

ASTOUNDING THE ANXIOLYTIC, ANTIDEPRESSANT AND COGNITIVE POTENTIAL OF FRAGARIA ANANASSA FRUITS AND LEAVES

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DOI: <https://doi.org/10.5281/zenodo.22684075>

Keywords

Fragaria ananassa, Anxiety, Depression, Cognitive, Leaf extract, physiology

Article History

Received: 01 June 2026

Accepted: 23 August 2026

Published: 10 September 2026

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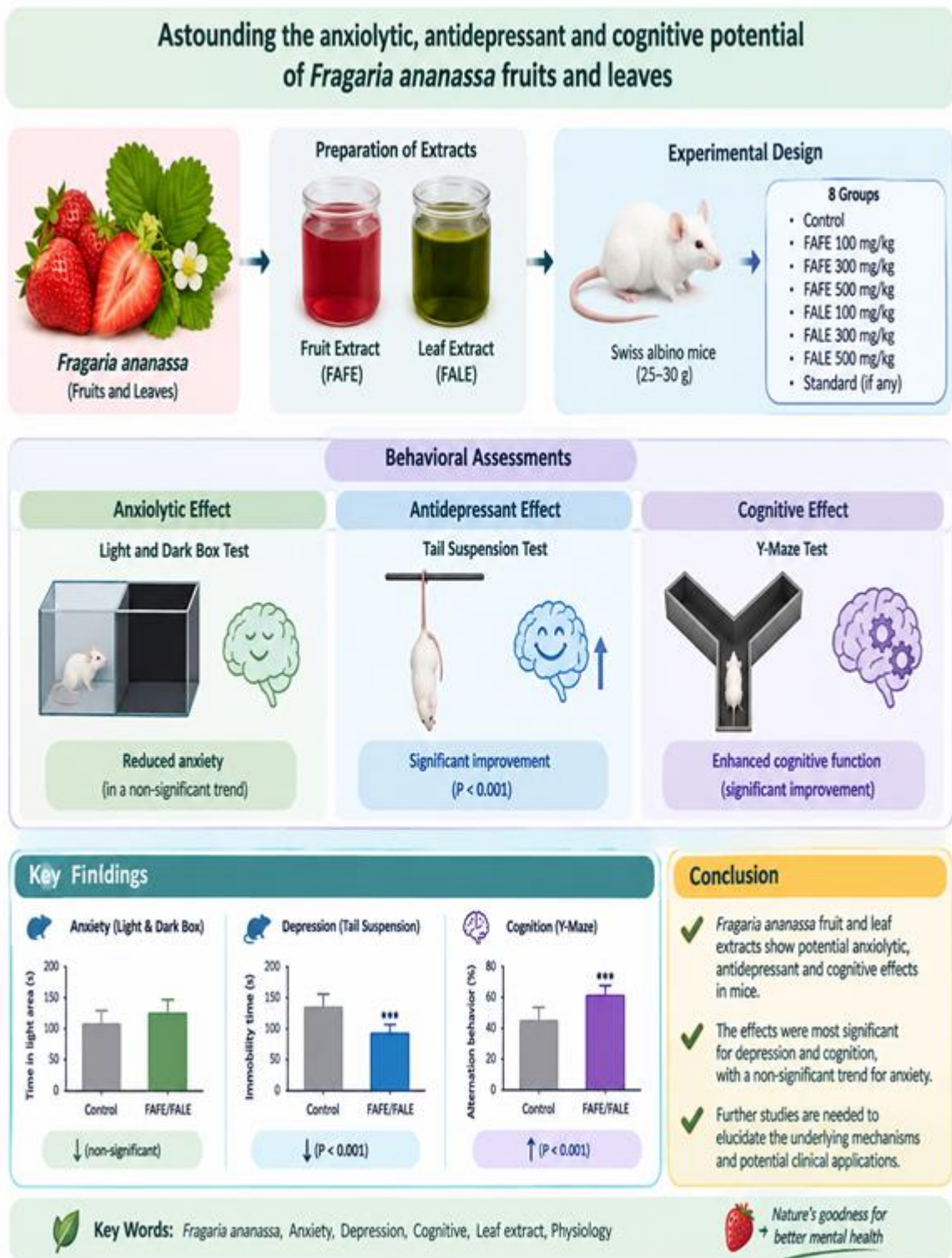
Abstract

Background: Several herbs are used in conventional medicine to treat a variety of ailments. *Fragaria ananassa* (FA) fruits and leaves have bioactive components like phenolic and polyphenolic and possess antioxidant properties. A 2013 report from the World Health Organization estimates that 450 million people have mental and behavioral illnesses. The purpose of this study was to evaluate the impact of *fragaria ananassa* fruits and leaves on animal behavior, specifically anxiety, depression, and cognition.

Methods: The study was conducted in Swiss albino mice weight between 25g-30g, divided into eight groups. Test groups received different doses of *fragaria ananassa* fruit extract (FAFE) and *fragaria ananassa* Leaf Extract (FALE) i.e. 100 mg/kg, 300mg/kg, 500mg/kg. Anxiolytic effect of Strawberry fruit and leaf extracts was determined by Light and Dark Box Test and Antidepressant activity was assessed by Tail Suspension Test. Cognitive analysis was done on Swiss albino mice weight between 25g-30g, using Y-maze test, animals were divided into 8 groups, two readings per day for three consecutive days were taken to evaluate cognitive behavior of mice. A p-value of <0.05 was considered statistically significant.

Results: Result illustrated that FA fruit and leaf extracts have a insignificant potential of reducing anxiety and significant (P < 0.001) potential in improving depression and enhancing cognitive effect.

Conclusion: The present study demonstrates improvement in anxiety, depression and cognitive effects with FA fruit and leaf extracts. However further additional studies will be necessary to determine the underlying exact mechanism and clinical uses.



