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# Evaluation of Anti-Depressant Activity of Ethanolic Extract of *Phoenix Dactylifera Lin.* And *Litchi Chinensis Sonn.* Using Experimental Animals.

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***Abstract***
*Depression is a basic mental condition, about which a mixture of neurochemical hypothesis exist and various anti-depression medications are accessible, anyway their adequacy doesn't remain constant with the whole scope of populace experiencing this issue. In addition, the symptoms and the medication side effects are significant limitations in its clinical utility. Additionally, herbal medications are generally utilized over the globe due to their wide appropriateness and restorative viability combined with least side impacts, which thus has quickened the logical research with respect to the stimulant action. The present study was proposed to evaluate the antidepressant activity of ethanolic extract of Phoenix dactylifera & Litchi chinensis, which is assessed by invivo screening models namely, tail suspension test in mice and forced swim test in rats. Depression is instilled in rats by giving diazepam p.o 5mg/kg b.w. for 8 consecutive days. Oral dosing of E.E.P.D, E.E.L.C & E.E.P.D+E.E.L.C modify behavior and also changes their neurochemical estimate. This is determined by monitoring behavioral parameters such as immobility time that is found to be 158.51± 0.087***, 136.00±0.016**, 123.00± 0.083* in tail suspension test and 153.34±0.56***, 137.32±0.72**, 113.68±0.67* in forced swim test as well as biochemical parameters such as altered monoamine neurotransmitters which are found to be DA (0.41±0.07 ***, 0.60±0.07**, 0.67±0.01); 5HT (0.31±0.08**, 0.41±0.29**, 0.64±0.04*); NE (0.33±0.05 **, 0.47±0.06**, 0.65±0.08 *) respectively when compared to vehicle and standard control . The rat brain of 1 animal from each group is dissected out hippocampal CA1 and cerebral cortex region is examined for histopathological studies. When the toxic, standard and test group slides are compared with one another, it was found with plant extracts, particularly E.E.P.D that neuronal degeneration is less when compared to toxic but not as much as standard.*

***Key Words:*** *Depression, Neurochemical, Phoenix dactylifera, Litchi chinensis, Diazepam, Monoamine neurotransmitters.*

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## I. Introduction

Depression might be identified as a particular change in state of mind, trouble, lack of care, sadness, unresponsiveness. A negative self-idea related with self-censures and self-fault. Backward and self-reformatory wishes, wants to get away, cover up or kick the bucket. Other changes like loss of appetite, a sleeping disorder, loss of moxie. Additionally change in action level, for example, hindrance, or fomentation.[1]

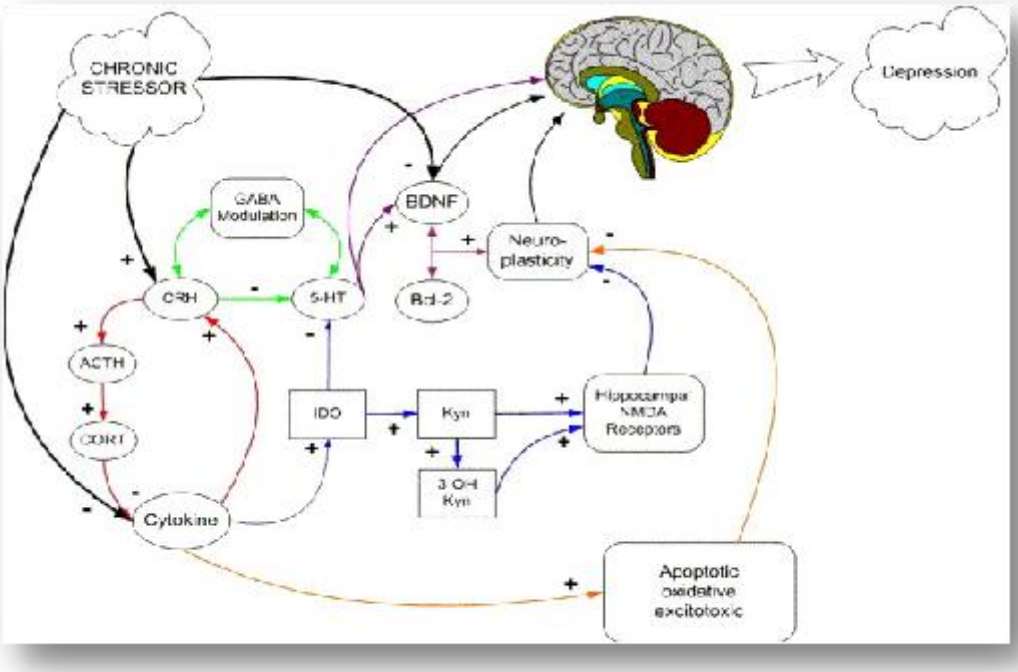



**Fig. 1) pathophysiology of depression**

Depression alludes to a wide scope of psychological wellness issues portrayed by the non-attendance of constructive outcome (loss of intrigue and delight in common things and encounters), low state of mind and a scope of related emotional, subjective, physical and social symptoms. Brain determined neurotropic factor (BDNF) that is nerve development factor are basic and the proof recommend that downturn is caused with the deficiency of neurotropic help. This is a noteworthy biochemical theory of depression, this theory states that the depression is connected with the functional deficiency of monoamine transmitters, noradrenaline and 5-Hydroxy tryptamine at certain areas of the brain. Hypothalamic neurons controls pituitary function and hypothalamic cells release corticotrophin release hormone (CRH), this hormone stimulates pituitary cells to release Adrenocorticotrophic hormone (ACTH), which inturn leads to cortisol secretion. Therefore in depressed patient's plasma cortisol level is usually high. Corticotrophin releasing hormone is widely distributed in brain also has behavioural effects that are different from its endocrine functions. Therefore the hyper function of CRH and hypo function of of Monoamine can cause depression. Elevated CRH levels are linked with stress and in multiple cases depression gets severe by periods of chronic stress.[2]

