duration of administration
Group 1 (Control)	Saline	Oral gavage	15 days
Group 2	EGCG	25 mg kg^{-1}; Oral gavage	15 days
Group 3	EGCG	50 mg kg^{-1}; Oral gavage	15 days
Group 4	EGCG	100 mg kg^{-1}; Oral gavage	15 days
Group 5	venlafaxine	25 mg kg^{-1}; Oral gavage	15 days
Group 6	moclobemide	100 mg kg^{-1}; Oral gavage	15 days
Group 7	paroxetine	4 mg kg^{-1}; Oral gavage	15 days

2.5. Conducting and scoring the challenging swimming test

On the first day of the experiment, 30 minutes after the final dose had been administered, the mice were placed individually into a tank containing tap water at a temperature of 23–25 °C. The tank was 40 cm high, 25 cm in diameter and 30 cm deep. The mice were allowed to spend 15 minutes in the

water. After being removed from the tank, the mice were dried and placed in cages with heat lamps above them. The water in the tank was changed before each mouse was placed in it. Twenty-four hours after this acclimatisation period, a six-minute forced swimming test was conducted, and the four minutes after the second minute of water contact were recorded using a Sony HDR-CX116E Full HD high-resolution camera. The mouse was then removed from the water, dried, and returned to its cage. This method was applied to all animals in the same manner (Yankelevitch-Yahav et al., 2015; Can et al., 2012). Subsequently, an impartial observer scored the swimming and immobility times by 5-second intervals based on the camera recordings. Immobility was defined as floating motionless with only the head above water, with no effort or escape behaviour (, e.g. diving or swimming). Very small movements made by the mice to keep their heads above water, along with a motionless posture on the water surface, were also considered immobility. Swimming was defined as active movement in which the animal did more than was necessary to keep its head above water, crossed the length of the water tank, and swam horizontally (Polesak et al., 2015; Sachdeva et al., 2011).

2.6. Drugs used in the experiment

In our study, Epigallocatechin Gallate (E4143 SIGMA-ALDRICH, Saint Louis, Missouri, USA), was prepared by dissolving 25 mg kg^{-1}, 50 mg kg^{-1}, and 100 mg kg^{-1}in distilled water. When not in use, it was stored at 2–8°C. Venlafaxine was dissolved in distilled water and administered at a dose of 25 mg kg^{-1} (Zhu et al., 2012). moclobemide was dissolved in distilled water at a dose of 100 mg/kg and administered (Liu et al., 2013). Paroxetine was dissolved in distilled water and administered at a dose of 4 mg kg^{-1} (Sharma et al., 2017; Ortiz-López et al., 2016). The applications were performed via gavage at a volume of 1 mg kg^{-1}between 9:00 AM and 12:00 PM.

2.7. Experiment protocol

Prior to the experiment, a total of 70 male and female Swiss albino mice were acclimatised to the research environment and the researcher, and then randomly assigned to seven groups. Their initial weights were measured and the appropriate drug doses calculated. The drugs were then administered orally via gavage for 14 days. One day before the final dose, the mice were allowed to swim for 15 minutes to acclimatize. They were then dried and placed in cages with heat lamps. The mice's weights were measured one hour after the final dose, and a six-minute swimming test was conducted. After all procedures had been recorded on video and the experiment had been completed, a researcher, who was blind to the groups, calculated the swimming and immobility times at 5-second intervals between the second and sixth minutes of the recordings. At the end of the experiment, the control group and EGCG 100 group mice were euthanised, and their whole blood (approximately 1–1.5 ml) was collected in ice-cooled heparinized centrifuge tubes and then centrifuged to produce serum (at 4°C at 3000 rpm for 10 minutes). The serum was then transferred to two new tubes for measuring corticosterone and IL-6 levels. Serum samples were stored at -80°C until analysis. All samples in the experiment were measured in the same assay to minimise inter-assay variation. Corticosterone levels were measured precisely according to the instructions provided in the enzyme immunoassay kits (CORT, ml001959, IL-6, ml002293, MLBIO, China). It is crucial to rule out any potential effect of the daily hormone rhythm on mouse hormone levels. For this reason, blood samples were collected at the same time, between 4:00 and 5:00 AM.