Graphical abstract for Astounding the anxiolytic, antidepressant and cognitive potential of *fragaria ananassa* fruits and leaves

INTRODUCTION

Since the start of time, people have used plants, plant components, and extracted plant chemicals to avoid or cure a variety of illnesses. It is estimated that approximately 25% of medications prescribed globally are obtained from plants, and there are currently 121 active substances in use; of the 252 medications on the WHO's essential medicine list, 11% originate solely from plants (Rates SMK., 2001). There is evidence that plants have been used for medical reasons for as long as 60,000 years (Solecki RS., 1975) in both established and developing nations, as well as in western and eastern cultures. The glycosides of anthocyanidins, or anthocyanins, are commonly found in brightly colored veggies, fruit, berries, and grapes (Manach et al., 2005). In animal models of neurological pathology and aging, anthocyanin consumption has been repeatedly demonstrated to enhance cognitive function (Shukitt-Hale et al., 2008). The Europeans observed strawberries for the first time in 1588. Phytochemicals, particularly ellagic acid and anthocyanins, as well as vitamins, potassium, and fiber, are abundant in strawberries and have anti-inflammatory, antioxidant, (Hannum SM., 2004) and anti-hyperglycemic properties (Da Silva et al., 2007). Strawberry leaves extracts have been tested on animals and have demonstrated hypoglycemic effects in diabetic mice (Takács I. et al., 2020) and rats (El-Hawary SS. et al., 2021), as well as anti-inflammatory, antioxidant, and cognitive-improvement impacts in diabetic rats (Zhang L. et al., 2020). A 2013 World Health Organization report states that 450 million individuals are suffering from mental illness and behavioral diseases, which is nearly 12.3% of the population and is expected to increase even in the future (Herrera-ruiz et al., 2006). 450 million people worldwide are affected by some form of neurological or psychological disorder, and depression is a significant contributor to the global burden of disease (Murugan U. et al., 2011). Anxiety and mood disorders have been linked to serotonergic system dysfunctional behavior. This theory is supported by the observation that the initial antidepressant medications restored the brain's reduced monoamine activity. Later, it was

discovered that SSRIs by themselves were adequate to successfully treat depressive symptoms. This information further supported 5-HT's role in the disease's pathophysiology (Cowen P., 2008, Saldanha et al., 2009).

Many pharmacotherapeutic agents are utilized for treating depression and anxiety, but because of their reduce action, limit safety margin, and possible adverse effects, researchers are looking for novel drugs with faster action, fewer adverse reactions, and a greater safety margin (Sartori SB and Singewald N., 2019). Deposition of β -amyloid plaque and neurofibrillary tangles are hallmarks of Alzheimer's disease (AD), a neurodegenerative condition that impairs cognitive and memory abilities (Kesika P. et al., 2021). As the global population ages, the incidence of AD is rising globally (Waller J. and Budson A., 2018). Reactive oxygen and nitrogen species, oxidative stress, and inflammation are all significant factors in the development of Alzheimer's disease (Sochocka M. et al., 2019, Hatziagapiou k. et al., 2019). Age-related neurological alterations in the brain can affect learning and memory, posture, and balance. In certain situations, such alterations can cause very early dementia, cognitive impairment, or dangerous falls in older adults. For the treatment of mental illnesses like anxiety, depression, and dementia, among many others, natural medication has proven to be a sensible substitute (Klemens J., 2006). Because of the effectiveness of their treatment and decreased likelihood of adverse effects, creating antidepressants from medicinal plants seems like a sensible strategy (Rajput M. et al., 2011). The use of anxiolytic and antidepressant drugs causing side effect and need to dig out a natural remedy for improvement in learning and memory our objectives of this study includes, To assess the anti-immobility effect of the fruit and leaf extracts of fragaria ananassa using tail suspension test in mice. To determine cognitive behavior of the fruit and leaf extracts of fragaria ananassa using Y-Maze test.

MATERIAL AND METHODS**Experimental Animals**

The study was carried out after approval from ASRB/No/06254/Pharm. November 18, 2021, as per ASRB Resol. No. 10 (P) 05 dated 30-08-

2021. Animals used for this study were male albino swiss mice (6 –8 weeks, 20–30 g). These animals were obtained from the institutional animal house. Throughout the experiment, they were kept in conventional settings with a 12-hour light-dark cycle and a temperature of 25 ± 2 °C after spending a week getting used to the animal house amenities.

Preparation of Ethanolic Extract of *Fragaria Ananassa* fruit And Leaf Extract

Fresh strawberry with leaves were collected from the local market of Karachi, Pakistan, in the months of January 2023. The plant material was authenticated by the department of pharmacognosy, College of Pharmacy, University of Karachi, as *Fragaria Ananassa* FAF-14-20 and FAL-13-20. The *fragaria ananassa* fruit and leaves were washed with distilled water to remove impurities then dried at room temperature (25 °C). The fruit and leaves were blended to a mesh size of 1 mm. The fruit (2 kg) and leaves (800 g) were macerated in five liters of 98% ethanol for three days at room temperature, shaking them occasionally, in preparation for extraction. A rotating evaporator set at 40 degrees Celsius was used to filter and eliminate the extracted solvent. After being freeze-dried, the extract was kept for future research at 20°C.