The inference for depression are diminished cerebrum levels of monoamines like noradrenaline, dopamine and serotonin. In this manner, drugs re-establishing the diminished degrees of these monoamines in the cerebrum either by repressing monoamine oxidase or by restraining reuptake of these synapses may be productive in the treatment of depression.[3]

## II. Material And Methods

The current study is focused on identifying the individual and combination, anti-depressant effect of two different plants. The plants and parts of plants used here are mesocarp of *phoenix dactylifera lin.* and fleshy aril of *lichi chinensis sonn.* Depending upon the phytochemicals present in them. Generally, for anti-depressant activity phytochemicals responsible are carbohydrates, alkaloids, flavonoids, saponins, tannins, sterols, phenols, proteins and triterpenoids according to the literature review. The plants have also been chosen due to their indigenous nature. The above herbal drug extract is given to wistar rats and mice for evaluation of their anti-depressant action.

In-vivo screening methods used for evaluation of anti-depressant activity are tail suspension test in mice and forced swim test in rats. Various examinations are done to identify the anti-depressant effect such as assessment of behavioural parameters, neurochemical estimation of monoamines in blood samples, and microscopic examination of isolated rat brain for neuronal activity in hippocampus and cerebral cortex.

**Phoenix dactylifera**

**Fig. 2) dried date fruit.**

Chemical constituents: contains carbohydrates (glucose, sucrose, fructose), alkaloids, steroids, flavonoids, tannins and vitamins. Four phenolic acids and nine bound phenolic acids were probably distinguished. (glucose, sucrose, fructose) , dietary fibres, fats, proteins, minerals, lipids, vitamins, rich in phytochemicals like phenols, sterols, anthocyanins, carotenoids, procyanidins and flavonoids.

Medicinal uses: anti-mutagenic, anti-fungal, anti-viral, hepato-protective and nephro-protective properties, anti-inflammatory, anti-oxidant property, anti-hyperlipidemic, gastro-protective agent, anti-cancer, immunostimulatory, gonadotropic activity.[4]

**Litchi chinensis**

**Fig. 3) lychee fruit**

Chemical constituents: All parts of the plant are rich sources of phytochemicals such as epicatechin; procyanidin A2 and procyanidin B2; leucocyanidin; cyanidin glycoside, malvidin glycoside, flavanoids and saponins; butylated hydroxytoluene; isolariciresinol; kaempferol; rutin; and stigmasterol.[5]

Medicinal uses: anti-cancer, anti-oxidant, hypoglycemic, anti-bacterial, anti-viral properties anti-inflammatory activity, anti-tussive, anti-pyretic, and haemostatic, analgesic activity.[6]

## III. Materials:

The fresh fruits of *Phoenix dactylifera* and *litchi chinensis* were obtained from a local manufacturing company. The plant specimens were authenticated by DR. K. MADHAVA CHETTY Assistant professor of botany, Department of Pharmacognosy, Sri Venkateshwara University, Tirupathi.

**Standard drug:** Imipramine (15mg/kg) i.p is used as a reference standard drug.

**Other chemicals:**

- Ethanol – solvent for extraction.
- Diazepam (5mg/kg) p.o – to induce depression.
- Normal saline – for reconstitution of plants P.D and L.C
- Ethanolic extract of P.D, L.C, and P.D+L.C

## IV. Methodology:

**1. Extraction method:** Maceration technique was used for extraction of plants. Requirements are as follows;

Solvent: Ethanol (99.9%)

Apparatus: Porcelain jars, Beakers, Glass dishes, Foil wrap and Muslin cloth.

Maceration process:

The seeds of the fruits were carefully removed and the fleshy region of the fruit (mesocarp) is dried at room temperature prior to extraction. After drying the flesh, it is crushed into coarse powder (500kg) each and then each one macerated with 1 litre of analytical grade of ethanol for 48 hours. Firstly, in a clean and dry porcelain jar, the grounded drug and ethanol (500ml) is added in 1:2 ratio and the powdered drug is left to be soaked in ethanol at room temperature, after 24 hours again the remaining quantity of ethanol (500ml) is instilled to the same porcelain jar and is again kept aside for another 24 hours. After completion of 48 hours, all the contents in the porcelain jar was filtered through muslin cloth. Extracts were obtained when the filtrate was concentrated by evaporating the filtrate at room temperature.

**Fig.4) Ethanolic extract of phoenix dactylifera and litchi chinensis**

**2. Phytochemical screening**

The crude extract was then screened for the presence of secondary metabolites like; carbohydrates, alkaloids, sterols, phenols, saponins, tannins, flavonoids, proteins, triterpenoids and amino acid by following standard procedures given in practical pharmacognosy by K.R. Khandelwal and C.K. Kokate. All the chemicals and reagents used were of analytical grade.

