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Research Article

Pharmacological Evaluation of Anti-depressant activity of *Aegle Marmelos* ethanolic leaves extract in mice

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Abstract

Bael (A. marmelos) is an important medicinal herb which has been and extensively used in Ayurveda, Siddha and other medicinal systems. The aim of this study is to evaluate the pharmacological activity of leaves part of the plant Aegle marmelos. Ethanolic extract of Aegle marmelos leaves prepared by successive extraction technique. This research carroed out to find out the Percentage Yield of Extract of *Aegle marmelos*, determination of LD_{50} of the EEAML as per OECD guidelines and to investigate the anti-depressant effect of *Aegle marmelos* leaves extract using tail suspension test (TST) and forced swim test (FST) parameters at dose levels of 200 mg/kg and 400 mg/kg respectively in albino swiss mice. *Aegle marmelos* leaves extract showed significant antidepressant activity probably due to GABA facilitatory action of phytoconstituents such as flavonoids, tannic acid, marmesinin, phenols, saponin etc. Results suggested that cortisol and corticosterone responded differently to severe stressors with cortisol being a quicker responder than corticosterone.

Keywords: *Aegle Marmelos,* phytoconstituents, Anti-depressant activity

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INTRODUCTION

Depression is defined as disorders of mood rather than disturbances of thought or cognition; it may range from a very mild condition, bordering on normality, to severe psychotic depression accompanied by hallucinations and delusions. Major depression is a common disorder that continues to result in considerable morbidity and mortality despite major advances in treatment.[1]

Different types of depression:

1. Unipolar depression: in which mood swings in same direction and are common, non –familial, clearly associated with stressful life events.

2. Bipolar depression: also called endogenous depression. Itshaving familial pattern, usually found in adults' life and is much less common.[2]

The antidepressive pathways involved in the monoamines noradrenaline (NA) and 5-HT, which act on a kinase linked receptor (TrkB), switching on the genes that protect neurons against apoptosis and also promote neurogenesis[3,4]

Aegle Marmelos[5-10]

Bael (*Aegle marmelos*), a plant of Indian origin having tremendous therapeutic potential, it is belonged to family Rutaceae, it is known by the several other names in the different parts of the country and also outside of the country. The utility of bael is mention in the Indian ancient system of medicine, every part of the bael tree such as root, bark, leaf, flower, fruits, seed and even its latex are also important in several traditional system of medicine, that's why it is one of the most important plants in the India. The bael fruit is having lots of pharmacological activity, fruit of it possesses anti dyspepsia, anti diarrhea and anti dysentery. The fruit is also used as a dietary supplement, it is also used to cure intermittent fever, mental disease, hypoglycemic effect, anti fungal effect, anti microbial, analgesic, anti inflammatory, among its many properties are antipyretic, anti-dyslipidemic, immune-suppressive, anti-proliferative, wound-healing, anti-fertility, and insecticidal.

Bael plant acts as a "Sink" for chemical pollutants as it absorbs poisonous gases from atmosphere and makes them inert or neutral. It is a member of plant species group known as 'Climate Purifiers', which emit a greater percentage of oxygen in sun light as compare to other plants. The tree is likewise classified as a "Fragrant" species. Aegle marmelos is one of the medicinal plants of India. The Aegle marmelos, (Bael) leaves, bark, roots and fruit have been used for over 5000 years in the Indian traditional system of medicine, the Ayurveda and in various folk medicine to treat various diseases. The

Rutaceae family includes Aegle marmelos, sometimes referred to as Bael. The leaves of the aegle marmelos have long been presented in worship to Shiva and Parvathi.[9-11]

Bael tree is a moderate sized, slender, aromatic tree, 6.0 -7.5 m in height, and 90 to 120 cm in girth. It grows up to 18 meters tall it has leaf with three leaf lets ovate-lanceolate lateral subsessile and terminal long petiolate.[12]

Numerous secondary metabolites, primarily alkaloids, coumarinoids, terpenoids, steroids, flavonoids, etc., have been documented to be present in A. marmelos.
Leaf: Aegle marmelos leaves included rutin, marmeline, marmesinin, lupeol, aegelin, and limonene. % of α-Phellandrene and % of p-cymene were found in leaf oil.

