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Research Article

Evaluation of Antidepressant Activity of Ethanolic Extract of Celery Leaves (*Apium graveolens* L.) Using Behavioral Tests in Male Mice

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ABSTRACT

Depression is a prevalent mental disorder associated with dysregulation of monoaminergic neurotransmission and chronic stress exposure. Apium graveolens L. (celery) leaves have been reported to possess neuroactive properties, including monoamine oxidase A (MAO-A) inhibition, suggesting potential antidepressant activity. The objective of this study was to evaluate the antidepressant-like effects of a 70% ethanolic extract of Apium graveolens leaves (EDS) in male Deutch Democratic Yokohama (ddY) mice using the Forced Swim Test (FST) following chronic mild stress (CMS) induction, and to determine an effective dose. Male ddY mice were randomly divided into five groups: negative control, positive control (amitriptyline 5.05 mg/kg body weight), and three EDS-treated groups receiving doses of 100, 150, and 200 mg/kg body weight. The treatments were administered orally in a once-daily. The presence of depressive-like behavior was evaluated through the utilization of the FST, with the duration of immobility being identified as the primary outcome measure. The data were analyzed using one-way analysis of variance (ANOVA) followed by appropriate post hoc tests. The results showed no significant differences in immobility time among groups during the initial treatment phase, indicating that short-term administration did not produce immediate antidepressant-like effects. However, after repeated administration, EDS at a dose of 200 mg/kg body weight significantly reduced immobility time and exhibited an antidepressant-like effect comparable to that of the positive control. Lower doses produced only partial behavioral responses. These findings indicate that the antidepressant-like activity of EDS is both dose-dependent and time-dependent.

Keywords: *Apium graveolens*; antidepressant; depression; FST; monoamine oxidase-A

INTRODUCTION

Depression represents a prevalent and incapacitating psychological disorder delineated by enduring melancholia, diminished interest, cognitive dysfunction, and modified emotional regulation, which collectively compromise daily functioning and overall quality of life. According to the World Health Organization, depressive disorders continue to be among the foremost contributors to disability on a global scale, significantly influencing the prevalence of years lived with disability (YLDs) and constituting a fundamental aspect of the worldwide disease burden, as evidenced by the recent global assessments on 2019 data regarding the impact of mental disorders (World Health Organization, 2017). At the neurobiological level, depression is associated with monoaminergic neurotransmission dysregulation, especially serotonin, norepinephrine, and dopamine. Additionally, maladaptive stress responses via the HPA axis are significant, with persistent hyperactivity identified as a crucial mechanism in depressive disorders (Cui et al., 2024).

Monoamine oxidase-A (MAO-A) is a crucial enzyme that degrades serotonin, norepinephrine, and dopamine in the brain. Elevated MAO-A levels have been associated with major depressive disorder (MDD) and are considered a target for antidepressant therapies that inhibit MAO-A. Positron emission tomography studies indicate increased MAO-A binding in various brain regions of MDD patients compared to controls, supporting the theory of monoamine depletion in depression (Patel et al., 2025).

The substantial significance of this discovery, coupled with the lack of alternative persuasive justifications for the depletion of monoamines during episodes of major depression, has culminated in the inference that increased MAO-A density represents the principal mechanism responsible for the reduction of monoamines in the context of major depressive disorder (Meyer et al., 2006). Elevated MAO-A expression is implicated in the metabolic regulation of serotonin and norepinephrine, serving as a fundamental pathogenic element in depressive disorders. Preclinical studies indicate heightened MAO-A levels in stress-related depression models, which enhance monoamine degradation and exacerbate depressive characteristics (Tie et al., 2025). Although synthetic antidepressants such as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) are clinically effective, their long-term use is often associated with adverse effects, including sedation, anticholinergic effects, weight gain, and treatment resistance, which may reduce patient adherence (Nurfahanum, 2022)

Saffron is favored for its safety and minimal side effects, rendering it appropriate for individuals sensitive to standard medications (Remali et al., 2024). Moreover, its antioxidant characteristics may provide additional health advantages (Chauhan et al., 2024). Saffron demonstrated promising results in the treatment of varying degrees of depression. Its side effects were comparable to those of established antidepressants such as imipramine and fluoxetine (Fazilat et al., 2024). Chinese herbal medicine is an established alternative treatment for depression in Chinese culture (Kang et al., 2023). St. John's wort (SJW) extracts are currently being used to treat depression of various degrees of severity. The medication exhibits superior tolerability and reduced adverse effects relative to standardized antidepressants (Canenguez et al., 2022). A multicenter randomized controlled trial demonstrates the antidepressant efficacy of Silexan, exhibiting favorable tolerability in comparison to both a placebo and a conventional selective serotonin reuptake inhibitor (SSRI) (Kasper et al., 2024).