Experimental Design

For anxiolytic, antidepressant and cognitive effects forty-eight male outbreed of 6-8 weeks old mice strain swiss albino with average body weight of 20-30 grams were divided into eight groups of six mice each, as follows:

- 1) Control Group (Received 1ml distilled water)
- 2) Standard Group (Clonazepam 0.5 mg/kg an antianxiety, Fluoxetine 5mg/kg an antidepressant) as a comparison group.
- 3) *Fragaria Ananassa* fruit extract (with dose of 100 mg/kg)
- 4) *Fragaria Ananassa* fruit extract (with dose of 300 mg/kg)
- 5) *Fragaria Ananassa* fruit extract (with dose of 500 mg/kg)
- 6) *Fragaria Ananassa* leaf extract (with dose of 100 mg/kg)

7) *Fragaria Ananassa* leaf extract (with dose of 300 mg/kg)

8) *Fragaria Ananassa* leaf extract (with dose of 500 mg/kg)

Antianxiety Evaluation

Light And Dark Box Model

The instrument is used to measure the potential effects of test compounds on the unconditioned anxiety-like behavior of rodents. The apparatus consists of two $25 \times 33 \times 24$ compartments in a wooden box. By connecting the two compartments with a 10×10 opening, the mice were able to move between them. One compartment was lit and open, but the other remained dark. The mice were placed in the dark box and left there for five minutes, during which time their time in the open, lighted compartment was recorded using a stopwatch. The mice were given their doses thirty minutes before they were placed in the box (Campos AC. et al., 2013).

Antidepressant Effect

Tail Suspension Test

The observation that animals will assume an immobile posture when subjected to the brief, inevitable stress of being suspended by their tail forms the basis of the tail suspension test (TST). The TST was conducted on days 7, 14, and 21 of drug treatment in compliance with the protocol outlined by Steru L. et al., (1985).

Cognitive Behavior

Y-Maze Test

The dimensions of the Y-maze are 18 cm in height, 6 cm in width, and 28 cm in length. It's a 120-degree horizontal maze with three arms. For six minutes after the mice were initially placed in one arm, the quantity and sequence of arm entries were monitored. To show an actual alternation, a mouse entered all three arms on consecutive choices (i.e., ABC, BCA, or CAB, but not CAC, BAB, or ABA).

Data Analysis

The data obtained from the experiment was evaluated by SPSS windows version 27 using mean difference from control (p-value using RM two-way ANOVA and post-hoc (LSD with

Bonferroni correction at $\alpha = 0.05/16 = 0.003125$)

RESULTS

Antianxiety characteristics using Light and Dark Box

In this study, the outcome measurements showed a no significant group-time interaction, for entries in light box (ELB) ($F_{14, 80}=0.574$, $MSE=4.475$, $p=0.877$, $\eta_p^2 = 0.091$), for time spend in light box (TSLB) ($F_{14,80}=0.224$, $MSE=746.469$, $p=0.998$, $\eta_p^2 = 0.038$), for time spend in dark box (TSDB) ($F_{14,80}=0.239$, $MSE=747.007$, $p=0.998$, $\eta_p^2 = 0.040$) (Table 01).

Entries In Light Box (ELB)

At 1st and 2nd week, insignificant increase in number of entries in light box (ELB) is observed with all groups in comparison to the control group. At 3rd week, insignificant increase in ELB is observed with all groups except animals received leaf extract at 500mg/kg dose in comparison to the control group (Table 01).

Time Spend In Light Box (TSLB)

At 1st and 2nd week, time spend in light box (TSLB) is found to be insignificantly increased with all groups in comparison to the control group (Table 01). At 3rd week, time spend in light box (TSLB) is found to be insignificantly increased with all groups except animals received leaf extract at 500mg/kg dose in comparison to the control group (Table 01).

Time Spend In Dark Box (TSDB)

At 1st, 2nd and 3rd week, TSDB is found to be insignificantly reduced with all groups in comparison to the control group (Table 01).

Inter-group comparison

No statistically significant clinical improvement is observed with any group in comparison to the control group (Table 03).

Entries In Light Box (ELB)

At 1st week entries in light box (ELB) in animals received clonazepam (CLO) showed insignificant clinical improvement (4.17) in comparison to all test groups. At 2nd week,

maximum insignificant clinical improvement in ELB is observed with FE100 group (3.67) in comparison to the CLO group (3.50). At 3rd week, maximum insignificant improvement in ELB is observed with CLO group (3.67) (Table 02).

Time Spend In Light Box (TSLB)

At 1st week, maximum insignificant clinical improvement on TSLB is observed with CLO group (26.8). At 2nd week, maximum insignificant clinical improvement on TSLB is observed with FE300 group (30.7) and LE100 group (29.3) and LE300 group (28.0) in comparison to the CLO group (27.2). At 3rd week maximum insignificant improvement on TSLB is observed with FE300 group (26.8) in comparison to the CLO group (22.2) (Table 02).

Time Spend In Dark Box (TSDB)

At 1st week, maximum insignificant clinical improvement on TSDB is observed with LE100 group (-20.5) and LE300 group (-19.9) in comparison to the CLO group (-19.7). At 2nd week, maximum insignificant clinical improvement on TSDB is observed with FE300 group (-30.7), LE100 group (-29.3) and LE300 group (-28.0) in comparison to the CLO group (-27.2). At 3rd week, maximum insignificant clinical improvement on TSDB is observed with FE300 group (-26.9) in comparison to the CLO group (-22.2) (Table 02).

Antidepressant Characteristics Using Tail Suspension Test

In this study, the outcome measurements showed a no significant group-time interaction, for period of immobility (POI) ($F_{14, 80}=0.843$, $MSE=1686.975$, $p=0.622$, $\eta_p^2 = 0.129$). Table 03 showed that period of immobility is insignificantly reduced with all animal groups at 1st, 2nd and 3rd week in comparison to the control group. At 1st week, among maximal reduction in POI is seen with Fluoxetine (FLO) group (77.7 $\pm$ 27), Animals received fruit extract at three different doses i.e. 100mg/kg, 300mg/kg and 500mg/kg maximal reduction in POI is observed with FE300 group (85.4 $\pm$ 55.3) and among animals received leaf extract at three different doses i.e. 100mg/kg, 300mg/kg and

500mg/kg maximal reduction in POI is observed with LE100 group (73 ± 23) in comparison to the control group (156 ± 79.4). At 2nd week maximal reduction in POI is observed with FLO group (62 ± 16.1), among animals received fruit extract maximal reduction in POI is observed with FE100 (64.2 ± 33.4) and among animal groups received leaf extract maximal reduction in POI is observed with LE300 (64.2 ± 30) in comparison to the control group (132 ± 62). At 3rd week, maximal reduction in POI is observed with FLO group (61 ± 32.2), among animals received fruit extract maximal reduction in POI is observed with FE100 (98 ± 49) and among animal groups received leaf extract maximal reduction in POI is observed with LE300 (55.3 ± 27) in comparison to the control group (147 ± 93.2) (Table 03).