Fruit: A. marmelos fruit consist of Marmelosin, Luvangetin, Aurapten, Psoralen, Marmelide, α-Phellandrene, p-cymene, Tannins. January is when the bael fruit's tannin concentration reaches its peak. Fruit's light coloration is attributed to carotenoids. Umbelliferone, marmelosin, and skimmianine are the bael plant's three medicinally active constituents. Fruits in addition contain alkaloids like aegeline and marmelline.

Root: A. marmelos root contain coumarins such as scoparone, scopoletin, umbellliferone, marmesin and skimming.

Bark: A. marmelos bark contains Skimmianine, Fagarine, Marmin.

Seed: Seed contains Anthraquinones, Linoleic acid, Linolenic acid, Palmitic acid, Stearic acid, Essential oil: D-limonene, A-D-phellandrene, Cineol, Citronellal, Citral, P-cyrnene, Cumin aldehyde.[13,14,15]

MATERIALS AND METHODS

Source of data: All experiments were planned to generate data from the laboratory studies i.e.; experiments were performed as described in reference, experimental studies in journals and in textbooks accessible with Jalandhar's SSIP library, the college, and other establishments.

The whole study was divided into four Phases to generate the data as follows.

Phase I: To prepare extract of leaves of Aegle marmelos (ethanolic) by successive extraction technique.

Phase II: To find out the Percentage Yield of Extract of Aegle marmelos.

Phase III: The third phase involves determining the kind of phyto-constituents found in Aegle marmelos.

Phase IV: To perform Antidepressant activity of extract of Aegle marmelosat various dose level (200& 400mg/Kg).

Methods of collection of data:

The methods for extract of ethanolic Aegle marmeloscan be used by the dose dependent study and time dependent study. Dose is fixed at 200& 400mg/Kgof each extract of Aegle marmeloson the basis of the literature review and dosage regimen is scheduled.

The data will be collected, based on laboratory animal experimentation. The Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA), Ministry of Environment and Forests, Government of India, authorized the experimental protocol, which was then conducted in accordance with its recommendations. (Reg. No. 2011/PO/Re/S/ 18/CPCSEA and date of registration is 1/5/2018) for the use and care of experimental animals. Adequate measures were taken to minimize pain or discomfort with animal's experimental procedure. Research protocol is duly approved by IAEC/CPCSEA (IAEC/SSIP/2022/PR-027).

Chemical:

All chemicals of analytical grade were procured from Sigma chemical, USA and S. D. Fine Chem. Ltd., India.

Collection and Preparation of plant material:

The ethanolic extract ofleaves part of plant Aegle marmeloswereprocured from Shreedha Phyto Extract, Jaipur. The same group also provided a certification of the plant's identity and quality (Certificate of Analysis).

General Methods of Extraction of Medicinal Plants[16-23]

The general techniques of medicinal plant extraction include[16]

Maceration.
Infusion.
Digestion.
Decoction.
Cold percolation.
Hot continuous extraction.

Hot continuous extraction (Soxhlation):[17]

The Soxhlet method, which was described in 1879, is the most commonly applied for continuous extraction of plant materials. In this method, the finely ground crude drug is placed in a porous bag or "thimble" made of filter paper, which is placed in chamber E of the Soxhlet apparatus. Condenser D receives the condensed vapours of the heated extracting solvent in flask A. The crude medication is extracted by contact when the condensed extractant drops into the thimble holding it. The liquid in chamber E siphons into flask A when the volume of liquid reaches the top of siphon tube C. This procedure is repeated repeatedly until a drop of solvent from the siphon tube evaporates without leaving any trace, the liquid contents of chamber E siphon into flask A.This process is continuous and is carried out until a drop of solvent from the siphon tube does not leave residue when evaporated.

Aqueous extract[18]

Approximately 100 g. of shade-dried powder of leaves plant was taken in a 1 L beaker and chloroform: water (1:99) was added up to a sufficient level to immerse the drug completely. To stop microorganisms from growing, a preservative called chloroform was applied. This setup

was left alone for 72 hours while stirring periodically. In order to get a clear, watery extract with a greenish hue, the contents of the beaker were finally vacuum-filtered. The extract was fully dried in a desiccator and concentrated under high vacuum. The extract was concentrated under high vaccum and completely dried in a desiccator.