**3. Experimental animals**

Male Albino wistar rats weighing 180-200 g, and swiss albino mice 15-25g are fed with food (rat chow) and water ad libitum, and maintained at a relative humidity of 65% to 86%, temperature of 23℃ to 25℃, in a schedule of 12 hours of light and 12 hours of dark. All experiments were performed according to the guidelines of the Ethical committee (CPCSEA).

**Fig 5) Experimental rats and mice**

**4. Acute toxicity studies**

Effective dose and LD50 of test drugs were determined by performing ATS following OECD guidelines 425. 4 gatherings of 3 mice and 3 rats each with 5 chosen dosages of the test substance i.e 200mg/kg, 400mg/kg, 1600mg/kg, 2000mg/kg by oral gavage. Animals are looked for mortality, signs of gross harmfulness and lead changes at 30 min, 2, 4 and 6 hours after the starting and therefore consistently for 14 persistent days. Body weight is recorded going before dosing, and on days 7 and 14.

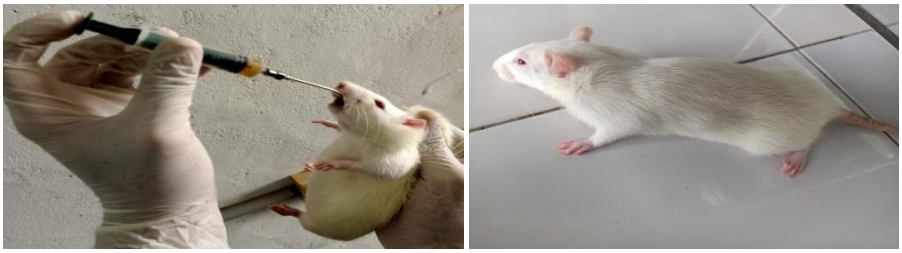


**Fig 6) ATS of test drugs in experimental animals.**

**5. Experimental design**

**Albino wistar rats (180-200g), Swiss albino mice (15-25g)**

| Groups | Age of animals in weeks | Number of animals | Treatment | Dose |
|---|---|---|---|---|
| Group I | 12 | 6 | Normal control (Normal saline) | 0.2ml/100g p.o |
| Group II | 12 | 6 | Negative control (Diazepam) | 5mg/kg p.o |
| Group III | 12 | 6 | Standard drug (Imipramine) | 15mg/kg i.p |
| Group IV | 12 | 6 | Ethanolic extract of Phoenix dactylifera | 200mg/kg p.o |
| Group V | 12 | 6 | Ethanolic extract of litchi chinensis | 200mg/kg p.o |
| Group VI | 12 | 6 | Ethanolic extract of phoenix dactylifera + litchi chinensis | 200mg/kg p.o |

**6. Screening models for Anti-depressant activity**

**i. Tail suspension test in mice.**

- **Procedure :**

Male mice weighing 20–25 g are utilized specifically. They are housed in plastic enclosures for minimum 10 days preceding testing in a 12 hour light cycle with food furthermore, water easily available. Grouping of 6 animals are given test drug and the vehicle orally 30 min preceding testing. For the test the mice are suspended on the edge of a rack 58 cm above a table top by sticky tape set roughly 1 cm from the tip of the tail. The term of idleness is recorded for 5 min. Mice are considered stationary when they hang inactively and totally unmoving for minimum of 1 minute.

- **EVALUATION**

The percentage of animals demonstrating the inactive behaviour is checked and compared with vehicle and standard treated controls.

**Fig. 7) Tail suspension test in mice.**

**ii. Forced swim test in rats**

- **Procedure:**

Test medications or standard are regulated 1h preceding testing. Credulous rats are independently compelled to swim inside an upward Plexiglas chamber (diameter:18cm ,tallness: 40cm; containing 15cm of water kept up with at 25ºC) Initially rats are hyperactive. After 2-3 min action starts to die down and is sprinkled with immobility or coasting of expanding length. After 5-6 min fixed status arrives at a level where the rat stays fixed for approximately 80% time. After 15min in water rodents are taken out and permitted to dry in a warmed fenced in area, prior to being gotten back to their home enclosures. They are again positioned in the chamber 24h later and the all-out span of fixed status is estimated during a 5min test.

- **Evaluation:**

Duration of immobility is measured in controls and animals treated with various doses of a test drug or standard.

**Fig. 8) Forced swim test in rats**

**7. Biochemical estimation**

Blood is collected by retro-orbital puncture for asessment of mono-amine neurotransmitters namely, dopamine, serotonin, norepinephrine.

**Fig. 9) Collection of blood samples from experimental animals by retro orbital puncture.**

**8. Histopathological studies**

**Extraction of rat brain:** 1 rat from each group were anaethetized using isoflurane and later euthanized. Brains were extracted out and kept in 10% neutral buffered formalin for laboratory testing. Cerebral cortex and hippocampus was examined during histological studies.

