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EXPLORING NEUROPHARMACOLOGICAL EFFECTS OF *PRUNUS BRIGANTINA* AND *MANGIFERA INDICA* FRUIT EXTRACTS: AN EXPERIMENTAL STUDY ON ANXIETY AND DEPRESSION IN MICE

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Abstract
Traditional medicine and natural products have historically played a pivotal role in combating various ailments. With approximately 70% of the global population relying on herbal medicines for primary healthcare needs, these remedies represent an enduring reservoir of therapeutic compounds. Amidst this landscape, depression emerges as a multifaceted condition, intricately intertwined with neurotransmitter imbalances, often refractory to conventional treatments. Despite the prevalence of allopathic antidepressants, characterized by modest response rates and significant side effects, the exploration of alternative therapeutic modalities remains paramount. This study delves into the neuropharmacological effects of ethanolic fruit extracts from *Prunus brigantina* and Mangifera indica, shedding light on their potential to address depression and related disorders. Through meticulous experimentation involving behavioural assays, including the cage crossing test, open field test, head dip test, forced swimming test, stationary rod test and light and dark field test statistically significant outcomes (*$P < 0.05$, **$P < 0.01$) were observed. Intriguingly, *Prunus brigantina* exhibited anxiolytic and calming properties, contrasting with the stimulating effects of *Mangifera indica*. These findings not only underscore the intricate interplay between botanical extracts and behavioral responses but also offer promising avenues for the development of novel therapeutic interventions, bridging the chasm between traditional wisdom and contemporary pharmacology.

Keywords: *Mangifera Indica*, Prunus Brigantina, depression, CNS, Complementary and Alternative Medicine (CAM).

INTRODUCTION:

Diving into the vast world of healthcare, we encounter a realm often overlooked by conventional medicine: Complementary and Alternative Medicine (CAM). CAM encompasses a diverse array of medical practices existing outside the mainstream healthcare systems of nations worldwide. From acupuncture to herbal remedies, CAM offers a holistic approach to wellness, drawing on ancient traditions and natural remedies. CAM isn't just a supplement to traditional medicine; it stands as a standalone treatment option, captivating the interest of millions globally [1]. In Western nations, CAM usage ranges from 9.8% to a staggering 76% over 12 months, while in East Asia, countries like Malaysia, South Korea, and Japan boast over 50% utilization rates [2]. Why the fascination with CAM? For many, it's the promise of a more natural, holistic approach to healing compared to allopathic medicine. Others are drawn to its affordability and accessibility. Notably, CAM's impact extends beyond physical health to mental well-being. Studies suggest CAM therapies, such as exercise and herbal medications, can effectively alleviate mental stress and disorders[3]. Individuals experiencing moderate mental stress in the US are more likely to turn to CAM for relief. However, CAM isn't a one-size-fits-all solution. Factors like gender, education, income, and ethnicity influence its usage patterns, with higher-income nations exhibiting greater prevalence [4].

Herbal medicine, a cornerstone of CAM, has witnessed a resurgence in popularity. From Europe to Australia to the United States, the use of herbal remedies has surged in recent decades. Drawing on centuries-old practices, herbal medicine taps into the therapeutic properties of plants, enriching our understanding of ancient healing traditions[5].

Take, for instance, Mangifera indica, commonly known as the mango tree. Beyond its delectable taste, mangoes boast an impressive array of pharmacologically active compounds, offering anti-inflammatory, antioxidant, and neuroprotective properties. Research into mango's potential health benefits continues, hinting at its promising role in natural medicine[6].

Similarly, Prunus brigantina, the humble apricot, packs a punch in terms of B-group vitamins essential for neurological health. With its potential to prevent neous system disorders, apricots stand as a testament to nature's healing prowess [7].

As we navigate the complexities of modern healthcare, CAM emerges as a beacon of hope, bridging ancient wisdom with contemporary science. Whether it's the soothing touch of reflexology or the therapeutic power of herbal teas, CAM invites us to embrace the healing wonders of nature, unlocking a world of possibilities for holistic well-being [8].