Ethanolic extract[19]

The leaves of plant were shade-dried and powdered separately. The powder (100 g.) was packed in a soxhlet apparatus and subjected to continuous hot percolation for about 8 h. with ethanol (350 ml.) as solvent. Under vacuum, the extract was concentrated into a semi-solid mass, and a desiccator was used to dry it entirely.

Percentage Yield of Extract[20]

The percentage yield of extract of Aegle marmelosleaveswas calculated using the formula given below.

Percentage yield= (weight of extract in gram/weight of drug powder in gram) x100

Preparation and administration of crude extracts/standard drugs[21-22]

The commonly employed technique for separation of active constituents from the crude drugs is called extraction. Using specific solvents in typical extraction processes, extraction is the process of separating the medicinally active parts of plant or animal tissues from the inactive or inert components. The somewhat impure liquids, semisolids, or powders that are made from plants in this way are only meant to be used topically or orally. Standardized extraction techniques for crude pharmaceuticals, or medicinal plant components, are intended to extract the parts that are therapeutically desirable and remove any undesired material by treating the substance with menstrum, a selective solvent. Following standardization, the resulting extract may be employed as a therapeutic agent. These extracts contain complex mixture of many medicinal plant metabolites such as alkaloids, glycosides, terpenoids, flavonoids and lignans.

Acute oral toxicity study[23]

Acute toxicity study for the ethanolic leaves extract of "Aegle marmelos" was done according to the OECD guidelines No: 423 and low, medium and high dose was selected for treatment.

Method: - The overnight fasted mice were divided into 04 groups, each group consisting of 3 animals. The EEAML was given in various doses (5, 50, 300 and 1000) by oral route with a gawage. Following extract administration, the animals were watched closely for the first two hours and the next day to look for behavioral changes, as well as for tremors, convulsions, salivation, diarrhea, lethargy, sleep, and coma. They were also watched for toxic symptoms and mortality for up to fourteen days. The mice that survived the 14 days of acute oral toxicity were rehabilitated and utilized again in experiments.

Behavioral tests for depression in mice/ Mouse as a model for depression:

Forced swimming test: The most frequently used behavioral model for screening antidepressant effect in mice. All mice were individually forced to swim in open glass chamber (25 ×15 × 25cm) containing fresh water to a height of 15 cm maintained at 26°±1°C. Each animal will show enthusiastic movement during initial 2 min period of the test. The duration of immobility will be manually recorded during the next 3 min of the total 5 min testing period. Mice will be considered to be immobile when they ceased struggling and remained floating motionless in water, making only those movements necessary to keep their head above water. Following swimming session, mice will be towel dried and returned to their housing conditions.[24]

Tail suspension test in mice: In this model, Groups of animals are treated with the test compounds or the vehicle by intra peritoneal injection/ oral 30 min prior to testing. The mice are hung during the test by adhesive tape that is positioned about 1 cm from the tip of their tails on the edge of a shelf that is 58 cm above a table top. The period of immobility is noted for five minutes. When mice hang silently and still for at least a minute, they are deemed immobile.[25]

Rapid effects of Forced Swimming Stress/Tail Suspension Test Stress on dynamics and correlation of plasma corticosterone

To study the rapid effects of severe stresses on dynamics and correlation of plasma corticosterone, mice were exposed to forcedswimming for different times before being selected to collect blood for hormone assays. During forced swimming stresses, whereas the concentration of cortisol increased to the highest level within 3 min, the concentration of corticosterone did not reach the highest level until 40 min of the stresses. A strong correlation was observed between the two hormones during both forced swimming test and tail suspension test. Cortisol responded to severe stresses more quickly than corticosterone, according to the results, which also revealed that the two hormones behaved differently.

<u>Biochemical estimation: -</u>

Collection of Blood Samples:

On 15th day, blood (0.3 ml) was withdrawn from tail vein from all groups of mice. Blood samples were centrifuged at 2500 rpm for 10 min using refrigerated centrifuge (Paramount scientific works, Ambala cantt, India) to separate the plasma, which was used for estimation of corticosterone levels.