Celery is a consumable therapeutic plant widely recognised for its culinary and medicinal applications, containing a diverse array of bioactive constituents, including flavonoids (including apigenin and luteolin), phthalides, and polyphenols, which have been documented to possess antioxidant, neuroprotective, and psychotropic properties. (Momin et al., 2002; Tan et al., 2023). Empirical research has demonstrated that celery extracts can modulate neurotransmitter systems and inhibit MAO-A enzymatic activity, thereby suggesting a potential role in therapeutic interventions for affective disorders (Boonruamkaew et al., 2017) Moreover, celery is documented in the Indonesian Herbal Pharmacopoeia as a phytotherapeutic species that contains flavonoids and volatile oils, thereby supporting its historical use in traditional medicine (Ministry of Health of the Republic of Indonesia, 2017). Celery leaves have been scientifically demonstrated to possess sedative properties. Celery fractions exhibit superior sedative effects in comparison to extracts. Furthermore, the water-methanol fraction administered at a dose of 200 mg/kg body weight is identified as the most efficacious, exhibiting the highest sedative potency. (Kusuma et al., 2018).

Celery is known to contain various bioactive compounds, particularly flavonoids, that contribute to its antioxidant and protective biological activities (Sánchez-Mateo et al., 2012). These antioxidant effects suggest that celery extracts may play an important role in protecting biological systems against oxidative stress–induced damage (Popovic et al., 2006). Apigenin, a flavonoid found in medicinal plants like celery, exhibits notable antidepressant-like effects in chronic stress-induced mouse models. The research indicated that apigenin markedly reduced MAO-A activity in brain tissue, enhancing the levels of monoamine neurotransmitters such as serotonin and norepinephrine. These biochemical alterations correlated with behavioral enhancements in standard depression assessments, reinforcing the hypothesis that flavonoid-mediated MAO-A inhibition may underlie the antidepressant efficacy of phytochemicals (Olayinka et al., 2023). Based on this data, the extract may possess antidepressant effects. The association. While certain antidepressants may induce sedation due to anticholinergic effects, sedation alone does not imply antidepressant efficacy. Consequently, behavioral evaluations were tailored to assess antidepressant-like activity specifically, excluding general central nervous system suppression (Belzung et al., 2015).

Several preclinical studies have reported that celery exhibits central nervous system activity, including sedative and antidepressant-like effects, depending on the extract type and dosage (Kusuma et al., 2018). Animal models of depression utilize stress or genetic methods to elicit depressive-like behaviors in rodents, facilitating the examination of symptoms similar to human depression and the assessment of potential antidepressants (Becker et al., 2021). Chronic unpredictable mild stress in mice induces depressive-like behaviors, evaluated through various behavioral tests, establishing it as a prevalent preclinical model for depression (Chen et al., 2025). Rodent models predicated on acute stress paradigms, including the forced swimming test and the tail suspension test, are employed extensively to investigate behaviors analogous to depression and to evaluate prospective antidepressant agents (Lu et al., 2025). FST is one of

the most widely validated behavioral models for evaluating antidepressant-like activity in rodents (Sahin, 2023). Anxiety and depression-related behaviors were assessed through the implementation of the forced swimming test and the open field test (Sahin et al., 2019).

Despite accumulating empirical evidence supporting the antidepressant properties of celery, numerous research deficiencies persist. Prior investigations have not definitively delineated the effective dosage range for a 70 % ethanolic extract derived from celery leaves, nor have they systematically assessed its antidepressant-like effects in male ddY mice. Additionally, discrepancies in dosage reporting and treatment duration across studies have constrained the comparability and reproducibility of results. Consequently, the current study seeks to assess the antidepressant-like effects of a 70 % ethanol extract of celery leaves administered at varying doses in male ddY mice, employing the FST subsequent to the induction of chronic mild stress, and to ascertain the most efficacious dose that elicits a behavioral response analogous to that of a standard antidepressant. This investigation presents novel evidence regarding the dose and time-dependent antidepressant-like effects of a 70 % ethanolic extract of celery leaves within a chronic mild stress paradigm, thereby identifying a potent dosage that yields behavioral outcomes akin to those produced by a standard antidepressant in male ddY mice.