MATERIALS AND METHODS

Chemicals and Reagents

The study used different chemical agents and solvents, including absolute ethanol, distilled water, Caffein 1g, all are of standard analytical grade chemical.

Experimental animals

The study used 84 albino Swiss mice from the University of Karachi animal house. The animals were given a standard diet and water and handled according to welfare guidelines. The study was approved by the University of Karachi's ethical review board. The animals were housed separately and maintained under standard conditions. Before the study, the animals underwent an overnight fast but had unrestricted access to fresh water.

Origin of plant material
Fresh fruits of Mangifera indica/*Prunus brigantina* collected from the University of Karachi. The plant was verified, and a voucher specimen (MIF-04-17/19) has been deposited at the University to be used for future reference and approval purposes.

Synthesis of plant extract
The Mangifera indica/*Prunus brigantina* fruits have undergone a process of pounding with tap water to remove impurities followed by hand-cutting into small pieces and then shade drying. The resulting dried fruit was then finely ground into powder and parted into two portions for extraction.

Synthesis of 80% Ethanol Fruit Extract of *Mangifera indica* and Prunus brigantina:
To obtain the fruit extract, 100 grams of dried fruit powder was soaked in 400 millilitres of 80% ethanol for three days. The mixture was then filtered and concentrated using a Rotavapor at 40°C. Finally, the extract was freeze-dried and stored in a desiccator until needed [9] .

CENTRAL NERVOUS SYSTEM ACTIVITY
Cage crossing test:
Cage crossing equipment was used to evaluate exploratory and anxiolytic activities. A transparent perspex home cage with a sawdust-covered floor was employed. After a 5-minute acclimatization phase, the number of cage crossings was recorded for 30 minutes to compare the difference within groups. The test was conducted in a quiet, isolated environment [10].

Open Field Test:
The Open Field Test is used to assess exploration, mobility, and anxiety in mice. The testing apparatus consists of a square surface enclosed by walls. Each mouse undergoes individual evaluation for 10 minutes, during which they are granted freedom to explore the arena. Following the assessment, the mice are returned to their respective housing enclosures. The Open Field Test provides crucial insights into the exploration, mobility, and anxiety levels of mice [11].

Stationary rod test:
The study entailed positioning an animal on a stationary rod apparatus with a 5/8" diameter and 2" length horizontal steel rod situated 18" above a table surface. The table boasted platforms on both ends. Prior to conducting observations, mice were trained to traverse from the center of the rod to the platforms on either side. The duration each mouse required to maintain balance on the rod and reach the designated platform was meticulously recorded. The study was conducted on a daily basis for 5 days [12].

Head Dip Test:
The head dip test measures exploratory behavior in mice, linked to anxiety. It uses a wooden container with 4 holes on each side. Mice are transferred to the lab in their original cages to reduce stress. Each mouse explores the device for 10 minutes, and head pokes are recorded. The equipment is cleaned with ethanol after each observation to prevent scent cues from previous mice[13].

Light and dark box test:
The light and dark box test is a tool used to assess anxiety-related behaviors in mice. It comprises two compartments of equal dimensions, one brightly lit and perceived as aversive, and the other dark, offering a sense of safety. An increase in the time spent in the light area and transitions between compartments signifies a decrease in anxiety, making it a reliable method for evaluating anxiety without prior animal training[14].

Forced Swim Test:
In 1977, Porsolt introduced a forced swim test to study antidepressant effectiveness on rats. The test involves placing a rat in a glass booth with 8 liters of water and recording the duration of its struggle to escape. The faster the rat surrenders and becomes motionless, the quicker it displays depressive-like symptoms. The test is considered valid as the administration of an antidepressant prolongs the duration of the rat's resistance and attempts to escape[15]

Statistical analysis:
Statistical analysis included one-way ANOVA, post-hoc Tukey test, and SPSS version 22. Significance levels: $p<0.05$ (significant), $p<0.01$ (highly significant), and $p<0.001$ (very highly significant).