Estimation of plasma corticosterone levels

The quantitative estimation of corticosterone levels in the blood plasma was performed by the method of Bartos and Pesez, 1979. To 1.0 ml of sample in ethanol, 0.50 ml of 0.10 % solution of p-nitroso-N, N-dimethylaniline in ethanol was added and After five minutes of cold water immersion, 0.50 ml of 0.10 N-sodium hydroxide was applied to the tubes. The tubes were sealed against light and filled with cotton-wool

before being left at 0°C for five hours. 2.0 ml of pH 9.8 buffer, 5.0 ml of phenol in ethanol (0.1% solution), and 0.50 ml of potassium ferricyanide (1.0% aqueous solution) were added to the solution above. For ten minutes, the tubes were maintained at 20±2°C in a water bath. The solution was measured using a UV-visible spectrophotometer at 650 nm.

On day 1, groups 1 through 6 had their tails drawn, and the average amounts of corticosterone in the tail blood were then calculated by adding their levels. Refer to the corresponding experimental design for the treatment of Groups.

Experimental Design:

Group 1: control (solvent)
Group 2: mice treated with EEAML (Low dose)
Group 3: mice treated with EEAML (High dose)
Group 4: mice treated with fluoxetine.

Statistical analysis:

All the results/values will be expressed as Mean ± standard error of mean (S.E.M.) n= 6 in each group. Data will be analyzed using one-way ANOVA (Graph pad prism version 5.00 software) followed by suitable post test like Tukey's test. $p<0.05$ will be considered as statistically significant.

RESULTS

Acute oral toxicity study

It was examined for the first 24 h and subsequently for 14 d for indicators of toxicity (changes in mucous membranes, skin, hair and eyes, circulatory, respiratory, somato-motor activity and behavior pattern) and death. It has been noted that no change in behavioural reactions and observation demonstrates any acute oral toxicity.Two weeks of observation and dosing were administered to the remaining four animals. The LD50 was then approximated.

Effect of *Aegle marmelos* extract on body weight (g) of mice

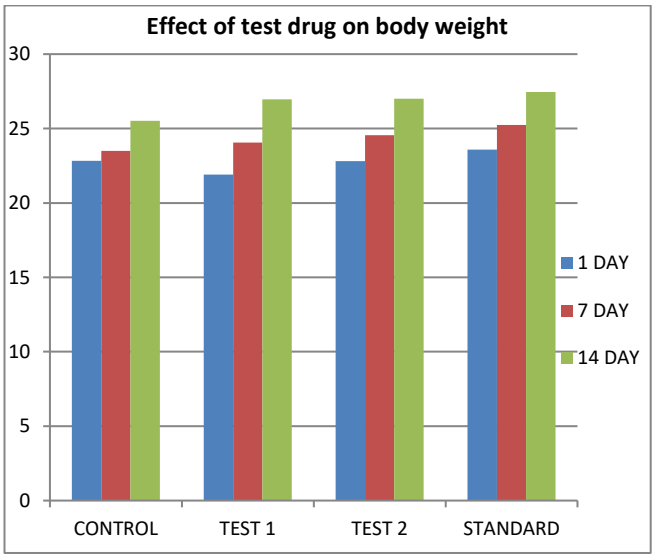

Figure 1: Graph Showing Effect of *Aegle marmelos* extract on body weight (g) of mice.

Effect of *Aegle marmelos*extract on Feed intake (g) of mice

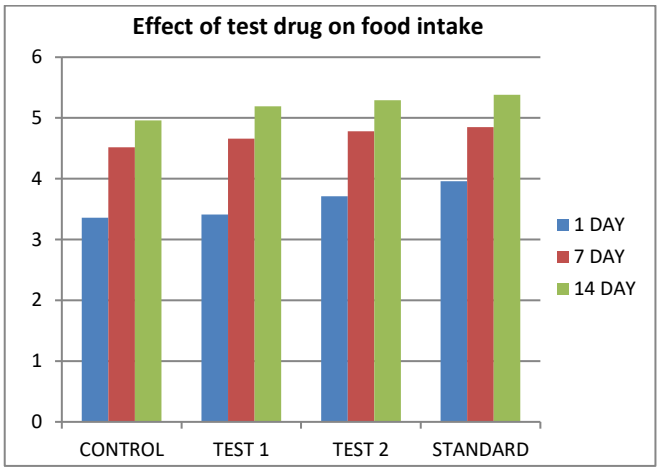

Figure 2: Graph Showing Effect of *Aegle marmelos* extract on Feed intake(g) of mice

All values represent = Mean ± SEM, n= 6 in each group [a] denotes $p<0.05$ as compared with to normal control group and [b] denotes $p<0.05$ as compared to FXT (10 mg/kg p.o.) treated group (One way ANOVA followed by Tukey's test).