METHODS

Ethical Approval

All experimental procedures involving animals were approved by the Ethics Committee of the Faculty of Pharmacy, Universitas Pakuan, Bogor, Indonesia (Approval No. 020/KEPHP-UNPAK/05-2022), and were conducted in accordance with internationally accepted guidelines for the care and use of laboratory animals.

Experimental Animals

Male ddY (Dutch Democratic Yokohama) mice (*Mus musculus*), weighing 25–30 g, were used in this study. Animals were housed under standard laboratory conditions (temperature 23–25 °C, 12 h light–dark cycle) with ad libitum access to food and water. Mice were acclimatized for 7 days before experimentation.

Experimental Design

This study employed a pretest–post-test control group experimental Design. A total of 25 mice were randomly divided into five groups (n = 5 per group): Negative control, Positive control (amitriptyline 5.05 mg/kg BW), Apium graveolens extract (EDS) 100 mg/kg BW, EDS 150 mg/kg BW, and EDS 200 mg/kg BW. Treatments were administered orally once daily throughout the experimental period.

Tools and Materials

Aluminium foil, stirring rods, beaker glasses (Pyrex), maceration bottles (Pyrex), Erlenmeyer flasks (Pyrex), measuring cups (Pyrex), mouse cages, flannel cloth, wire, cage boxes, silica crucibles, 250 mL measuring flasks, 40 mesh, trays, ovens, test tube racks, probes, test tubes, tubes over 25 cm tall and 10 cm wide, stopwatches, acetic acid, generic amitriptyline (Indofarma), distilled water, celery leaves with determination number B-1046/IV/DI.0507/4/2022 (BRIN), ether, 70% ethanol, $FeCl_3$, 2N HCl, concentrated H_2SO_4, Mg metal, Bouchardat reagent, Dragendrof reagent, and Mayer reagent, 25 male ddY strain (*Mus musculus*)

Methodology

Celery Extraction and Characterization

The dried celery powder was extracted by maceration using 70 % ethanol (1:10, w/v) at room temperature for 72 h, repeated three times. The extraction yield was calculated as the ratio of dried extract weight to initial dry plant material weight. Moisture content was determined using a gravimetric oven-drying method at 105 °C until constant weight, while total ash content was measured by incineration at 600 °C to assess inorganic residue (World Health Organization, 2011; Ministry of Health of the Republic of Indonesia, 2017

Preparation of Apium graveolens Leaf Extract

Dried celery leaf was macerated with 70 % ethanol (1:10, w/v) for 72 h at room temperature with periodic agitation. The maceration process was repeated three times. Combined filtrates were concentrated under reduced pressure using a rotary evaporator at 40–45 °C to obtain a viscous extract. The extraction yield was calculated based on the dry weight of plant powder.

Acclimatization Process

Before the commencement of the experiment, male ddY mice were acclimatized for 7 days. This process was intended to acclimatize the male mice to their new environment. Following the adaptation process, the male mice were utilized in the research process. A total of 25 mice, with a mean weight of approximately 20-30 g, were divided into five treatment groups, with each treatment group consisting of five mice.

Chronic Mild Stress (CMS) Induction

Following baseline behavioral assessment, mice were subjected to a Chronic Mild Stress (CMS) protocol for 7 days to induce depressive-like behavior.

Stressors included cage tilting, damp bedding, disruption of the light–dark cycle, dim lighting, and social isolation, applied unpredictably. Subsequent to the initial behavioral evaluation, murine subjects were exposed to a CMS regimen that was modified to conform to the rodent chronic unpredictable mild stress (CUMS) framework, wherein the animals are consistently subjected to unpredictable, mild stressors over an extended duration to elicit behaviors akin to depressive states. (Markov et al., 2022). The chronic mild stress model in mice is a validated preclinical tool for inducing depression-like behaviors and screening antidepressants. (Nollet et al., 2021). Animals are exposed to an array of mild stressors, including disruptive housing conditions and social stress, applied unpredictably across time to simulate chronic stress exposure and induce core depressive-like symptoms such as anhedonia and behavioural despair (Alqurashi, 2022).