RESULTS

Neuro Exploratory Effects:
The exploratory effects of mice were evaluated using the cage cross, open field, and head dip tests. The results were compared with those of a negative control group of untreated mice and a positive control group treated with caffeine at a standard dose of 2 mg/kg, which serves as the standard medication. Mean observations ±SEM are presented in Table 1 to display the findings in figure 1, 2 and 3.

Cage Cross-Test, Open Field Activity, and Head Dip Test:
Initial observations revealed a control group baseline of 32.27±1.2 in the cage cross-test. However, administration of *Prunus brigantina* and *Mangifera indica* extracts at varying dosages (200 mg/kg and 400 mg/kg) resulted in a remarkable dose-dependent enhancement in motor performance. Notably, the higher dosage of *Mangifera indica* rivalled the standard caffeine dosage (2 mg/kg), showcasing comparable outcomes.

Similarly, in the open field test, the control group exhibited results of 130±1.15. Yet, doses of 200 mg/kg and 400 mg/kg of *Prunus brigantina* and *Mangifera indica* showcased boosted motor function in a dose-dependent manner, surpassing even the efficacy of caffeine at the standard dosage. Even at lower doses, the ethanolic fruit extracts exhibited significant effects, hinting at their potent therapeutic potential.

Head dip values for both *Prunus brigantina* and *Mangifera indica* extract in the control group were initially recorded at 13.98±0.38. However, administration of these extracts at doses of 200 mg/kg and 400 mg/kg resulted in substantial improvements in motor function. Notably, the lower dosage of *Mangifera indica* outperformed the standard caffeine dosage, while *Prunus brigantina* at a higher dosage of 400 mg/kg yielded significant responses.

Table 1: Effect of *Prunus brigantina* and *Mangifera indica* extracts on Motor Function and Neurological Health

Groups	Dose	Cage-Cross-Test	Open Field Activity	Head Dip Test
		No.of central square cross in 30 min	No. of cage crossed in 10 min	No. of head dips in 10 min
DW	10 mL	32.27±1.2	130±1.15	13.98±0.38
Caffein	2 mg/kg	50.61±1.7	201±2.34	30.72±2.01
PB 1	200 mg/kg	45.87±1.4	197±1.91	27.09±2.12
PB 2	400 mg/kg	48.72± 1.8	210± 2.57	42.34±0.65
MIEE 1	200 mg/kg	52.13±2.2	250±2.25	52.97±2.15
MIEE 2	400 mg/kg	55.53±1.65	320±3.13	80.34±2.09