Intra-group comparison

With respect to the treatment groups showed no statistically significant improvements in POI in comparison to the control animal group (Table 04).

Period of Immobility (seconds)

Table 04 showed that, at 2nd week, period of immobility (POI) with FE100 group (32%), FE500 group (35%), LE300 group (33%) and LE500 group (28%) is insignificantly improved in comparison to the control group (10%). At 3rd week POI is insignificantly improved with FE300 group (-44%), LE100 group (-55 %), LE300 group (40%) and LE500 group (-55 %) in comparison to the control group (15 %).

Inter-group comparison

Table 05 showed that at 2nd week, clinical improvement in period of immobility (POI) is significantly improved with FLO group (≤ 0.001), FE100 group (0.001) and LE300 group (0.001) in comparison to the control group. At 1st week, the maximal insignificant mean clinical improvement in POI is seen with LE100 group (83.2) in comparison to FLO group (78.3). At 2nd week, the maximal significant mean clinical improvement (≤ 0.001) in POI is seen with FLO group (70) followed by FE100 group (67.2) and LE300 group (67.2). At 3rd week, the maximal mean clinical

improvement is seen with LE300 group (91.9) in comparison to FLO group (86.7) (Table 05).

Cognitive Effect Using Y-MAZ Test

In this study, the outcome measurements showed a no significant group-time interaction, for spontaneous cognitive effect (SCE) ($F_{35, 200} = 0.584$, $MSE = 166.223$, $p = 0.970$, $\eta_p^2 = 0.093$). Table 06 showed that, at 10 am and 2 pm on day -1, day-2 and day-3, there was an insignificant increase in spontaneous cognitive effect (SCE) observed with all test groups (FE100, FE300, FE500, LE100, LE300 and LE500) in comparison to the control group. On Day 1, 2 and 3 scopolamine group (SCOP) showed insignificant decrease in SCE in comparison to the control group.

Inter-group comparison

Table 07 showed that on day-3 (10am), clinical improvement in spontaneous cognitive effect (SCE) is significantly improved with FE300 group (0.001) in comparison to the control group. On Day-1 (10am), among the fruit extract groups the maximal insignificant mean clinical improvement in SCE is seen with FE300 group (-17.6) and among the leaf extract groups maximal insignificant mean clinical improvement in SCE is seen with LE100 group (-23.8) in comparison to the SCOP group (8.6). On Day-1 (2pm), among the fruit extract groups the maximal insignificant mean clinical improvement in SCE is seen with FE500 group (-13.5) and among the leaf extract groups maximal insignificant mean clinical improvement in SCE is seen with LE300 group (-24.8) in comparison to the SCOP group (8.5). On Day-2 (10am), among the fruit extract groups the maximal insignificant mean clinical improvement in SCE is seen with FE100 group (-16.7) and among the leaf extract groups maximal insignificant mean clinical improvement in SCE is seen with LE300 group (-20.3) in comparison to the SCOP group (7.4). On Day-2 (2pm), among the fruit extract groups the maximal insignificant mean clinical improvement in SCE is seen with FE500 group (-22.6) and among the leaf extract groups maximal insignificant mean clinical improvement in SCE is seen with LE300 group (-18.2) in comparison to the SCOP group (6.2).

On Day-3 (10am), among the fruit extract groups the maximal significant mean clinical improvement in SCE is seen with FE300 group (-24.8) and among the leaf extract groups maximal insignificant mean clinical improvement in SCE is seen with LE100 group (-19.1) in comparison to the SCOP group (7.9). On Day-3 (2pm), among the fruit extract groups the maximal insignificant mean clinical improvement in SCE is seen with FE500 group (-16.5) and among the leaf extract groups maximal insignificant mean clinical improvement in SCE is seen with LE300 group (-17.5) in comparison to the SCOP group (7.5) (Table 07).

DISCUSSION

The use of plant-derived supplements for improving health is gaining popularity because most people consider these natural products to be safer and produce less side effects than synthetic drugs (Raskin I. et al., 2002). In Pakistan, some areas of Punjab and KPK provinces produce strawberries as a yearly crop (Afridi, GS. et al., 2009). It is found that strawberry extract increased the activity of antioxidant and oxidative stress repair enzymes (Zhang Y. et al., 2008). Phenolic compounds, polyphenols, and flavonoids from fruits and vegetables modulate tau hyperphosphorylation and β -amyloid aggregation in animal models of AD (Román GC. et al., 2019). It was reported previously that anthocyanins possessed a neurodegenerative protective effect (Mattioli R. et al., 2020). Dietary interventions with strawberry (SB) have been associated with improvements in neuronal, psychomotor and cognitive functions in rodent models of ageing (Miller MG. et al., 2021). With the goal to find novel, effective natural remedies for the symptoms of anxiety, light and dark box test evaluated the anxiolytic properties of fragaria ananassa fruit and leaf extract in the present research. Table 01 showed antianxiety characteristics using Light & Dark Box Test.