Forced Swim Test (FST)

Antidepressant-like activity was assessed using the Forced Swim Test (FST). Each mouse was individually placed in a transparent glass cylinder (25 cm height, 15 cm diameter) filled with water to a depth of 16 cm at 23–25 °C. Each session lasted 7 minutes, and immobility time during the final 5 minutes was recorded. Immobility was defined as the absence of active escape-directed movements. On day 7 (post-test), immobility time was measured again using the FST under the same experimental conditions to evaluate changes in depressive-like behavior following treatment. All FST sessions were video-recorded to allow for accurate observation and blinded behavioral analysis. In the FST, immobility was operationally defined as the absence of active escape-directed behaviors, such as swimming, climbing, or vigorous limb movements, with the mouse exhibiting only minimal movements necessary to keep its head above the water surface. Passive floating without struggling was classified as immobility (Petit-Demoulière et al., 2005).

Each FST session was meticulously timed to last precisely 7 minutes, during which the test subjects' behavioral activities were systematically recorded with a sophisticated digital video camera. To effectively mitigate potential confounding effects arising from the initial acclimatization phase in the testing environment, it was determined that only the final 5 minutes of each session would be used for quantitative analysis and evaluation. The duration of immobility was quantified as the total cumulative time, measured in seconds, during which the murine subjects exhibited a state of complete immobility within the designated observation period assigned for the experiment. The duration of immobility was measured using either a stopwatch-based timing approach or a video analysis method, and the aggregated total immobility time recorded for each individual animal was subsequently used in statistical analyses (Serefko et al., 2025). Figure 1 provides a detailed schematic illustration of the procedural methodology employed during the FST in mice subjects.

Statistical Analysis

Data are expressed as mean ± standard deviation (SD). Normality was evaluated via the Kolmogorov–Smirnov test. Group differences were examined using one-way analysis of variance (ANOVA), followed by post hoc tests. The sequence of research methods is illustrated in Figure 2.

Figure 1. Schematic illustration of the Forced Swim Test (FST) procedure in mice.

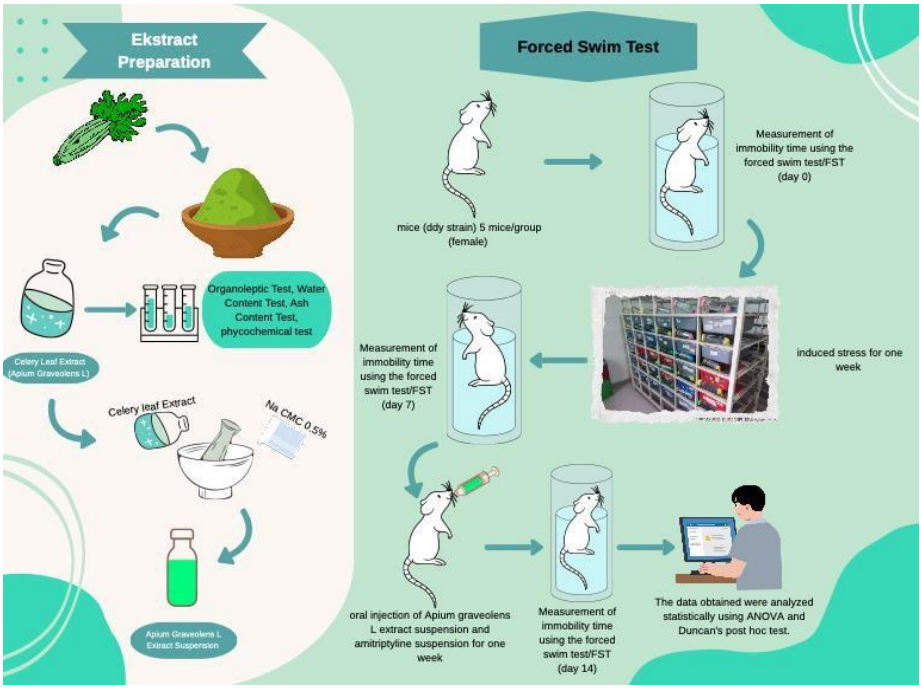

Figure 2. Illustration of work method flowchart

RESULTS AND DISCUSSIONS

Results of 70 % Ethanol Extraction of Celery Leaves

A total of 1 kilogram of fresh celery foliage was subjected to processing into a dry powder prior to the extraction procedure. The desiccated material was macerated with 70 % ethanol, yielding approximately 10 liters of macerate, which was subsequently concentrated using a rotary evaporator. This methodological approach yielded 135.5 grams of dried celery leaf extract utilizing 70 % ethanol. The extraction yield (19.11 %) was determined based on the dry weight of the celery leaf powder rather than the fresh plant material. Reporting the yield on a dry-weight basis mitigates variability attributable to moisture content in fresh foliage and facilitates more accurate comparison with other investigations employing analogous extraction methodologies.