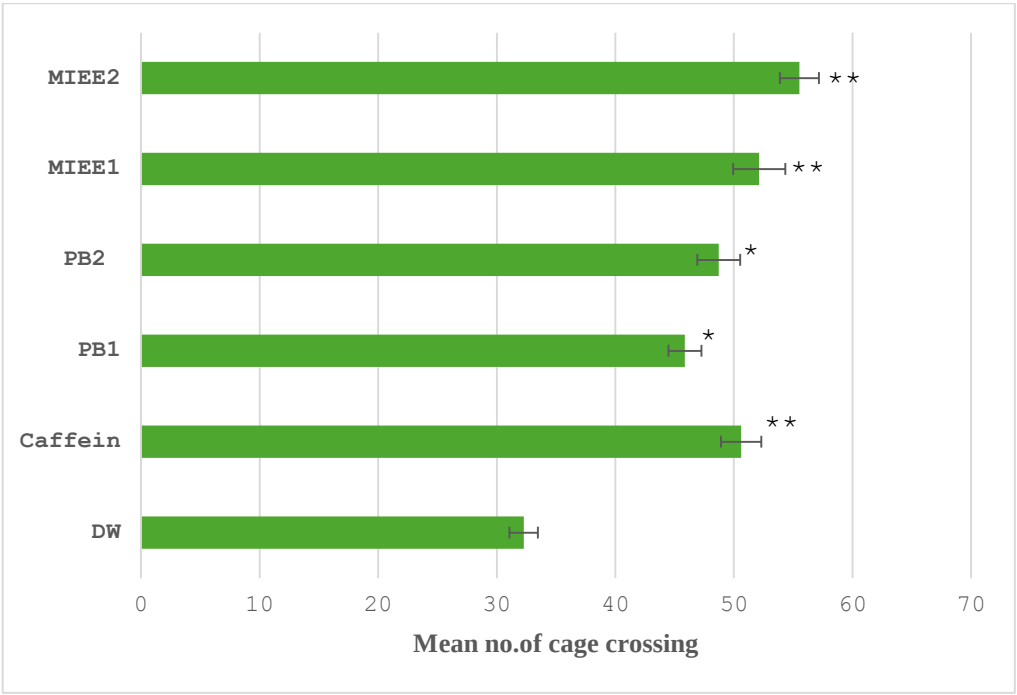

Figure 1: Number of cage crossings by mice, n = 5. The data is presented as the mean ± standard error for each group, with five mice per group. Statistical significance is denoted as *** for p<0.001, indicating high significance, and * for p ≤ 0.05, indicating significance. The groups include *Mangifera indica* ethanol extract at 200 mg/kg (MIEE1), *Mangifera indica* ethanol extract at 400 mg/kg (MIEE2), *Prunus brigantina* ethanol extract at 200 mg/kg (PB1), *Prunus brigantina* ethanol extract at 400 mg/kg (PB2), distill water (DW), and Caffein.

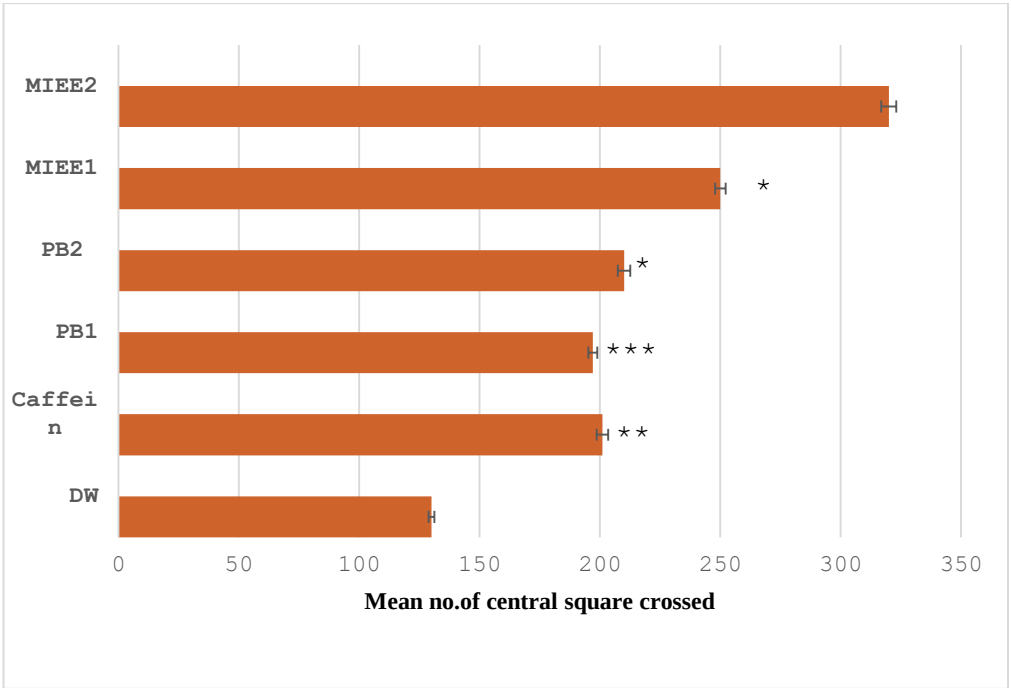

Figure 2: Number of central squares crossed by mice, n = 5. The data represents the mean values ± standard error obtained from five mice in each group. Statistical significance was denoted as *** for p<0.001, indicating high significance, and * for p ≤ 0.05, considered significant. The experimental groups included *Mangifera indica* ethanol extract at doses of 200 mg/kg (MIEE1) and 400 mg/kg (MIEE2), *Prunus brigantina* ethanol extract at doses of 200 mg/kg (PB1) and 400 mg/kg (PB2), along with a control group administered with distilled water (DW) and Caffein.