2.8. Statistical analysis

The data obtained in this study were analysed using the SPSS 20 software package. The Kolmogorov–Smirnov test was used to investigate whether the variables were normally distributed. When interpreting the results, a significance level of 0.05 was used, if $p < 0.05$, the variables were deemed not to come from a normal distribution; if $p > 0.05$, the variables were deemed to come from a normal distribution. To examine differences between groups, the Kruskal–Wallis H test was used when the variables did not come from a normal distribution. A significance level of 0.05 was used when interpreting the results; a p-value of <0.05indicatesa significant difference/relationship, while a p-value of >0.05 indicates no significant difference/relationship.

3. Results and Discussion

The weights of the mice, in grams, were measured prior to the administration of the drug and then again at the conclusion of the experiment. During the experiment, a total of seven mice from the venlafaxine, paroxetine, EGCG 25, and EGCG 100 groups perished due to asphyxiation from drug leakage into their lungs. These mice were excluded from the experimental results (Table 2).

The graph illustrating the mean weights of mice in all groups before and after treatment demonstrates that the mean weight of mice before treatment is lower than after treatment (Figure 2).

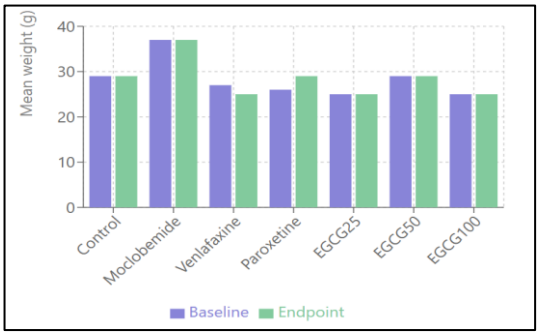

Figure 2. Pre- and post-treatment weight averages of mice in all group

Prior to the commencement of the experiment, no significant differences in weight were observed among the animal groups (Table 2).

Table 2. Average weights of the experimental groups at the beginning and end of the experiment.

Groups	Average weight (g)	
	Start of Experiment	End of Experiment
Saline	28.5 ± 1.71	28.9 ± 1.85
Moclobemide	36.7 ± 3.59	36.5 ± 3.37
Venlafaxine	27.3 ± 10.22	25.3 ± 12.25
Paroxetine	26 ± 17.78	29.3 ± 15.62
EGCG25	25 ± 13.45	25.2 ± 13.6
EGCG50	29 ± 2.78	29.2 ± 2.48
EGCG100	25.4 ± 13.88	25.5 ± 13.9

The analysis of the test results indicates a statistically significant difference in the pre- and post-treatment weights of mice in various groups ($p < 0.05$) (Table 2). This finding is particularly noteworthy within the control (saline) group, where a clear disparity is observed between the pre- and post-application weights. The post-application weights of the mice in the control (saline) group were significantly higher than their pre-application weights. In contrast, no significant difference was observed between the pre- and post-application weights of the mice treated with moclobemide and venlafaxine ($p>0.05$). Analogous outcomes were discerned in murine subjects administered to EGCG 25, EGCG 50, EGCG 100, and paroxetine, with no statistical differences between their pre- and post-treatment weights ($p > 0.05$).

The post-treatment weights of mice in the moclobemide group were significantly lower than those in the control (saline), venlafaxine, and EGCG 50 groups. The post-treatment weights of mice in the paroxetine group were significantly higher than those in the control (saline), venlafaxine, and EGCG 50 groups. A statistically significant difference was identified between the groups regarding post-treatment body weights ($p<0.05$) (Table 2).

The mean values and standard deviations of the immobile and mobile periods of mice in the groups are presented in Table 3.

Table 3. Average times mice remained inactive

	Mice's periods of immobility (s)
Control	236.80 ± 2.201
Moclobemide	192.60 ± 42.138
Venlafaxine	195.10 ± 73.49
Paroxetine	216.25 ± 5.726
EGCG25	219.3 ± 15.44
EGCG50	218.20 ± 5.07
EGCG100	171.60 ± 90.53

The following conclusion was drawn from the table that examined the descriptive information regarding the immobile and mobile periods of mice: the immobile periods were longer than their mobile periods.