Organoleptic Test Result

The organoleptic assessment of the 70 % ethanolic extract derived from celery leaves was performed to evaluate its physical and sensory properties. The extract manifested as a dense, viscous substance exhibiting a coloration ranging from dark green to brownish-green. It presented a unique aromatic scent typical of celery foliage and a slightly bitter flavor, which is frequently associated with flavonoids and various phenolic compounds. These organoleptic properties align with prior studies on ethanolic extracts of celery leaves and suggest satisfactory quality and stability for subsequent pharmacological investigations.

Forced Swim Test (FST) Result

Antidepressant-like efficacy was assessed using the FST. The primary outcome metric was immobility duration, which serves as an indicator of depression-like behavior in murine models. As illustrated in Table 1, disparities in immobility duration were observed across the experimental cohorts, indicating differential behavioral responses following treatment.

Table 1. Inhibitory zone width of *P. purpureum* extract against *S. aureus* and *E. coli*

Treatment group	Average of immobility time (seconds) week 1	Average of immobility time (seconds) week 2	Average of immobility time (seconds) week 3
Positive Control	228±78.934[a]	175.40±75.567[a]	187.40±153.074[a]
Negative Control	206±93.501[a]	199.20±74.687[a]	316±70.438[b]
EDS (100 mg/kg BW)	209.20±50.855[a]	207.80±44.014[a]	278.80±27.842[ab]
EDS (150 mg/kg BW)	211±94.570[a]	198.60±82.646[a]	225.40±62.240[ab]
EDS (200 mg/kg BW)	237.20±69.522[a]	229±40.454[a]	217.60±68.824[a]
Sig.	0.954	0.78	0.017

Note: The same superscript in the same column indicates no significant difference between treatments.

In week 1, the mean duration of immobility observed across all treatment cohorts was relatively consistent, and statistical analysis revealed no significant differences among the groups ($p = 0.954$), indicating comparable behavioral performance at this stage of testing (Kraeuter et al., 2019). This lack of early divergence suggests that neither the positive control, negative control, nor the EDS-treated groups at the tested doses produced measurable antidepressant-like effects during the initial phase of treatment, which is consistent with reports that many antidepressant interventions require sufficient exposure duration to elicit behavioral changes (Slattery & Cryan, 2017). Importantly, the absence of statistically significant differences among groups during early testing phases is commonly interpreted as evidence of baseline behavioral homogeneity rather than an absence of pharmacological potential (Cryan & Holmes, 2015). Methodological reviews of the Forced Swim Test emphasize that equivalence across groups prior to or early during treatment is expected and desirable, as it supports internal validity and reduces confounding by pre-existing behavioral variability (Belzung et al., 2015). Furthermore, the sensitivity of depression-related behavioral assays depends on factors such as treatment duration, dosing regimen, and sample size, and insufficient exposure time may limit the detection of antidepressant-like effects (Commons et al., 2017). Collectively, these findings indicate that the present nonsignificant result reflects uniform baseline behavioral profiles across experimental groups, supporting the need for extended treatment or additional behavioral endpoints to fully evaluate treatment-related antidepressant efficacy (Kraeuter et al., 2019).

In week 2, The findings persistently demonstrate the absence of statistically significant differences among the experimental groups ($p = 0.78$), which aligns with existing literature indicating that antidepressant-like effects in the Forced Swim Test (FST) may not be readily observable during the initial or intermediate treatment phases, particularly within paradigms characterized by chronic stress (Slattery & Cryan, 2017; Kraeuter et al., 2019). Notwithstanding the discerned variability in the immobility duration measurements, the categorization of all groups under the identical statistical letter designation (a) signifies overlapping behavioral responses and embodies the anticipated within-group variability typically documented in rodent FST investigations (Belzung et al., 2015). These findings imply that the administration of EDS for a duration of up to two weeks was inadequate to elicit statistically significant behavioral modifications in the FST, corroborating evidence that numerous antidepressant interventions—particularly those involving phytotherapeutic or non-synthetic agents—necessitate extended treatment periods to yield quantifiable antidepressant-like effects in preclinical models (Nollet et al., 2021).