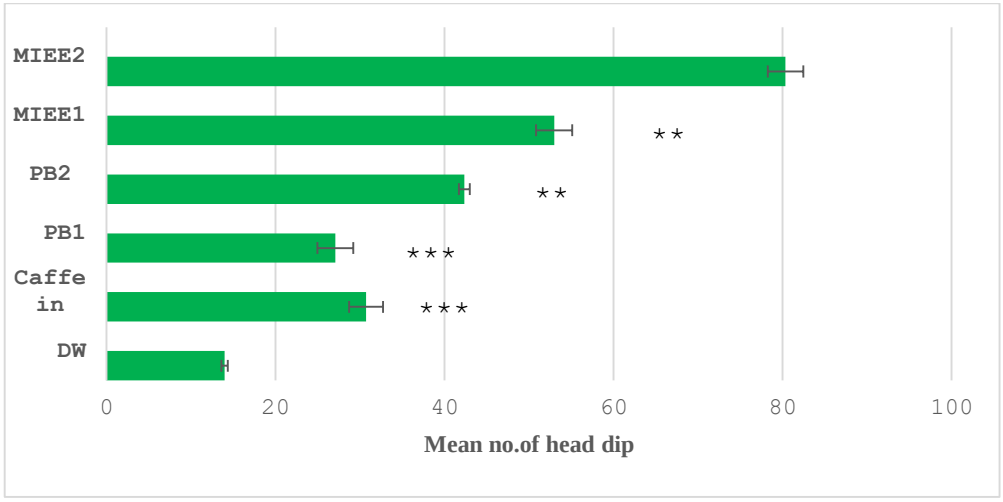

Figure 3: Number of heads dipped by mice, n = 5. The data represents the mean ± standard error obtained from five mice per group. Statistical significance was denoted as *** $p<0.001$ for highly significant results, and *$p \leq 0.05$ for results considered significant. The experimental groups included *Mangifera indica* ethanol extract administered at doses of 200 mg/kg (MIEE1) and 400 mg/kg (MIEE2), *Prunus brigantina* ethanol extract administered at doses of 200 mg/kg (PB1) and 400 mg/kg (PB2), as well as distilled water (DW) and caffeine.

Anti-depression effect:

Force Swim Test:

The forced swimming test measured mobility time, and mobility time was measured to see if there was striving or carefree activity. The mean observations SEM were used to show the results. At large doses, both fruit extracts provide superior effects. a rise in the mobility time demonstrated enhanced swimming. Table 2 and Fig. 4 indicate the struggle effect.

Table 2: Anti-Depressive Effect

Groups	Dose	Mean force swim Time in seconds
Control	10 mL	250.43±2.15
Caffein	2 mg/kg	310.8±1.57
PB 1	200 mg/kg	333.14±2.1
PB 2	400 mg/kg	350.67± 3.1
MIEE 1	200 mg/kg	300.91±1.8
MIEE 2	400 mg/kg	327.06±2.13