It represented the anxiolytic results of the effect of three different doses of fragaria ananassa fruit and leaf extracts on number of entries in light box (ELB), time spend in light box (TSLB) and time spend in dark box (TSDB) at 1st, 2nd and 3rd week of drug administration. The

outcome measurements showed no significant group-time interaction, for ELB ($F_{14,80}=0.574$, $MSE=4.475$, $p=0.877$, $\eta_p^2 = 0.091$), for TSLB ($F_{14,80}=0.224$, $MSE=746.469$, $p=0.998$, $\eta_p^2 = 0.038$), TSDB ($F_{14,80}=0.239$, $MSE=747.007$, $p=0.998$, $\eta_p^2 = 0.040$). There were no significant findings on number of ELB, TSLB and TSDB observed with all three different doses of fragaria ananassa fruit and leaves extracts at 1st, 2nd and 3rd week of drug administration.

However insignificant increase in entries in light box (ELB) is observed with all groups at 1st, 2nd and 3rd week of drug administration in comparison to the control group. Among all fruit extract groups at three different doses (100mg/kg, 300mg/kg and 500mg/kg), maximum increase in ELB is observed with FE100 group at 1st, 2nd and 3rd week and FE300 group at 1st week and among all leaf extract groups maximum increase in ELB is observed with LE100 group at 3rd week, LE300 group at 1st and 3rd week and LE500 group at 2nd week. At 1st, 2nd and 3rd week, time spend in light box (TSLB) is found to be insignificantly increased with all groups in comparison to the control group. Maximum duration in light box among fruit extract groups is observed with FE300 group at 1st, 2nd and 3rd week and among leaf extract groups with LE100 group at 1st and 2nd week and LE300 group at 1st and 3rd week. These effects highlighted the antianxiety-like behavior. At 1st, 2nd and 3rd week, time spend in dark box (TSDB) is found to be insignificantly decreased with all groups except FE500 group at 3rd week in comparison to the control group. Maximum reduction in duration in dark box among fruit extract groups is observed with FE100 group at 1st week and FE300 group at 1st, 2nd and 3rd week and among leaf extract group with LE100 group at 1st and 2nd week and LE300 group at 3rd week. The observations with light and dark box test supported the anxiolytic effects of the extract treatment as there was although insignificant increase in number of entries in light box and increase on time spend in light box displayed by all three doses of fruit and leaf extracts of fragaria ananassa.

The outcomes of the L&D box tests revealed that the doses of the *Fragaria* fruit and leaf extracts were able to display antianxiety-like response, did not exhibit significant change in anxiety behavior when compared with the control group. The potential of FA fruit to lessen anxiety is not as well-established as that of various foods or substances. Still, a few of the ingredients in strawberries may help lower anxiety. It has been found that strawberry fruit contain several anthocyanidin glycosides as well as phenolic substances such as ellagic acid, ellagic acid-glycoside, and coumaryl glycoside. Antioxidant, cancer prevention, anti-inflammatory, and anti-neurodegenerative qualities are also attributed to the FA fruit (Hannum SM., 2004, Seeram NP. et al., 2006). Furthermore, FA leaves are rich in beneficial compounds such as ellagitannins, caffeic acid, kaempferol derivatives, quercetin, and chlorogenic acid (Kärlund A. et al., 2017, Karlund A. et al., 2014). The antidepressant like capability of organic substances is extensively reported (Belozertseva IV. et al., 2007, Perviz S. et al., 2016).

Therefore in our study we explore possible antidepressant benefits of three different doses of *Fragaria ananassa* fruit and leaf extracts by observing the period of immobility in tail suspension test in mice. Three different doses of the FA fruit and leaf extracts (100mg/kg, 300mg/kg and 500mg/kg p.o.) were treated continuously for 21 days to mice. The treatment of FA fruit and leaf extracts at three doses levels showed no significant group-time interaction, for period of immobility (POI) ($F_{14,80}=0.843$, $MSE=1686.975$, $p=0.622$, $\eta_p^2 = 0.129$). However insignificant decline in the period of immobility in tail suspension test is observed in our results. Table 03 showed that among all test groups at 1st, 2nd and 3rd week of drug administration maximal insignificant reduction in period of immobility is observed with LE100 group (at first week), FE100 group, LE300 group (at 2nd week) and LE300 group (at 3rd week). With these outcomes we can not conclude that which dose has shown better antidepressant effect but obviously we can analyse that FA fruit and leaf extracts may have some antidepressant effect regardless of the

dose of the drug and the duration of the treatment.

However as shown in table 04 mean comparison from 1st week of antidepressant characteristics (POI) using tail suspension test among fruit extract groups insignificant maximal reduction in POI is observed with FE300 group (-44%) at 3rd week and among leaf extract groups LE100 (-55) and LE500 group (-55) at 3rd week in comparison to the 1st week. Table 05 showed mean comparison from control of antidepressant characteristics (POI) using tail suspension method represented that at 2nd week, significant improvement in period of immobility is observed with FE100 group (0.001) and LE300 group (0.001) in comparison to the control group. The results of tail suspension test (TST) in our study is supported by another study which concluded that strawberries are able to improve depressive symptoms by decreasing immobility time and increasing levels of serotonin compared with CMS group (Hazar S. and Fitri LL., 2015).

Similar patterns of the results were observed by comparing the strawberry with Imipramine antidepressant drug and performing Forced Swim Test and TST it is concluded that *fragaria ananassa* at 10ml dose produces a significant anti-depressant effect by reducing the immobility time (Alam S., 2022). Working memory can be determined by the Y-maze test's spontaneous alternation score. Behavior of animals is often investigated using the Y maze test, which is also frequently used in the neuroscience study of spatial learning and memory, which include drug studies, behavioral disorders, and addicting drug dependence etc (Hughes RN and Hancock NJ., 2017, Shu SY. Et al., 2015, Nozawa Y. et al., 2014). The results of different doses of *fragaria ananassa* fruit and leaf extracts on the learning and memory is shown on table 06 and 07. During the 1st, 2nd and 3rd day of dosing.