In contrast, in week 3, statistical evaluation revealed notable disparities among treatment cohorts ($p = 0.017$), signifying that the experimental intervention effectively yielded measurable behavioral outcomes in the FST, which is a rigorously validated and sensitive methodology for identifying stress-induced depressive-like behavior subsequent to chronic stress exposure (Gençtürk & Ünal, 2024). The negative control cohort demonstrated the most prolonged immobility duration and was categorized under a separate statistical letter group (b), indicative of the most pronounced depressive-like condition, in alignment with extensive literature substantiating that increased immobility in the FST is associated with maladaptive stress-coping mechanisms and elevated levels of behavioral despair (Slattery & Cryan, 2017; Commons et al., 2017). In aggregate, these results affirm the effective elicitation of a depressive-like phenotype in the experimental subjects and establish a vital reference point for assessing treatment efficacy, as validated models of depression with distinctly differentiated control groups are paramount for interpreting antidepressant-like effects and ensuring the internal validity of preclinical pharmacological investigations (Cryan & Holmes, 2015; Belzung et al., 2015; Becker et al., 2021).

The cohort administered a dosage of 200 mg/kg BW of EDS exhibited significantly reduced immobility durations and was categorized alongside the positive control, indicating that at this dosage, EDS elicited an effect comparable to that of established antidepressant pharmacotherapies (Gómez-Patiño et al., 2025). Conversely, the EDS cohorts receiving doses of 100 and 150 mg/kg BW were classified within a transitional category (ab), implying an observable trend towards decreased immobility that had not yet reached equivalence with the positive control. This finding is congruent with research documenting modest or subthreshold behavioral responses at diminished doses of phytochemical extracts (Fazilat et al., 2024). This observed dose-dependent relationship is consistent with contemporary preclinical and review literature suggesting that numerous plant-derived antidepressant candidates necessitate adequate dosing and/or extended exposure to elicit substantial antidepressant-like effects in the forced swim test and analogous paradigms (Remali, 2024; Cui et al., 2025).

Overall, these results indicate that the antidepressant effects of EDS are both time-dependent and dose-dependent, with the most pronounced efficacy observed following prolonged

administration at higher doses, a pattern that has been consistently reported for plant-derived antidepressant candidates evaluated in chronic stress and FST models (Nollet et al., 2021; Gençtürk & Ünal, 2024). The requirement for extended treatment duration and adequate dosing to elicit significant behavioral improvement is well documented in preclinical studies, as neuroadaptive processes underlying antidepressant responses, such as monoaminergic modulation, neuroplasticity, and stress-axis normalization, typically develop gradually over repeated exposure rather than acutely (Becker et al., 2021). Consequently, the present findings support the view that treatment duration and dose are critical determinants of EDS's pharmacological efficacy in reducing depressive-like behavior and reinforce EDS's potential as a promising natural antidepressant candidate when administered under optimized dosing regimens (Frost et al., 2025).

The findings suggest that EDS exhibits antidepressant effects influenced by both duration and dosage, with maximal efficacy observed after extended use at elevated doses—similar results have been reported for various plant-based substances in chronic stress and FST studies (Molendijk et al., 2021). Recent mechanistic and preclinical studies indicate that prolonged treatment and sufficient dosing are necessary for observable behavioral enhancement. Neuroadaptive processes, such as BDNF elevation, synaptic alterations, and HPA-axis normalization, generally manifest with repeated exposure rather than immediate effects (Rosas-Sánchez et al., 2024). The current results align with existing literature that demonstrates dose- and time-dependent responses to antidepressants from flavonoid and phytochemical sources. This highlights the necessity of optimizing dosage and treatment duration in preclinical studies (Alizadeh et al., 2024).