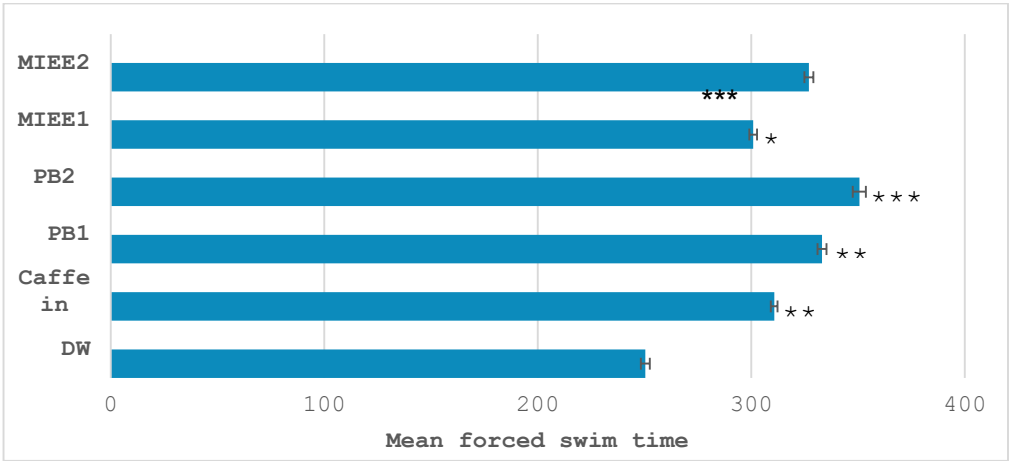

Figure 4: Mobility time in force swimming test by mice, n = 5. The data represent the mean ± standard error of five mice per group. Statistical significance was determined as *** $p<0.001$,

indicating high significance, while *p ≤ 0.05 denoted significance. Treatments included *Mangifera indica* ethanol extract at doses of 200 mg/kg (MIEE1) and 400 mg/kg (MIEE2), *Prunus brigantina* ethanol extract at doses of 200 mg/kg (PB1) and 400 mg/kg (PB2), as well as distilled water (DW) and caffeine.

Neurostimulator effect Stationary Rod Test and The Light and Dark Field Test:

The neurostimulator effects of the treatment group were evaluated through two tests: the stationary rod test and the light and dark field test. In the stationary rod test, motor coordination was assessed by recording the meantime taken to cross a rod, with standard error of the mean (SEM) provided. Results indicated that *Prunus brigantina* ethanol extract (PB) at doses of 200 mg/kg and 400 mg/kg showed improvements in motor coordination compared to the control group, with significant increases in crossing time. *Mangifera indica* ethanol extract (MIEE) also exhibited improvements, albeit to a lesser extent. In the light and dark field test, motor activity was measured by the percentage of time spent in the light field. PB at 400 mg/kg demonstrated the highest increase in light field exploration, followed by the caffeine group, while MIEE showed a decrease in light field exploration at both doses. These findings suggest differential neurostimulator effects of the tested substances on motor coordination and exploration behavior in mice as shown in table 3 and fig 5 and 6.

Table 3: Effects of Different Treatments on mice Behavior in Stationary Rod and Light-Dark Field Test

Groups	Dose	Stationary Rod Test (Mean Time in seconds ± SEM)	Light and Dark Field Test (% Time Spent in Light Field ± SEM)
DW	**10 mL**	**262.34 ± 1.3**	**30.23 ± 2.92**
Caffeine	**2mg/kg**	**302.61 ± 1.8**	**40.72 ± 2.66**
PB 1	**200 mg/kg**	**317.87 ± 2.35**	**45.09 ± 2.12**
PB 2	**400 mg/kg**	**402.12 ± 1.7**	**58.34 ± 0.65**
MIEE 1	**200 mg/kg**	**310.71 ± 2.09**	**25.97 ± 2.06**
MIEE 2	**400 mg/kg**	**370.24 ± 3.13**	**17.34 ± 2.94**