Animal groups received *fragaria ananassa* fruit and leaf extract at three different doses 100mg/kg, 300mg/kg and 500 mg/kg showed insignificant improvement in memory during the day-1, day-2 and day-3 of drug administration. Present study showed no significant group-time interaction, for

spontaneous cognitive effect (SCE) ($F_{35,200}=0.584$, $MSE=166.223$, $p=0.970$, $\eta_p^2 = 0.093$). However mean comparison from control of spontaneous cognitive characteristics (SCE) using Y-MAZ showed that on day-3 (10am), clinical improvement in spontaneous cognitive effect (SCE) is significantly improved with FE300 (0.001) in comparison to the control group. Table 06 showed that on Day-1 at two time intervals, among fruit extract groups maximal insignificant SCE is seen with FE300 group (10am) and among leaf extract groups maximal SCE is seen with LE 300 group (2pm) in comparison to the control group.

On Day-2 at two different time intervals, among fruit extract groups maximal insignificant SCE is seen with FE500 group (2 pm) and among leaf extract group maximal SCE seen with LE 300 group (10am) in comparison to the control group. On day -3 at two different time intervals, among fruit extract groups maximal insignificant SCE is seen with FE300 group (10 am) and among leaf extract group maximal SCE seen with LE300 group (2 pm) in comparison to the control group. Table 07 showed that on day-3 (10am), clinical improvement in spontaneous cognitive effect (SCE) is significantly improved with FE300 (0.001) in comparison from control group of spontaneous cognitive characteristics using Y-Maze Test. Our study did not show dose dependent or time dependent spontaneous cognitive effect in mice. In our study the SCO-induced amnesia group exhibited insignificantly reduction in spontaneous cognitive effect compared with the control group in Y-maze test. Recent research indicates that alterations in the production of enzymes that produce antioxidants are linked to the learning, memory and cognition dysfunction caused by SCO administration in experimental animals (Jeong EJ. Et al., 2009).

According to certain researchers, (Joseph JA. et al., 1998 & 1999, Bickford PC. et al., 2000., Youdim KA. and Joseph JA., 2001) keeping rats on antioxidant diets that contain strawberries extracts for two months can stop the onset of age-related behavioral and neurochemical alterations. Specifically, in contrast to animals supplied a standard diet, rats kept in diets

containing a strawberry extracts for two months showed elevated oxotremorine-enhanced dopamine output from striatal slices. Along with modifications in dopaminergic activity, there were also enhancements in spatial learning and motor behaviors.

One of the study by Miller MG. et al., 2021 concluded that strawberry (SB) containing nutritional supplements would enhance older adults' cognitive function and mobility. Further research with a larger sample size and longer follow-up is necessary to verify these findings, but they suggest that adding SB to the nutrition plans of healthy, older adults may benefit certain aspects of cognition but not gait or balance. Another study by Krikorian R., reported that decrease in memory interference and reduction in depressive symptoms seen with administration of strawberry powder to the participants for 12- weeks (Krikorian R. et al., 2023). The Morris Water Maze test outcomes after four weeks of daily strawberry leaf (SL) extract use showed that damage from oxidative stress may be linked to memory impairment in diabetic rodents, and SL may reduce diabetic memory disorder by preventing oxidative damage (Zhang L. et al., 2020).

Furthermore, new research revealed that dietary habits may also play a significant role in lowering the likelihood of Alzheimer's disease and other dementias. In particular, a decreased risk of Alzheimer's disease and related dementias was linked to diets containing more flavanol's, anthocyanins, and flavonoid polymers (Shishtar E. et al., 2020). This suggests that consuming more flavonoids over time from food items like fruits and berries can decrease the probability of Alzheimer's disease and associated cognitive disorders (Devore EE. et al., 2012, Agarwal P. et al., 2019, Shishtar E. et al., 2020).

Conclusion

The goal of this research is to provide information that will help develop new approaches to treating conditions like anxiety, depression and cognitive impairment. These approaches involve the use of natural products, that is FA fruit and leaf extracts as preventive or coadjuvant therapies. In conclusion, the findings of the present study on behavioral

evaluation of *Fragaria Ananassa* fruit and leaf extracts indicated that FA fruit and leaf interventions insignificantly reduced some anxiety parameters, shows significant beneficial effects in animal model of depression. Our study also showed improvement in cognitive behavior and memory enhancing activity in mice. Our neurobehavioral outcomes with these extracts in animal models represented that the alternative plant based dietary strategies might be successful in treating these

illnesses and must be developed along with the therapeutic interventions.

Limitations

It is novel that greater potency outcomes were not found, considering the promising improvement in behavioral and cognitive effects of FA fruit and leaf extracts in animal models. Limitations in this study include the small sample size, doses and the shorter duration of the intervention.

Table 01: Mean $\pm$ SD of antianxiety characteristics using light and dark box test