Effect of *Aegle marmelos*extract on Water intake (ml) of mice

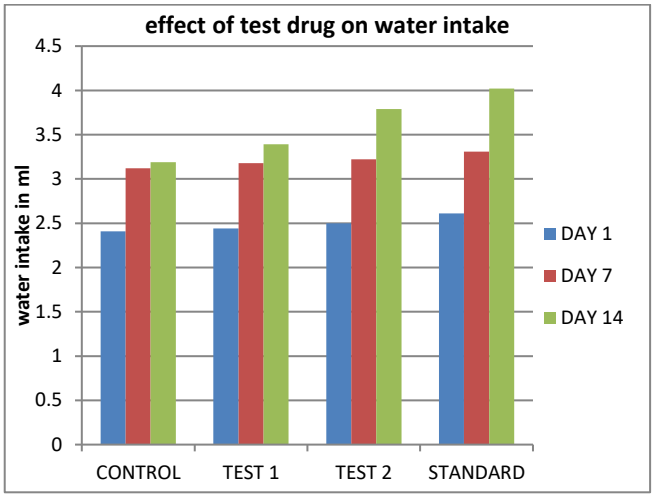

Figure 3: Graph Showing Effect of *Aegle marmelos* extracton Water intake (ml) of mice

All values represent = Mean ± SEM, n= 6 in each group [a] denotes $p<0.05$ as compared with to normal control group and [b] denotes $p<0.05$ as compared to FXT (10 mg/kg p.o.) treated group (One way ANOVA followed by Tukey's test).

Evaluation of antidepressant effect of Aegle marmelos Leaves extracts in TST model:

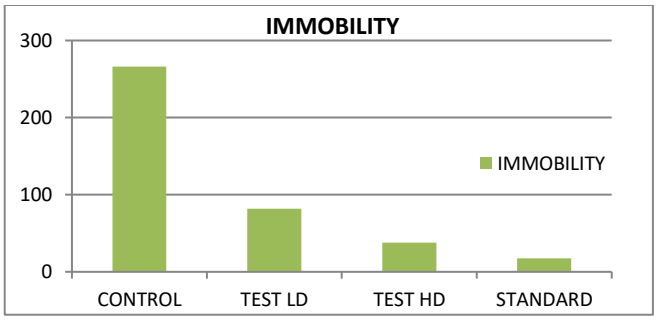

Figure 4: Tail Suspension Test (TST)

Evaluation of antidepressant effect of Aegle marmelosleaves extracts in FST model:

Forced swimming test:

TABLE 1: Observations and calculations

S.NO.	GROUP	Forced swimming test	
		Immobility	No. ofjumps
1	Control 0.9% w/v sodium chloride Normal saline (10 ml/Kg) or (1ml / 100gm, p.o.)	248.5 ± 2.964	2.5± 0.386
3	Ethanolic extract (Leaves AM)		
	200mg/kg (Test I)	97.8 ± 3.646[a]	11.2± 0.788 [a]
	400mg/kg (Test II)	38.6 ± 1.756[a]	14.6 ± 0.946 [a]
4	Standard dose (Fluxetine - 10 mg/kg)	34.2 ± 1.724[b]	17.8 ±0.824 [a]

Plasma corticosterone levels:

Groups 1 to 6 were tail bled on day 1 and then corticosterone levels were combined to obtainthe average levels in tail blood. For treatment of Groups see their respective experimental design.