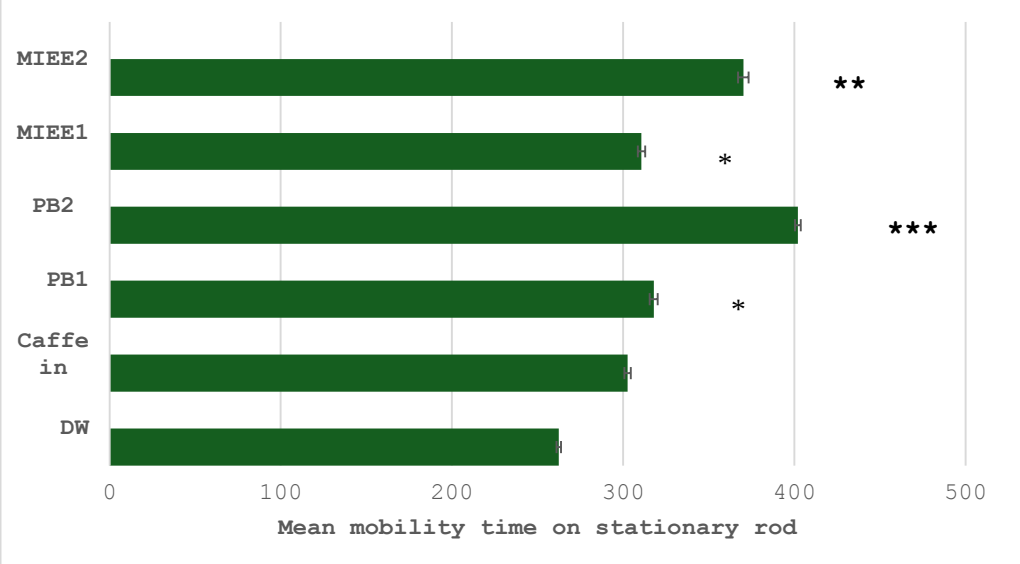

Figure 5: Mobility time on stationary rod by mice, n = 5. The data are presented as the mean ± standard error for five mice per group. Statistical significance is denoted as *** for p<0.001, indicating high significance, and * for p ≤ 0.05, indicating significance. The treatments included *Mangifera indica* ethanol extract at doses of 200 mg/kg (MIEE1) and 400 mg/kg (MIEE2), *Prunus brigantina* ethanol extract at doses of 200 mg/kg (PB1) and 400 mg/kg (PB2), distilled water (DW), and caffeine.

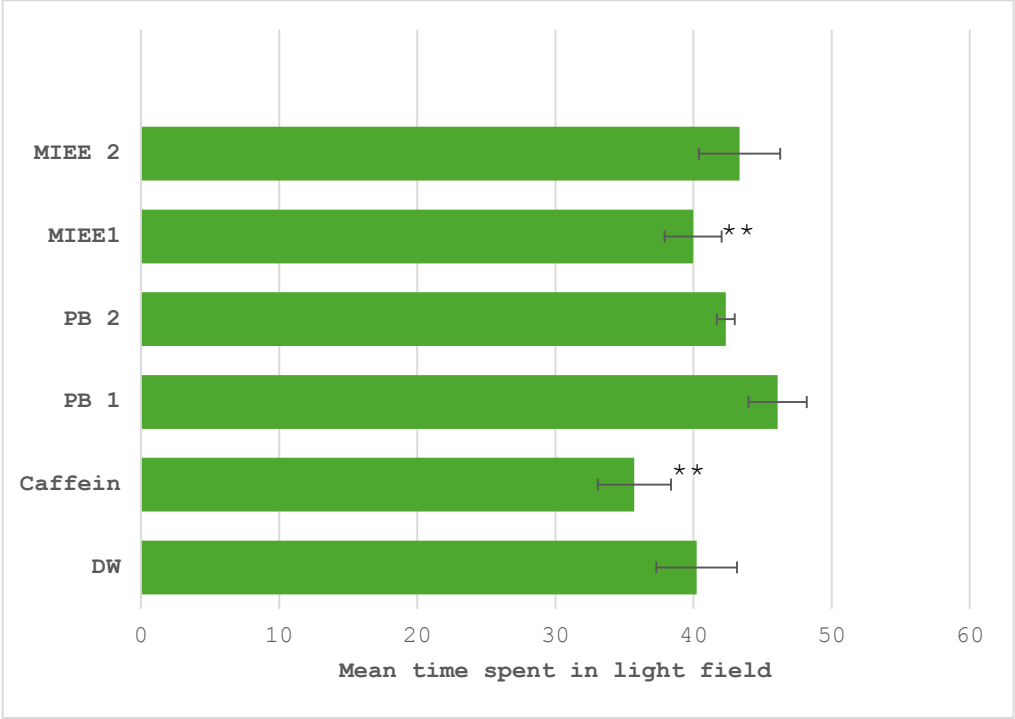

Figure 6: Mean time spent in light field by mice, n = 5. The data are presented as the mean ± standard error from five mice in each group. Statistical significance is indicated by *** for $p<0.001$, denoting high significance, and * for $p \leq 0.05$, indicating significance. The substances administered include *Mangifera indica* ethanol extract at doses of 200 mg/kg (MIEE1) and 400 mg/kg (MIEE2), *Prunus brigantina* ethanol extract at doses of 200 mg/kg (PB1) and 400 mg/kg (PB2), as well as distilled water (DW) and caffeine.