Antianxiety Characteristics	Control N = 6 (%)	CLO N = 6 (%)	FE100 N = 6 (%)	FE300 N = 6 (%)	FE500 N = 6 (%)	LE100 N = 6 (%)	LE300 N = 6 (%)	LE500 N = 6 (%)
ELB (Count)								
1 st Week	2.3 $\pm$ 1.21	6.5 $\pm$ 3.39	6.0 $\pm$ 1.41	6.0 $\pm$ 2.68	5.2 $\pm$ 2.14	5.2 $\pm$ 0.98	5.8 $\pm$ 2.23	5.5 $\pm$ 2.74
2 nd Week	2.3 $\pm$ 1.21	5.8 $\pm$ 3.66	6.0 $\pm$ 3.03	5.3 $\pm$ 2.16	4.0 $\pm$ 1.79	5.3 $\pm$ 2.66	5.7 $\pm$ 2.58	5.8 $\pm$ 3.06
3 rd Week	3.0 $\pm$ 1.67	6.7 $\pm$ 1.97	5.3 $\pm$ 2.73	5.2 $\pm$ 1.17	4.3 $\pm$ 1.75	5.5 $\pm$ 2.17	5.5 $\pm$ 1.52	3.0 $\pm$ 1.79
TSLB (Seconds)								
1 st Week	59 $\pm$ 37	86 $\pm$ 25	78 $\pm$ 26	78 $\pm$ 12	75 $\pm$ 24	79 $\pm$ 18	79 $\pm$ 24	74 $\pm$ 25
2 nd Week	51 $\pm$ 22	78 $\pm$ 31	76 $\pm$ 29	82 $\pm$ 28	54 $\pm$ 19	80 $\pm$ 41	79 $\pm$ 15	61 $\pm$ 20
3 rd Week	60 $\pm$ 28	83 $\pm$ 25	70 $\pm$ 26	87 $\pm$ 67	58 $\pm$ 20	75 $\pm$ 29	80 $\pm$ 13	60 $\pm$ 20
TSDB (Seconds)								
1 st Week	241 $\pm$ 37	222 $\pm$ 30	222 $\pm$ 26	222 $\pm$ 12	225 $\pm$ 23	221 $\pm$ 18	222 $\pm$ 24	227 $\pm$ 25
2 nd Week	249 $\pm$ 22	222 $\pm$ 31	225 $\pm$ 29	218 $\pm$ 28	246 $\pm$ 19	220 $\pm$ 41	221 $\pm$ 15	239 $\pm$ 21
3 rd Week	240 $\pm$ 28	218 $\pm$ 25	230 $\pm$ 26	213 $\pm$ 67	242 $\pm$ 20	225 $\pm$ 29	221 $\pm$ 13	240 $\pm$ 20

ELB: Entries in Light & Box; TSLB: Time Spend in Light Box; TSDB: Time Spend in Dark Box, CLO: Clonazepam, FE: Fruit Extract, LE: Leaf Extract

Table 02: Mean comparison from control of antianxiety characteristics (ELB, TSLB & TSDB) using light and dark box test

Antianxiety Characteristics	CLO N = 6 (%)	FE100 N = 6 (%)	FE300 N = 6 (%)	FE500 N = 6 (%)	LE100 N = 6 (%)	LE300 N = 6 (%)	LE500 N = 6 (%)
ELB (count)							
1 st Week	4.17 (0.003)	3.67 (0.007)	3.67 (0.007)	2.83 (0.034)	2.83 (0.034)	3.50 (0.010)	3.17 (0.019)
2 nd Week	3.50 (0.026)	3.67 (0.020)	3.00 (0.054)	1.67 (0.277)	3.00 (0.054)	3.33 (0.033)	3.50 (0.026)
3 rd Week	3.67 (0.002)	2.33 (0.039)	2.17 (0.055)	1.33 (0.230)	2.50 (0.028)	2.50 (0.028)	1.11x10 ⁻¹⁵ (>0.99)
TSLB (seconds)							
1 st Week	26.8(0.064)	18.8 (1.89)	19.5 (0.175)	16.5 (0.249)	20.5 (0.154)	19.8 (0.168)	14.7 (0.305)
2 nd Week	27.2 (0.084)	24.5 (0.118)	30.7 (0.052)	3.00 (0.846)	29.3 (0.063)	28.0 (0.075)	10.3 (0.504)
3 rd Week	22.2 (0.235)	9.3 (0.614)	26.8 (0.152)	-2.3 (0.900)	14.7 (0.430)	19.2 (0.303)	-0.2 (0.993)
TSDB (seconds)							
1 st Week	-19.7 (0.183)	-18.9 (0.201)	-19.5 (0.186)	-16.5 (0.262)	-20.5 (0.165)	-19.9 (0.179)	-14.7 (0.318)
2 nd Week	-27.2 (0.084)	-24.5 (0.118)	-30.7 (0.052)	-3.0 (0.846)	-29.3 (0.063)	-28.0 (0.075)	-10.3 (0.504)
3 rd Week	-22.2 (0.235)	-9.3 (0.614)	-26.9 (0.152)	2.3 (0.900)	-14.7 (0.430)	-19.2 (0.303)	0.2 (0.993)

ELB: Entries in Light Box; TSLB: Time spend in Light Box; TSDB: Time Spend in Dark Box, CLO: Clonazepam, FE: Fruit Extract, LE: Leaf Extract., Δ: mean difference from control (p-value using RM two-way ANOVA and post-hoc (LSD with Bonferroni correction at $\alpha = 0.05/21 = 0.0024$)

Table 03: Mean ± SD of antidepressant characteristics using tail suspension test

Antidepressant Characteristics	Control N = 6 (%)	FLO N = 6 (%)	FE100 N = 6 (%)	FE300 N = 6 (%)	FE500 N = 6 (%)	LE100 N = 6 (%)	LE300 N = 6 (%)	LE500 N = 6 (%)
POI (seconds)								
1 st Week	156 ± 79.4	77.7 ± 27	94 ± 38	85.4 ± 55.3	121±48	73 ± 23	97±33	109±45
2 nd Week	132±62	62 ± 16.1	64.2±33.4	69 ± 27	72± 15	68.2±16	64.2±30	74 ±44
3 rd Week	147 ± 93.2	61 ±32.2	98 ±49	101± 66.2	111± 38	98.2±65	55.3±27	144.2± 60

POI: Period of immobility; FLO: Fluoxetine, FE: Fruit Extract, LE: Leaf Extract.