**Fig. 10) Extraction of rat brain for histopathological studies.**

## V. Results

### *1.* Phytochemical results of E.E.P.D and E.E.L.C

**Table 1) observation table of preliminary phytochemical test of E.E.P.P and E.E.L.C**

| Assay | E. E. of *phoenix dactylifera* | E. E. of *litchi chinensis* |
|---|---|---|
| **Carbohydrates** | | |
| Molisch's test | +++ | ++ |
| Osazone test | – | – |
| Test for ketones (selivanoff's test) | | |
| Barfoed's test | ++ | +++ |
| | +. | – |
| **Alkaloids** | | |
| Dragendroff's test | ++ | – |
| Hager's test | + | – |
| Mayer's test | – | – |
| **Sterols** | | |
| Salkowski's test | + | – |
| Libermann-Burchard's test | ++ | +++ |
| **Phenols** | | |
| Ferric chloride test | + | + |
| Lead acetate test | – | ++ |
| **Saponins** | | |
| Froth test | +++ | + |
| Foam test | – | – |
| **Tannins** | + | +++ |
| **Flavonoids** | | |
| Alkaline reagent test | ++ | + |
| Lead acetate test | ++ | +++ |
| Ferric chloride test | + | – |
| **Proteins and amino acid** | | |
| Biuret test | – | – |
| Millon's test | +++ | +++ |
| Ninhydrin test | – | + |
| **triterpenoids** | ++ | + |

**+ = positive, - = negative**

Ethanolic extract of the mesocarp of *phoenix dactylifera* showed presence of carbohydrates, alkaloids, flavonoids, saponins, tannins, sterols, phenols, proteins and triterpenoids. Whereas, Ethanolic extract of the fruit of *litchi chinensis* had shown the presence of carbohydrates, sterols, phenols, saponins, flavonoids, tannins, triterpenoids and proteins and amino acids.

### 2. GCMS analysis of phoenix dactylifera

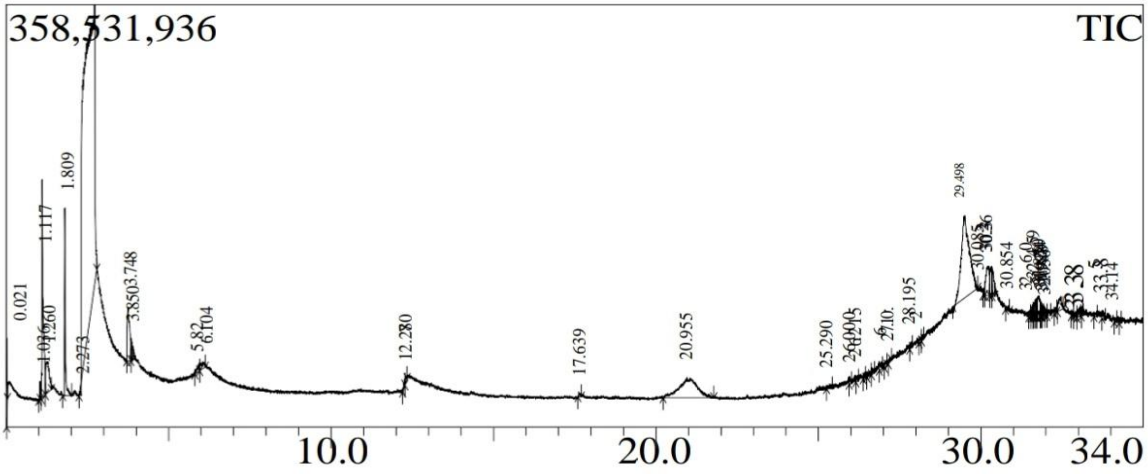



**Table 2) GCMS analysis of E.E.P.D**

| S.no | Retention time | Chemical constituents | Area % | uses |
|---|---|---|---|---|
| 1 | 12.270 | (3,4-Dihydroxyphenyl)hexylamine | 1.21 | **Anti-depression,** astringent, demulcent, emollient. |
| 2 | 34.125 | Cinnamic acid, 3,4-Dimethoxy, trimethylsilyl ester | 1.63 | **Anti-depression**, anti-fungal, anti-oxidant. |
| 3 | 31.751 | L-norephedrine | 1.59 | **Anti-depression,** myasthenia gravis |
| 4 | 32.794 | Caffeic acid | 1.33 | **Anti-depressant,** anti-cancer, anti-viral. |