In the analysis comparing the periods of immobility between groups, no significant difference was found between the moclobemide group and the venlafaxine group in terms of periods of immobility (χ^2 = 70.000, p = 0.283). A similar result was observed between the group of 25 and the group of 50, with no significant difference in the duration of immobility (χ^2 = 43.333, p= 0.331) ($p>0.05$). A significant difference was identified between the activity and inactivity durations in the 100 group (χ^2 =70.00, p= 0.026). Furthermore, a substantial discrepancy was identified between the activity and inactivity periods within the 50 group (χ^2 = 50.00, p= 0.002). No significant differences were identified between the other groups ($p > 0.05$) (Table 4).

In hormone tests conducted on the control group mice, serum corticosterone levels were observed to increase significantly at the end of the 15th day following the application of the strenuous swimming test. In mice administered 100 mg/kg/day of EGCG, a significant decrease in oxidative stress markers was observed. The mean CORT levels before and after the experiment are shown (Table 5, Figure 3).

In another analysis, IL-6 levels were measured in mice at the end of the experiment. The results showed that the IL-6 level in the EGCG 100 group was significantly lower than that in the control group after the Forced Swimming Test (Table 6, Figure 4).

Table 4. Test results regarding differences between groups based on the duration of immobility and mobility of mice

		Groups						Kruskal Wallis H Test		
		Sayı	**Mean**	**Median**	**Min**	**Max**	**SD**	**Mean Rank**	**H**	**p**	**Multiple Comparison**
Mice's periods of immobility	10	236.80	237.00	231.00	239.00	2.20	10	58.85	29.568	0.000	1-2 1-4 1-6 1-7
	10	192.60	201.50	94.00	232.00	42.14	10	21.25			
	9	216.78	230.00	153.00	238.00	28.11	9	38.94			
	8	216.25	215.50	208.00	228.00	5.73	8	23.31			
	10	219.30	223.00	180.00	236.00	15.45	10	35.00			
	10	218.20	218.00	207.00	223.00	5.07	10	29.25			
	8	214.50	215.00	205.00	220.00	4.57	8	20.56			
	65	216.40	219.00	94.00	239.00	23.41	65				
Mice's periods of activity	10	3.20	3.00	1.00	9.00	2.20	10	6.95	30.179	0.000	1-2 1-4 1-6 1-7
	10	46.40	36.00	8.00	146.00	40.88	10	45.80			
	9	24.33	17.00	2.00	87.00	27.63	9	28.11			
	8	23.75	24.50	12.00	32.00	5.73	8	42.44			
	10	20.70	17.00	4.00	60.00	15.45	10	30.10			
	10	21.80	22.00	17.00	33.00	5.07	10	36.05			
	8	25.50	25.00	20.00	35.00	4.57	8	45.44			
	65	23.60	21.00	1.00	146.00	22.86	65				

Table 5. Corticosterone levels after application

	Post-experiment control group corticosterone levels (pg mL^{-1})	Post-experiment corticosterone levels in the EGCG 100 group (pg mL^{-1})
Average	9387.75 ± 160.44	6147.06 ± 232.78

Table 6. IL-6 levels after application

	IL-6 level at the end of the experiment in the control group (pg mL^{-1})	IL-6 level at the end of the EGCG 100 group experiment (pg mL^{-1})
Average	158.98 ± 11.35	128.33 ± 11.44

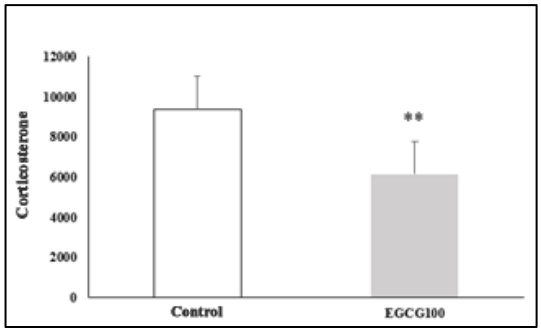

Figure 3. Average corticosterone levels before and after the experiment, *p<0.05 Data are presented as mean ± standard deviation compared to control.

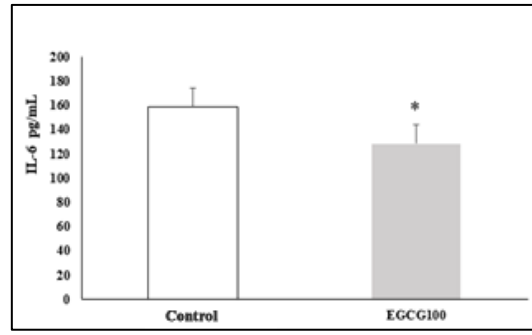

Figure 4. Mean IL-6 levels before and after the experiment, *p<0.05 Data are presented as mean ± standard deviation compared to control.