Table 04: Mean comparison from 1st week of antidepressant characteristics (POI) using tail suspension test

Antidepressant Characteristics	Control N = 6 (%)	FLO N = 6 (%)	FE100 N = 6 (%)	FE300 N = 6 (%)	FE500 N = 6 (%)	LE100 N = 6 (%)	LE300 N = 6 (%)	LE500 N = 6 (%)
POI (seconds)								
2 nd Week, Δ	24.7	16.3	29.9	16.5	49.2	4.7	32.7	35.3
Improvement (%)	10	9	32	-6	35	-6	33	28
P-value	0.184	0.376	0.110	0.371	0.010	0.799	0.081	0.060
3 rd Week, Δ	8.9	17.2	-3.7	-15	10.3	-25.3	41.5	-35.3
Improvement (%)	15	9	-7	-44	5	-55	40	-55
P-value	0.760	0.553	0.899	0.604	0.721	0.383	0.156	0.226

POI: Period of immobility, FLO: Fluoxetine, FE: Fruit Extract, LE: Leaf Extract. Δ: mean difference from 1st week. [†]RM two-way ANOVA and post-hoc (LSD with Bonferroni correction at $\alpha = 0.05/16 = 0.003125$)

Table 05: Mean comparison from control of antidepressant characteristics (POI) using tail suspension test

Antidepressant Characteristics	FLO N = 6 (%)	FE100 N = 6 (%)	FE300 N = 6 (%)	FE500 N = 6 (%)	LE100 N = 6 (%)	LE300 N = 6 (%)	LE500 N = 6 (%)
POI (seconds)							
1 st Week	78.3 (0.006)	62(0.027)	70.7 (0.012)	34.9(0.2 04)	83.2(0.00 4)	59.2(0.03 4)	47.2(0.088)
2 nd Week	70 (≤0.001)	67.2 (0.001)	62.5 (0.003)	59.3(0.0 04)	63.2 (0.002)	67.2 (0.001)	57.9(0.005)
3 rd Week	86.7 (0.013)	49.5(0.14 3)	46.9(0.16 6)	36.3(0.2 80)	49(0.147)	91.9(0.00 8)	3.0(0.928)

POI: Period of immobility, FLO: Fluoxetine, FE: Fruit Extract, LE: Leaf Extract. Δ: mean difference from control (p-value using RM two-way ANOVA and post-hoc (LSD with Bonferroni correction at $\alpha = 0.05/21 = 0.0024$)

Table 06: Mean ± SD of spontaneous cognitive effect using Y-Maze Test

Cognitive Effect	Control N = 6 (%)	SCOP N = 6 (%)	FE100 N = 6 (%)	FE300 N = 6 (%)	FE500 N = 6 (%)	LE100 N = 6 (%)	LE300 N = 6 (%)	LE500 N = 6 (%)
Entries (%)								
Day 1 at 10AM	40.8±14.6	32.3±5.1	50.9±11.4	58.3±14	57.2±20.8	64.6±13.6	54.7±20.2	59 ±9.2
Day 1 at 2PM	43.9±16.6	35.5±14.2	50.2±4.8	54.5±7.5	57.4±13	59.7±17.8	68.7±13.2	49.4±15.1
Day 2 at 10AM	45±12.7	37.6±7.6	61.7 ±17.3	50.9±14.7	60.4±7.7	61.7±13.7	65.2±13.9	63.5±17.3
Day 2 at 2PM	43.1±16	36.9±9.7	50.9±12.1	55.2±15.9	65.6±12.4	58.6±12.5	61.2±11.6	57.5±6.8
Day 3 at 10AM	41.9±16.5	34.1±9.7	53.3±5.4	66.6±6.4	58.5±9.7	60.9 ±19.8	57.3±4.8	59 ±17.1

Day 3 at 2PM	45.6±12.6	38.1±16.4	51.4±14.8	51.3±17	62.1±12	57.3±11.6	63 ±7.8	58.6±8.5
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SCE: Spontaneous Cognitive effect, SCOP: Scopolamine FE: Fruit Extract, LE: Leaf Extract.

Table 07: Mean comparison from control of spontaneous cognitive characteristics (SCE) using Y-MAZ

Cognitive Effect	SCOP N = 6 (%)	FE100 N = 6 (%)	FE300 N = 6 (%)	FE500 N = 6 (%)	LE100 N = 6 (%)	LE300 N = 6 (%)	LE500 N = 6 (%)
Entry							
Day 1 at 10 AM	8.6 (0.312)	-10.2 (0.232)	- 17.6(0.042)	-16.4 (0.057)	- 23.8(0.007)	- 13.9(0.104)	- 18.2(0.036)
Day 1 at 2 PM	8.5 (0.283)	- 6.3(0.421)	- 10.6(0.179)	-13.5 (0.088)	-15.8 (0.048)	-24.8 (0.003)	- 5.5(0.482)
Day 2 at 10 AM	7.4 (0.350)	- 16.7(0.038)	-5.9(0.455)	-15.5 (0.054)	-16.7 (0.039)	-20.3 (0.013)	-18.6 (0.022)
Day 2 at 2 PM	6.2 (0.397)	- 7.8(0.283)	-12.2 (0.097)	-22.6 (0.003)	-15.6 (0.036)	-18.2 (0.015)	- 14.5(0.050)
Day 3 at 10 AM	7.9 (0.282)	-11.5 (0.118)	-24.8 (0.001)	-16.7 (0.026)	-19.1 (0.011)	-15.4 (0.038)	-17.2 (0.021)
Day 3 at 2 PM	7.5 (0.321)	-5.8 (0.443)	-5.8 (0.447)	-16.5 (0.033)	-11.8 (0.125)	-17.5 (0.025)	- 13(0.090)

SCEI: Spontaneous cognitive effect, SCOP: Scopolamine, FE: Fruit Extract, LE: Leaf Extract., Δ: mean difference from control (p-value using RM two-way ANOVA and post-hoc (LSD with Bonferroni correction at $\alpha = 0.05/21 = 0.0024$)

DECLARATIONS:

Ethical approval & consent to participate:

The study was approved by University of Karachi, ASRB/No/06254/Pharm. November 18.

Consent for publication:

The consent for publication was taken from all participants.

Competing interests:

The authors declare that they have no competing interests.

Funding:

The current study did not receive any funding.

Acknowledgements:

I would like to thank my family and all the participants specially Dr. Waqas Ahmed Farooqui and Mr. Kashif who cooperated with us, without whom this study would not have been possible.

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