### 3. GCMS analysis of ethanolic extract of *litchi chinensis*

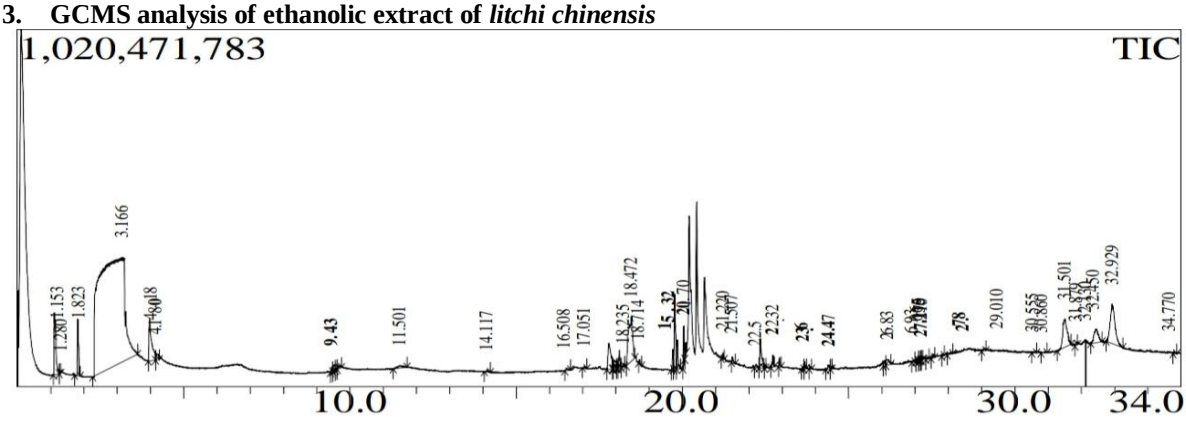



**Table 3) GCMS analysis of E.E.L.C.**

| S.no | Retention time | Chemical constituents | Area % | uses |
|---|---|---|---|---|
| 1 | 22.200 | Eicosanoic acid | 1.94 | **Anti-depressant,** anti-inflammatory. |
| 2 | 31.879 | β-amyrin | 2.26 | **Anti-depression,** Anti-oxidant. |
| 3 | 34.770 | 9-[4-Hydroxybutyl] hypoxanthine | 1.11 | **Anti-depression,** anti-inflammatory, |

### 4. Acute toxicity study

ATS for the E.E.P.D and E.E.L.C were carried out in rats and mice as per OECD Guideline No. 425. The results of these studies are as follows:

**LD50:** lethal dose range for ethanolic extract of both the plants could be considered to be above 2000mg/kg.

**ED50:** 1/10$^{th}$ of the median lethal dose (2000mg/kg) that is 200mg/kg was considered as effective.

### 5. Evaluation of behavioral parameters.

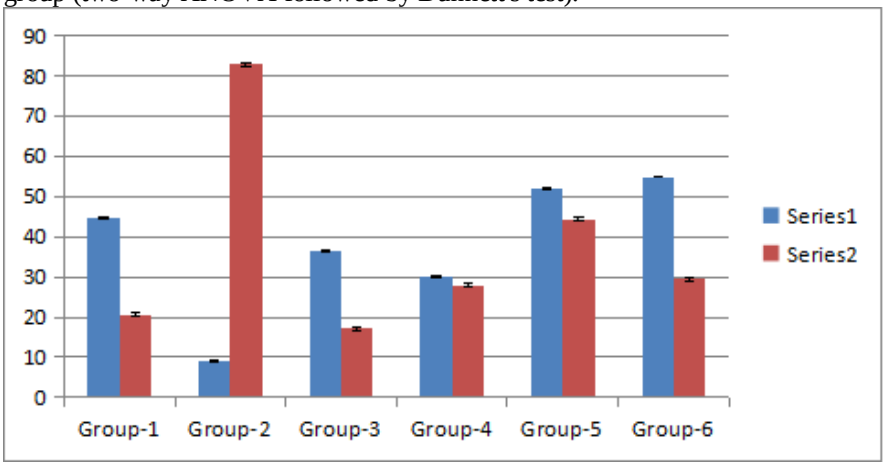
**Anti-depressant activity**

**a) Effects of phoenix dactylifera and litchi chinensis extracts on the immobility time in the Force swim test.**

**Table 4) Effect of extracts of E.E.P.D, E.E.L.C, E.E.P.D + E.E.L.C extracts and imipramine on immobility time in force swim test in albino mice.**

| Sample | Immobility time (sec.) (Mean±SEM ) | |
|---|---|---|
| | 3$^{rd}$ day | 6$^{th}$ day |
| **Normal control** | 188.01±0.99 | 186.18±0.21 |
| **Negative control:** Diazepam 5mg/kg | 54.02±1.004 | 26.31±1.033 |
| **Standard:** Imipramine (10mg/kg) | 167.01±0.88*** | 172.84±0.827** |
| **Plant 1:** E.E.P.D 200mg/kg | 142.08±0.36** | 153.34±0.56*** |
| **Plant 2:**E.E.L.C 200mg/kg | 141.68±0.63* | 137.32±0.72** |
| **Plant 1+2:** E.E.P.D 100mg/kg + E.E.L.C 100mg/kg | 107.51±0.004 | 113.68±0.67* |

Values are expressed as mean±S.E.M. (n=6). *P≤0.05, **P≤0.01, ***P≤0.001 compared with the vehicle treated control group (two-way ANOVA followed by Dunnett's test).