DISCUSSION

Throughout human history, natural products have played a pivotal role in treating various illnesses, with herbal remedies being a rich source of natural compounds. According to the World Health Organization (WHO), approximately 70% of the global population relies on herbal medicines for primary healthcare needs, and it's estimated that around 80% of drugs are derived from natural sources. These natural remedies offer potential lead structures and standardized phytochemical substances with assured quality, safety, and efficacy. They are particularly prevalent in developing countries and have garnered increased interest for drug isolation in recent years [16].

Depression, a complex condition affecting mood, well-being, and behavior, remains a significant global health concern. It can be triggered by various factors, including medical treatments like reserpine, which depletes key neurotransmitters such as norepinephrine, serotonin, and dopamine. The WHO reports that around 450 million individuals experience mental or behavioral disorders, with depression alone contributing to 12% of the global disease burden. Current antidepressants face challenges like delayed efficacy, significant side effects, and low response rates. Consequently, there is a growing interest in herbal remedies as alternatives for managing depression [17, 18].

The combination of serotonin-selective reuptake inhibitors and serotonin reuptake transporter inhibitors has shown promise in enhancing synaptic concentration and prolonging the half-life of serotonin. Many herbal remedies contain ethanolic extracts rich in compounds like phenols, flavonoids, triterpenoids, and steroids, offering less harmful and cost-effective alternatives to synthetic drugs. Consequently, researchers are increasingly exploring plant-derived compounds for managing depression and anxiety disorders [19].

In the study, extracts from *Prunus brigantina* and *Mangifera indica* fruits were administered to mice to assess their neuropharmacological effects. Results revealed significant impacts on motor function and behavior across various tests, including the head dip test, forced swimming test, and stationary rod test. *Prunus brigantina* extract exhibited potent anxiolytic and calming effects, while *Mangifera indica* extract demonstrated stimulating effects. These findings suggest that *Prunus brigantina* extract may offer a more potent calming effect, while *Mangifera indica* extract may be more stimulating [20, 21].

Overall, the study highlights the potential of herbal extracts in managing depression and anxiety disorders, offering promising alternatives to traditional antidepressants. Further research is warranted to elucidate the mechanisms underlying these effects and to explore their clinical applications [22] [23].

CONCLUSION

In conclusion, our study highlights the significant potential of herbal remedies, derived from natural products, in addressing mood disorders such as depression and anxiety. With a substantial portion of the global population relying on herbal medicines, exploring these natural compounds offers promising alternatives to traditional antidepressants. Our investigation into the neuropharmacological effects of *Prunus brigantina* and *Mangifera indica* extracts reveals notable impacts on motor function and behavior in animal models. Notably, *Prunus brigantina* demonstrates potent calming effects, while *Mangifera indica* exhibits stimulating properties. These findings underscore the diverse therapeutic potential of botanical extracts in managing mood disorders, warranting further research and clinical exploration.

Conflict of interest: No conflicts of interest are disclosed by the authors**.**

Author's Contribution:

The "Conceptualization is by S.A.; methodology by, S.A and H.T.; software by, H.T, H.A and H.Y.; the validation by, R.B, S.I and A.A.; formal analysis done by, H.T and H.A; investigation done by, H.T.; resources arranged by, H.A and H.Y and S.I.; data curation, H.T.; writing, H. T; writing—review and editing by, S.A, R.B, H.A, H.Y and S.I.; visualization, H.T.; supervision, S.A and A.A.; project administration, H.A, R.B and H.Y.; funding acquisition, H.T and S.A.

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