Effect of Ethanolic extract of *Aegle marmelos*leaveson plasma corticosterone levels (CORT)

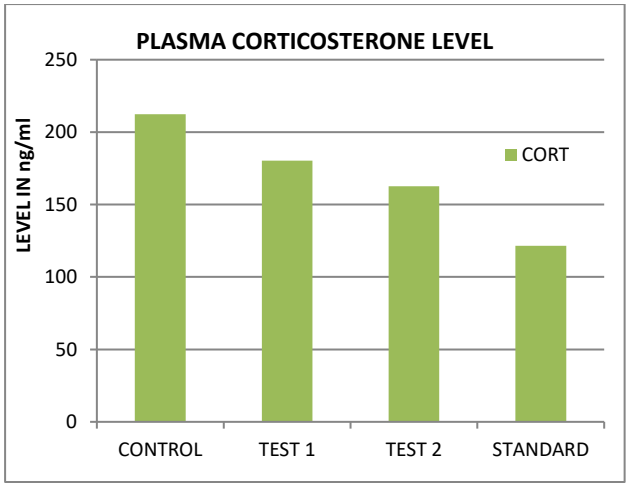

Figure 5: Graph showing the corticosterone levels in Post Tail Suspension Test Experiments

It is recommended that each laboratory establish its own normal range since corticosterone levels can vary due to handling and sampling techniques.

DISCUSSION

Following the selection of Aegle marmelos, ethanolic extracts (EEAML) at doses of 5, 50, 300, and 1000 mg/kg were shown to cause acute oral toxicity; however, there was no change in behavioral responses, and observation revealed no acute oral toxicity. Hence depending upon it, Dose was selected 200 mg/kg &400 mg/kg for our experimental work.

The traditional healers use primarily water as the solvent but we found in this study the plant extracts by ethanol provided more consistent activity compared to those extracted by water. The results of antidepressant activity of plant Aegle marmelos against the investigated FST and TST parameters are shown in table. The lower dose produced less effect comparative to higher in both parameters. Further trials using solvents of various polarities will explore the effects of solvent composition on extract efficacy. [3]

Preliminary phytochemical analysis of Aegle marmelos revealed the presence of phenolic compound, Proteins, tannins, glycosides, Carbohydrate, Starch, Vitamins &Minerals etc. It is not surprising that there are differences in the antimicrobial effects of plant species, due to the phytochemical properties and differences among species.[4-6]

It is possible that the active chemical constituents were not soluble in ethanol or water. The drying process may have caused conformational changes to occur in some of the chemical constituents found in these plants.[7] Active compound(s) may be present in insufficient quantities in the crude extracts to show activity with the dose levels employed.[8] Lack of activity can thus only be proven by using large doses.[9]

Alternatively, if the active principle is present in high enough quantities, there could be other constituents exerting antagonistic effects or negating the positive effects of the bioactive agents.[10]with no significant activity, extracts may be active against other biological activity which were not tested.[11]

Aegle marmelos (200 mg/kg &400 mg/kg) ethanol extract was evaluated in albino mice in Tail Suspension test (TST) and forced swim test (FST)The effects of fluoxetine (FXT; 10 mg/kg) were also being assessed.

In **TST (Tail suspension test),** Group - Control 0.9% w/v sodium chloride (10ml/ kg, p.o) administration have shown their immobility (266 ± 3.828) is insignificant. When Ethanolic extract of Aegle marmelos (200 mg/kg) orally administered, have shown immobility (82±2.744) issignificant. When Ethanolic extract of Aegle marmelos (400 mg/kg) orally administered, have shown immobility (38.8±2.666) is significant. When standard dose of fluoxetine (10 mg/kg) was orally administered, have shown immobility (17.4±1.626) is more significant.

In **FST (Forced swimming test),** Group - Control 0.9% w/v sodium chloride (10ml/ kg, p.o) administration have shown their immobility (248.5 ± 2.964) and number of jumps (2.5± 0.386) is insignificant. When Ethanolic extract of Aegle marmelos (200 mg/kg) orally administered, have shown immobility (97.8 ± 3.646) and number of jumps (11.2 ± 0.788) is significant. When Ethanolic extract of Aegle marmelos (400 mg/kg) orally administered, have shown immobility (38.6± 1.756) and number of jumps (14.6 ± 0.946) is significant. When standard dose of fluoxetine (10 mg/kg) was orally administered, have shown immobility (34.2 ± 1.724) and number of jumps (17.8 ±0.824) is more significant.