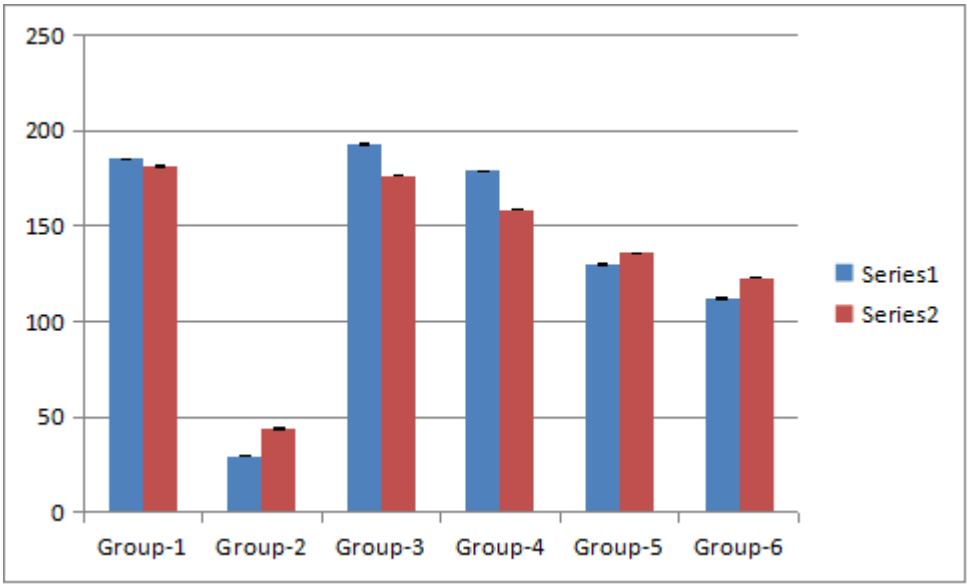



**b) Effect of phoenix dactylifera and litchi chinensis extracts on the immobility time in the tail suspension test**

**Table 5) Effect of extracts of E.E.P.D, E.E.L.C, E.E.P.D + E.E.L.C and imipramine on immobility time in the tail suspension test in albino mice.**

| Sample | Immobility time (sec.) (Mean±SEM ) | |
|---|---|---|
| | 3rd day | 6th day |
| **Normal control** | 185.21±0.036 | 181.49±0.033 |
| **Negative control:** Diazepam 5mg/kg | 29.54±0.175 | 43.97±1.023 |
| **Standard dose:** Imipramine (10mg/kg) | 193.21±0.098** | 176.68±0.11*** |
| **Plant 1:** E.E.P.D 200mg/kg | 179.00±0.034** | 158.51± 0.087*** |
| **Plant 2:** E.E.L.C 200mg/kg | 129.84±0.08* | 136.00±0.016** |
| **Plant 1+2:** E.E.P.D 100mg/kg + E.E.L.C 100mg/kg | 112.00±0.160 | 123.00± 0.083* |

Values are expressed as mean±S.E.M. (n=6). *P≤0.05, **P≤0.01, ***P≤0.001 compared with the vehicle treated control group (two-way ANOVA followed by Dunnett's test)



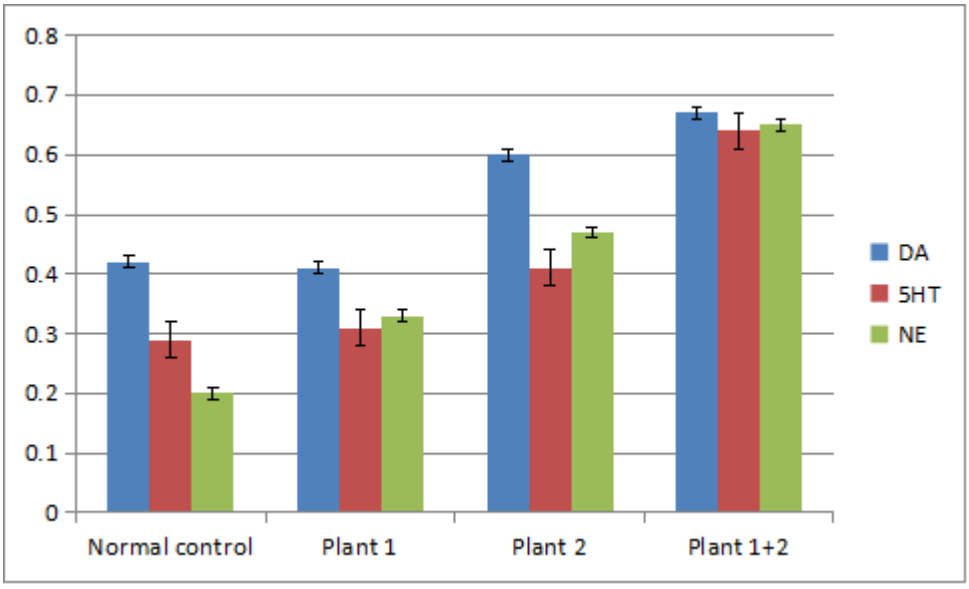

**6. Biochemical estimation of effects of *phoenix dactylifera* and *litchi chinensis* on monoamines level in Non-stressed and stressed rats.**

Effect of E.E.P.D (200mg/kg)p.o, E.E.L.C (200mg/kg)p.o, E.E.P.D (100mg/kg)+ E.E.L.C (100mg/kg)p.o or vehicle (10 ml/kg) p.o on 5-HT , DA and NE level in blood samples of nonstressed and stressed experimental rats.