4. Discussion

In this study, the potential antidepressant effect of EGCG was investigated in mice using Porsolt's forced swimming test. When compared to classic antidepressant drugs with different mechanisms of action, the EGCG group demonstrated antidepressant effects at a level equivalent to these drugs. A statistically significant difference was observed when the weights of mice in the control (saline) group, and in the other groups were compared pre- and post-treatment ($p<0.05$). However, in the venlafaxine, moclobemide, paroxetine, EGCG 25, EGCG 50, and EGCG 100 groups.

In a comparable study, it was observed that the body weights of mice in the EGCG 25, 50, and 100 groups did not decrease compared to the control group under stress. In a similar vein, a study conducted by Sachdeva and colleagues in 2011 revealed that mice administered EGCG orally via gavage for 30 days did not experience weight loss when compared to the control group subjected to chronic fatigue and stress, instead, the mice gained weight (Raposo et al., 2015; Sachdeva et al., 2011). As demonstrated in Table 2 the present study revealed that in contrast to the moclobemide and venlafaxine groups, no decline in body weight was observed from the commencement to the conclusion of the experiment. This finding is consistent with the outcomes of previous studies.

In the second finding of our study, it was determined that EGCG, based on its potential antidepressant effect, shortened the immobility time and extended the activity time of mice in the forced swim test. It was demonstrated that EGCG exhibited antidepressant effects like those of other established antidepressant medications, including moclobemide, venlafaxine, and paroxetine. At the conclusion of the experiment, a statistically significant difference was observed between the groups with respect to the duration of immobility exhibited by the mice. The immobility times of mice in the saline group were significantly higher than those in the venlafaxine, moclobemide, paroxetine, EGCG 25, EGCG 50, and EGCG 100 groups as demonstrated in Figure 10. A study conducted by Zhu et al. in 2012 investigated the antidepressant effects of green tea polyphenols and reported a similar effect (Zhu et al., 2012). In this study, it was determined that green tea polyphenols significantly reduced immobility in the forced swimming test, resulting in antidepressant-like effects in mice. It was observed that the depression-like symptoms induced by the forced swimming test were alleviated by green tea polyphenols, which reduced HPA axis hyperactivity (Zhu et al., 2012). In a similar study, Liu et al. (2013) observed that tea polyphenols shortened immobility times in the forced swimming test and exhibited antidepressant effects.

A 2017 study by Sharma et al. examined the antioxidant responses as well as the HPA axis responses to EGCG in rats. It was found that a dose of 100 mg/kg of EGCG had immunomodulatory effects, reduced HPA axis hyperactivity, and exhibited antidepressant-like effects (Sharma et al., 2017). In a 2016 study, Ortiz-López and colleagues reported that 14 days of EGCG treatment had positive effects on the process of hippocampal neurogenesis and direct effects on neural precursors (Ortiz-López et al., 2016). The EGCG dose administered in this study ranged from 0.625 to 10 mg/kg, indicating that neuroprotective effects of EGCG were observed at low doses (Bhattacharya et al., 2015; Wang et al., 2012), and at high doses, it may act as a prooxidant and proapoptotic agent. It is evident from the available data that the antistress and antidepressant effects of the substance may be observed at doses of 25–50, and 100 mg/kg.

A subsequent comparison of the active movement times of mice following a challenging swimming test revealed that the active movement times in the venlafaxine, moclobemide, paroxetine, the EGCG 25, EGCG 50, and EGCG 100 groups were significantly higher than those of mice in the control group. In a study conducted by Yankelevich and colleagues in 2015, it was observed that EGCG significantly prolonged the activity duration of mice in a challenging swimming test (Yankelevich-Yahav et al., 2015).

As demonstrated in the research by Mazzio et al. (1998), green tea polyphenols have been found to reduce monoamine oxidase B levels and elevated levels of monoamines. Furthermore, EGCG has been observed to alter monoamine metabolites in iron-induced epileptic discharges. Considering these findings, it is proposed that green tea polyphenols and EGCG, may possess a mechanism that modifies the potential antidepressant activity of monoaminergic neurons in the central nervous system. In the present experiment, EGCG, which exhibits effects analogous to those of the reversible MAO inhibitor moclobemide, a classic antidepressant agent, may demonstrate antidepressant effects through the same mechanism. It can, thus, be hypothesised that EGCG exerts antidepressant-like effects through changes in neuroplasticity, like the mechanisms of hippocampal neurogenesis observed with classical MAO inhibitors.