Biochemical estimation: -

When estimating the levels of plasma corticosterone Stress is known to stimulate the activity of the hypothalamus-pituitary-adrenal (HPA) axis and cause the adrenal cortex to secrete more corticosteroids. For this reason, cortisol and corticosterone are frequently employed as biomarkers for depression and stress. Despite the fact that corticosterone is thought to be the primary glucocorticoid involved in controlling stress responses in rats, convenience and the availability of kits frequently lead researchers to select cortisol detection as a stress indicator.

Group - Control 1% w/v sodium CMC (0.5mg/ kg, p.o) drug administration have shown their corticosterone level is (11.87 ± 0.53) insignificant. When Ethanolic extract of Aegle marmelos (200 mg/kg) orally administered, have shown corticosterone level (5.16±1.27) issignificant. When Ethanolic extract of Aegle marmelos (400 mg/kg) orally administered, have shown corticosterone level (4.48±0.30) is significant. When standard dose of fluoxetine (10 mg/kg) was orally administered, have shown corticosterone level (0.82±0.35) is more significant.

The Ethanolic extract of leaves of Aegle marmelos showed the most remarkable activity. This plant can be further subjected to isolation of the therapeutic Antidepressant compound and carry out further pharmacological evaluation.

CONCLUSION

Bael (A. marmelos) is an important medicinal herb which has been and extensively used in Ayurveda, Siddha and other medicinal systems. A. marmelos contains a number of phytoconstituents Like flavonoids, tannic acid, phenols, ascorbic acid, eugenol, alkaloids, coumarins (marmelosin, marmesin, marmin, imperatorin, scopoletin), skimmianine and saponin etc which may possesses anxiolytic properties. Almost all parts of this plant such as leaves, fruit, seed, bark and roots are used to cure different diseases, especially for diarrhea, dysentery, diabetes, ulcer, inflammation, fever and hyperlipidaemia. Further improvements are required to encourage research interest on Aegle marmelos. So, more pre clinical studies need to be conducted to find the hidden properties of *Bael (A. marmelos)*.

In conclusion Aegle marmelos leaves extract showed significant antidepressant activity probably due to GABA facilitatory action of phytoconstituents such as flavonoids, tannic acid, marmesinin, phenols, saponin etc.

Due to plants provides medicinal properties in several attempts and then have been done to identify and validate the plant derived substance for the treatment of different illness, and the result is that today more than 25% of the modern medicine are directly or indirectly derived from plants. A number of drugs from natural source either in the form of extracts or as active principles is isolated or evaluated for anxiolytic properties.

In conclusion, Aegle marmelos fruit extracts possess a broad spectrum of activity against a panel of factors responsible for the most common psycosis diseases. These promissory extracts open the possibility of finding new clinically effective antidepressant compounds. The ethanolic and aqueous extracts of Aegle marmelos fruit, investigated individually for Antidpressant activity by FST and TST methodat the dose level of 200&400mg/ml.The ethanolic extract of Aegle marmelos fruit showed considerably high activities in higher dose.These results were compared with standard antidepressantfluoxetine. But the exact active components of the extract that showed this effect were not isolated. In conclusion, although active components were not isolated, but antidepressant active plant principles were observed in the extract.

Although the active components were not isolated but antidepressant active plant principles present in various part of Aegle marmelos leaves. Ethanolic extract of Aegle marmelos leavespossess effective antidepressant properties. The spectrum of activity observed in the present study may provide a new plant source for safe antidepressant drugs.

Advancement and future scope of research in depression: -

Research on depression has provided a lot of useful information about the role of genetics and environmental influences. Although there are numerous treatment options available, they target different symptoms of depression. Researchers are still trying to develop new ways of treating depression disorders and to improve the existing treatment methods. In the future, more effective and perhaps hybrid treatments of several options need to be explored in order to increase the success and duration of depression relief.

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Source of Support: Nil

Informed Consent Statement: Not applicable.

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Ethics approval: Research protocol is duly approved by IAEC/CPCSEA (IAEC/SSIP/2022/PR-027). (Reg. No. 2011/PO/Re/S/ 18/CPCSEA and date of registration is 1/5/2018)

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