**Table 6) Effect of E.E.P.D and E.E.L.C, E.E.P.D + E.E.L.C on monoamines level in blood samples of Non-stressed and stressed rats.**

| Sample | DA | 5HT | NE |
|---|---|---|---|
| **Control: Vehicle** | 0.42±0.05 | 0.29±0.04 | 0.20±0.02 |
| **Plant 1 : E.E.P.D (200mg/kg)p.o** | 0.41±0.07 *** | 0.31±0.08** | 0.33±0.05 ** |
| **Plant 2 : E.E.L.C (200mg/kg)p.o** | 0.60±0.07** | 0.41±0.29** | 0.47±0.06** |
| **Plant 1 + 2 : E.E.P.D (100mg/kg)+ E.E.L.C (100mg/kg)p.o** | 0.67±0.01 | 0.64±0.04* | 0.65±0.08 * |

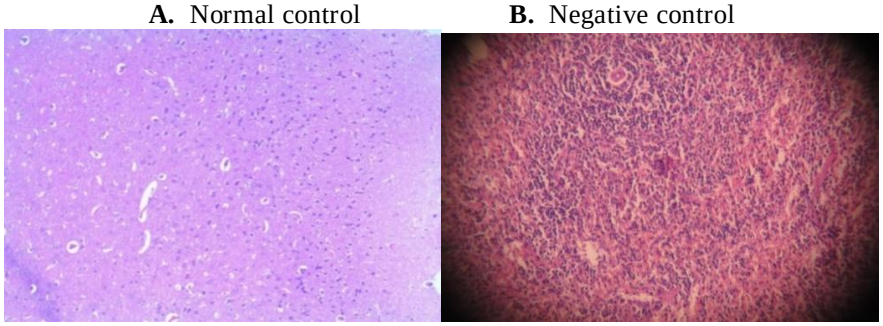
Experimental data was analyzed by two-way ANOVA test and expressed as mean±SEM (n=6), $^{*}p<0.01$ compared to nonstressed vehicle group, $^{**}p<0.001$ compared to stressed + vehicle control group.



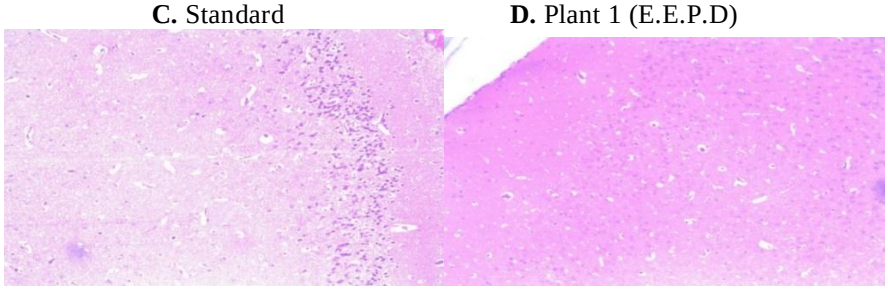

**7. Histopathological studies.**

**Cerebellar cortex**

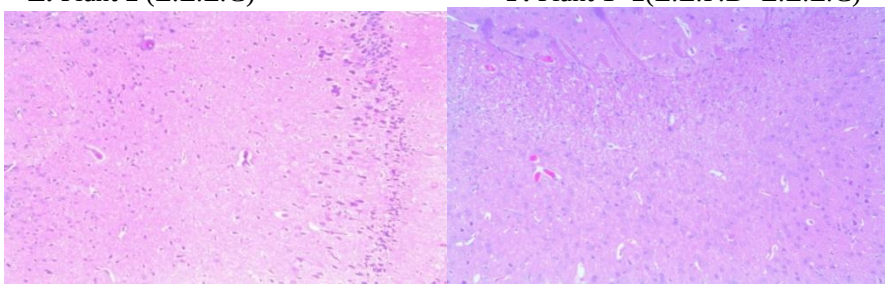
**A.** Normal control **B.** Negative control