At the conclusion of the experiment, cortisol levels in the control group were compared with those in the EGCG 100 group, which exhibited the most pronounced antidepressant effect. A significant decrease was observed in the EGCG 100 group in

comparison with the control group. The dysfunction of the hypothalamic-pituitary-adrenal axis, characterised by elevated plasma glucocorticoids (corticosterone in rodents, cortisol in humans), has been demonstrated to contribute to the development of depression (see Gold et al., 1999; Young et al., 1991). Corticosterone (CORT) is a glucocorticoid secreted by the cortex in mice. The release of this hormone occurs as a response to adrenocorticotropic stimulation. In murine models, CORT has been employed as a stress indicator. As Gallagher et al. (2007) demonstrated, patients with major depression exhibited higher plasma cortisol levels in comparison to healthy individuals. As demonstrated by Lee et al. (2023), an increase in serum corticosterone levels has been observed in mice subjected to an experimental depression model. In their 2013 study, Lee and colleagues demonstrated that catechins reduced corticosterone levels in mice with chronic depression induced by corticosterone administration. In a comparable study, the administration of green tea polyphenols was found to reduce serum corticosterone levels in mice exposed to a stressful swimming test.

At the conclusion of the experiment, serum IL-6 levels were measured in the control group and the EGCG 100 group, following a strenuous swimming test which exhibited the most significant antidepressant effect. Upon comparison of the values, it was determined that the IL-6 levels in the EGCG 100 group were significantly lower than those in the control group. Interleukins constitute a group of cytokines, which are secreted signalling molecules first observed in white blood cells known as lymphocytes. Interleukin 6 (IL-6) is a multifunctional cytokine that exerts both pro-inflammatory and anti-inflammatory effects, playing a role in both innate and adaptive immunity (Connor & Leonard, 1998). IL-6, which is categorised as a pro-inflammatory cytokine, can be released in response to exposure to a pathogen, tissue damage, or psychosocial stressors and serves as a mediator between the immune system and the brain. The increase in pro-inflammatory cytokines is generally regulated, with their effects being temporary, and they can be counteracted by anti-inflammatory cytokines. However, if an individual's exposure to stress becomes chronic, inflammatory effects may lead to behavioural changes, depression, and anxiety, among other neuropsychiatric disorders. The hypothesis that pro-inflammatory cytokines play a role in the etiopathogenesis of depression has been proposed (Connor & Leonard, 1998; Sharma et al., 2017). In studies that support these findings, Ahmed and colleagues observed that serum IL-6 levels decreased in mice treated with EGCG, suggesting that EGCG can regulate IL-6 (Ahmed et al., 2008).

5. Conclusion

In this study, EGCG doses were compared to other antidepressant agents in Porsolt's challenging swimming test. The EGCG dose of 100 mg/kg showed the strongest antidepressant effect. CORT and IL-6 levels were reduced in the EGCG 100 group compared to the control group at the end of the study. In their 2016 study, Nair and Jacob scaled this mouse dose to humans, finding that it is equivalent to a human dose of 486.48 mg of EGCG per day for a 60 kg adult (Nair & Jacob, 2016). This dose, obtainable by consuming 4-5 cups of green tea a day, clearly exhibits anti-inflammatory, antioxidant, and antidepressant effects, while also enhancing cellular immune prevalence and robustness in humans. Our study definitively shows that bioactive phytochemicals such as EGCG are useful agents for the treatment and prevention of psychosocial disorders and depression either alone or in combination with new drugs and nutraceuticals. Further development of the study is required to investigate the differences in the effects of EGCG in female and male mice and to examine whether it has genotoxic properties.

Author Contributions

All authors fulfil the criteria for authorship. A.S. and N.İ.K. conceived and designed the research, performed the statistical analysis, drafted the manuscript, and summarized the recommendations for the research. Made critical revisions to the manuscript for key intellectual content. All authors read and approved the final version of the manuscript and have agreed to the authorship and order of authorship for this manuscript.

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