In contrast, a significant difference among groups was detected in the third week of treatment ($p = 0.017$), consistent with evidence that antidepressant-like effects in the FST typically emerge after sustained treatment rather than during early exposure periods. The negative control group exhibited the highest immobility time, confirming the persistence of depressive-like behaviour and validating the effectiveness of the chronic stress–based experimental model, as prolonged stress exposure reliably increases immobility in the FST (Kraeuter et al., 2019). Meanwhile, the positive control showed a significantly lower immobility time, which aligns with well-documented findings that clinically effective antidepressants reduce immobility following repeated administration in rodent models (Mezadri et al., 2011). Collectively, these findings support the sensitivity of the FST for detecting chronic antidepressant effects and are consistent with its continued use as a predictive behavioural model for antidepressant efficacy, particularly when treatment duration and dosing are appropriately optimized (Can et al., 2012).

Notably, EDS administration led to a dose-dependent decrease in immobility time at week three, mirroring patterns in preclinical antidepressant studies utilizing the Forced Swim Test after chronic treatment. The highest dose (200 mg/kg BW) yielded effects comparable to positive controls, aligning with findings that high doses of plant extracts can produce antidepressant-like efficacy akin to standard pharmacological agents in rodent models. This suggests that EDS can provide significant antidepressant-like effects at an appropriate dosage and duration, corroborating recent systematic reviews which emphasize the importance of dose and time in the efficacy of phytotherapeutic antidepressants.

Such dose-dependent behavioral enhancements have been regularly documented for plant extracts abundant in bioactive secondary metabolites, which affect monoaminergic neurotransmission and stress-related signaling pathways in contemporary preclinical research. The intermediate responses noted in the EDS 100 and 150 mg/kg BW groups, categorized in the transitional Duncan group (ab), signify partial efficacy, often interpreted as subthreshold antidepressant-like activity at lower doses. This pattern indicates that lower doses may initiate neurobiological changes linked to antidepressant action, but these changes may not suffice to elicit a fully expressed behavioral response, particularly in chronic stress contexts. Gradual neuroadaptations, such as BDNF upregulation, HPA axis modulation, and inhibition of monoamine oxidase, have been proposed as mechanisms that require sustained exposure and appropriate dosing, as supported by recent neurobiological and pharmacological literature.

Overall, the study's findings indicate that EDS exhibits a time- and dose-dependent antidepressant-like effect, with notable efficacy after prolonged high-dose administration. These results underscore the significance of treatment duration in assessing herbal antidepressants and endorse EDS as a candidate for further research. Future investigations should examine the molecular mechanisms underlying this behavioral effect, particularly its influence on monoaminergic pathways, neurotrophic signaling, and stress-related hormonal regulation, to clarify its therapeutic potential. Similar observations have been noted for various natural products, in which only certain dose ranges yield significant antidepressant effects, suggesting that subtherapeutic doses may not alleviate immobility or could even mimic untreated controls (Castrén et al., 2021).

In accordance with this study, celery extracts display antidepressant-like activity in rodents by reducing immobility and influencing oxidative stress and neurotransmitter systems. Celery essential oil at doses of 50-100 mg/kg body weight significantly decreased immobility in the FST and improved antioxidant status. A recent report specifically assessed the antidepressant effects of celery in mice, revealing significant reductions in immobility in both the Tail Suspension Test and the FST. This reinforces the notion that higher doses, such as 200 mg/kg body weight, can produce substantial antidepressant-like effects comparable to conventional pharmacological treatments (Mehrdad et al., 2019).

Amitriptyline, a TCA, primarily increases synaptic monoamines by inhibiting serotonin and norepinephrine reuptake, a mechanism well-documented in the pharmacological literature (Taylor et al., 2021; Stahl, 2023). As a tertiary amine TCA, it also demonstrates significant affinity for various receptors, influencing its sedative and anticholinergic side effects (Brunton et al., 2023). Celery exhibits antidepressant-like effects due to its flavonoid content, particularly apigenin and luteolin, which have shown neuroprotective and mood-regulating effects in recent studies. Apigenin has been shown to enhance adult neurogenesis and neuronal differentiation, both of which are significant for antidepressant efficacy and neuroplasticity (Olasehinde et al., 2024).

CONCLUSION

Based on the findings derived from this research, the proposition that a 70% ethanolic extract of Apium graveolens leaves demonstrates antidepressant-like properties is only partially corroborated. The extract failed to elicit notable antidepressant-like effects after a brief administration period; nevertheless, following repeated dosing, a marked decrease in immobility duration was observed at an appropriate dosage, with 200 mg/kg body weight recognized as the most efficacious compared to the established antidepressant, amitriptyline.

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CONFLICT OF INTEREST

All authors declared no conflict of interest in the manuscript.

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