**C.** Standard **D.** Plant 1 (E.E.P.D)



**E.** Plant 2 (E.E.L.C) **F.** Plant 1+2(E.E.P.D+E.E.L.C)



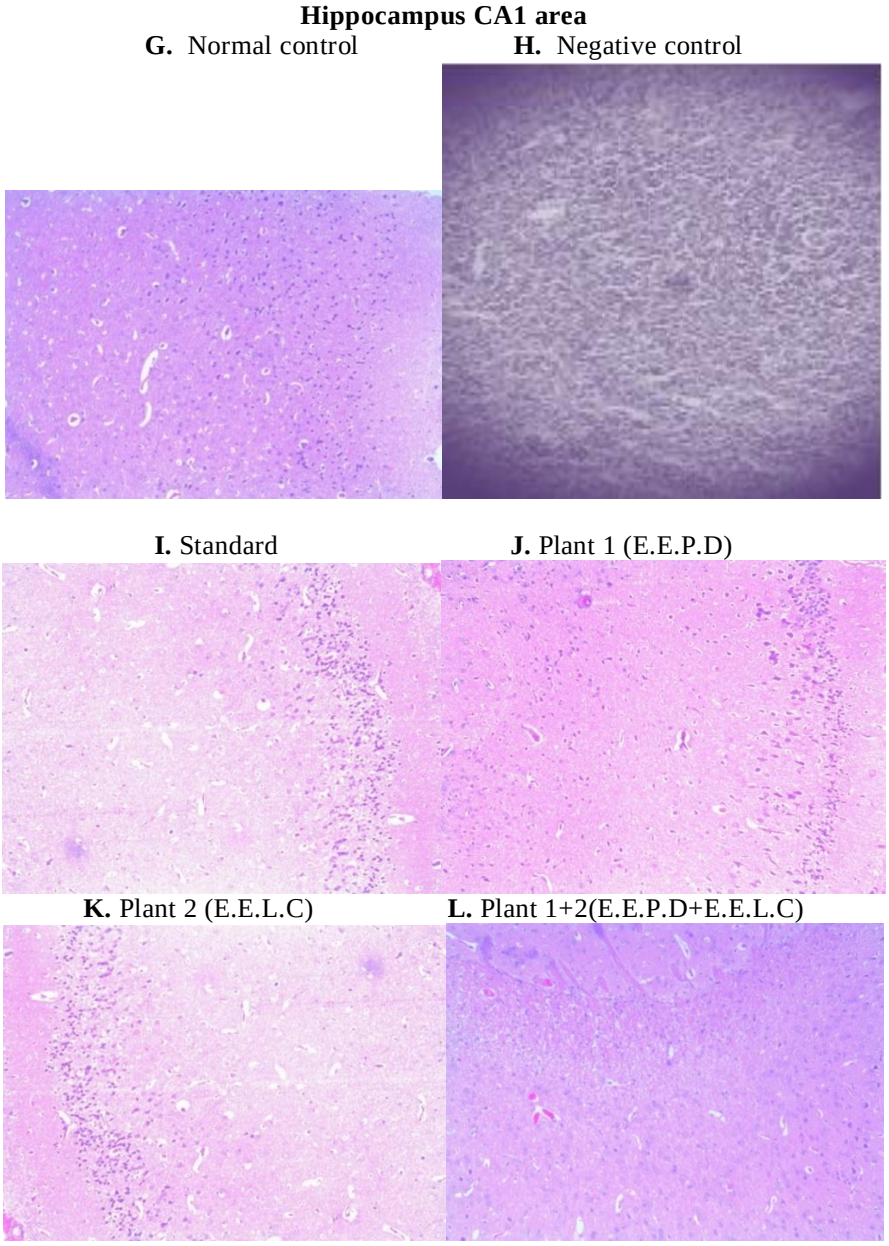



**Fig.11) Histopathology slides of cerebral cortex and hippocampus of albino wistar rats.**

Photomicrographs illustrating stained sections (x400, scale bar = 50 μm) of Wistar rats. (A-F): Cerebellar cortex sections, (G-L): Hippocampal CA1 sections. (A, G): Control sections representing normal architecture, neurons having large vesicular nuclei, and small dense neuroglial cells. (B, H): Negative control groups channeling shrunken degenerated neurons with perineural spaces that also exhibit areas of neurons loss, tied up surrounding neuroglial cells, wide neuropil and congested capillary. (C, D, E) in the upper panel and (I, J, K) in the lower panel shows treated groups normal neural architecture with large vesicular nuclei with minute perineural spaces indicating few tethered neuroglial cells. (F, L) demonstrating treated neural cells with reduction in the thickness of pyramidal layer and granular cell layer with few areas of neurons loss.

## VI. Discussion And Conclusion

*Phoenix dactylifera* is popular for its nutritional value and numerous medicinal properties. It is rich in fatty acids like stearic acid, palmitic acid, and linoleic acid. *Phoenix dactylifera* due to the presence of rich pheonlic content such as caffeic acid, ferulic acid, catechin, procatechuic acid, gallic acid, p-coumaric acid, resorcinol, syringic acid and flavonoids such as quercetin, luteolin, apigenin, rutin, isoquercitrin is an anti-oxidant. All these phytochemical constituent are highly beneficial for many diseases.[7]

*Litchi chinensis* is widely accepted in many sub-tropical and tropical regions as a healthy, beneficiary fruit. Used for curing number of ailments, similar to dates; litchi is rich in phenolic and flavonoid content.

Polyphenols and flavanols are well known for their anti-depressant activities in different animal models. Anti-depressant properties of polyphenols are closely linked to their anti-oxidant properties.

The GCMS analysis of E.E.P.D is undertaken in the present investigation confirms the chemical constituents such as 3,4-Dihydroxyphenyl)hexylamine, Cinnamic acid, L-norephedrine, Caffeic acid which are scientifically known to have anti-depressant effect. The GCMS analysis of E.E.L.C confirms the phytochemical constituents namely, Eicosanoic acid, β-amyrin, 9-[4-Hydroxybutyl] hypoxanthine which numerous studies and researches demonstrated to possess anti-depressant effect.

The acute toxicity studies were conducted according to the OECD guidelines 425. It was found that the extracts of phoenix dactylifera and litchi chinensis even at the 2000mg/kg dose had not shown any signs of toxicity confirming its non-toxic nature.

During the study of behavioural parameters as well as neurotransmitters, the extracts of phoenix dactylifera and litchi chinensis individually have shown results almost like the standard dose. While the extract of phoenix dactylifera being the most effective one throughout the study. While the combination of the plant's extracts seemed to have very less impact comparative to their individual doses.

Histological slides of group 4 (D, J) and 5 (E, K) displayed to be effective, whilst group 4 (D, J) showed the most effective action and group 6 (F, L) were seen exerting the least effect comparative to standard activity.

Outcomes of present work indicate that *phoenix dactylifera* and *litchi chinensis* exert anti-depressant effects by altering behavioural and molecular patterns in the hippocampal and cortical regions of rats exposed to stress. Therefore, the present studies confirmed the presence of such phenols and flavonoids and their content by performing GCMS analysis of the test plants. i.e *phoenix dactylifera* and *litchi chinensis* and evaluated these constituents for the active anti-depressant activity in animal models as they possess similar physiology to humans for the positive result and active neurological effect of these drugs in humans.

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