




DOSE-DEPENDENT ANTI-DEPRESSANT EFFECT OF CITRUS PARADISI IN REHABILITATION OF PSYCHOLOGICAL DISORDERS

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ABSTRACT

With advancement in the modern world, psychological issues, including anxiety and depression has become the leading cause of mental illness. Herbal products have been explored to observe their effects in helping such conditions and citrus fruits are found to be among these helping tools. To study this, current research was designed to explore the antidepressant effects of Citrus paradisi in various doses on rodents. Swiss Albino mice were used and fresh extract of Citrus paradisi was prepared. Imipramine was used as the standard drug. Ethical approval was taken from the Board of Advanced Studies, University of Karachi. The animals were divided into controlled, standard and test groups. All the animals were recruited from the animal house of University of Karachi. Forced Swimming Test was used to analyse the efficacy. It is a standard test, which is commonly used to evaluate the behavioral

response in animals using a cylinder at room temperature. After the completion of dosing and monitoring the animals for 30 days, it was observed that marked improvement in the test animal's behavior with significant p-values indicating that the extract has improved the animal's psychological response towards the external stress and animals showed noteworthy improvement in the mobile phase as compared to the immobile phase. It can be concluded from the experimental results that protocol established in this study can be used as an alternative for patients suffering with depression as an herbal option, keeping in mind the other co morbidities of patient and drug interactions of Citrus paradisi.

Keywords: Dose-dependent, anti-depressant, citrus paradise, rehabilitation, psychological disorders, healthcare.

Introduction

Homicides, suicides, demotivation and heartbreaks are among the most common phrases we hear these days from all age groups, irrespective of the ethnicity, race or financial scenarios which coincides with the fact that many studies have stated already quoting one of the leading healthcare issues of the modern world as psychological issues like depression and anxiety which is affecting

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almost all the age groups to various extents in different parts of their life span. The extent and outcomes to which it affects an individual may vary from person to person and region to region, but it is present in almost every part of the world. One of the main reasons behind the increasing cases of depression is that most of the times it remains undiagnosed and untreated^{1,2}. According to a study conducted in 2017, an approximately of 10.7% people around the globe are suffering from mental disturbances with more cases present in females as compared to males. Most of the times, the patients suffering from such depression episodes or psychological conditions starts consuming abusive substances or alcohol or were previously using them. A similar kind of study was conducted in almost 30 different countries from year 1994 to 2014. Major depression is usually associated with disability and is found to be more common in the young adults and elderly people as compared to kids showing its association with external factors like professional, academic, and personal issues. Mostly affected people complaint of difficulty in performing normal activities and in previous years, there is no significant change in these patterns^{3,4,5}. Selective Serotonin Reuptake Inhibitors (SSRIS) and Tricyclic Antidepressants are the drug of choice for patients suffering from depression. However, very limited data is available as to how these drugs are affecting at the molecular level. Mostly the data is interpreted based on Monoamine theory which states that it is because of alteration in the neurotransmitters in the brain but it still lacks clarity in many issues like explaining the pathophysiology of disease and presence of multiple side effects while using classical management^{6,7}. With the advancement in modern ways of living and presence of multiple luxuries, a shift has been observed from allopathic to herbal medicines mainly because of less potential side effects and health hazards. A study suggests earlier that depression will be the second highest occurring reason of illness by the year we are currently living i.e. 2021/22 and since there is a constant fear of getting side effects from allopathic medicines. People now tend to use herbal alternatives more like Chinese herbal products, researchers these days are working to explore more from herbal and naturally occurring substances rather than choosing from various drug categories already being explored⁸. Patients with previous exposure to physical or psychological injuries and traumas often suffers from depression or anxiety which later on affects their rehabilitation and recovery, a study suggested that cardiac abnormalities and rehab requires simultaneous management of depression in those patients too^{9,10}. The current study will help us to understand how these herbs and citrus products can help us in fighting the most serious but hidden issues of present world without causing any major financial burden on the already vulnerable population.

Methodology

Extract Preparation

The fresh extract of test substance i.e. Fresh grape fruit juice/ *Citrus Paradisi* was prepared according to the previously reported protocol^[11]. We leave around a kilogram of the pulp of *Citrus paradisi* fruit in 3 liters of ethanol for about 20 days where ethanol was refilled from time to time in order to maintain the soaking. After this, removal of residues through filtration was carried out to isolate the fresh juice for experiment. All the readings were observed and evaluated in the research lab of Pharmacology department for a period of 30 days.

Animals

35 Swiss albino mice of either sex (22-25gm) were recruited from the animal house of University of Karachi, Pakistan. Throughout the experiment, it was made sure by the researcher to maintain a constant environment. Standard and approved food and water was fed to all the animals. All the

ethical guidelines as provided by the ethical review committee (ERC) of University of Karachi were followed and maintained during the research trials (ERC No: 04179/Pharm). Only those animals were included in the study which were not previously used for any other study. Animals previously used for any study were excluded. Animals which were fed with any stuff other than the approved ones were excluded. Sample size was designed by randomized sampling techniques with keeping the same number in all the three test groups. The animals were divided into three groups (n= 5-10 mice per group) for behavioral study. Randomized sampling technique was used.

The groups were as follows:

1. Control group, received normal feed, i.e., pelleted mice feed, which is a supplemental diet. 10 mice were used as control for anti-depressant activity.
2. Standard Group, received 25 mg/kg P/O Imipramine for anti-depressant trials. 10 mice were used for anti-depressant activity observations.
3. Test Group, A: received 0.025 mg/ml of *Citrus paradisi*; B: received 0.0375 mg/ml of *Citrus paradisi*; C: received 0.05 mg/ml of *Citrus paradisi*.

15 mice were used as test animal for anti-depressant observations. Each of the 15 test animals were further divided into 3 groups (5 animals in each group to administer 3 different doses of extract).

Drugs

4 drug vials were prepared:

1st vial: Imipramine (standard drug for evaluation of antidepressant activity)

2nd vial: Test extract (100 mg strength)

3rd vial: Test extract (150 mg strength)

4th vial: Test extract (200mg strength)

- a. The samples (test and control) were fed to animals by feeding tubes.
- b. For induction of depression in animals, sticking tapes were used.
- c. Different color markers were used to mark all groups to avoid confusion.

Forced Swimming Test

This test is specifically designed to assess the effects of anti-depressant substances or depression inducers on rodents by observing their behavior in the cylinder usually 46cm high and 20cm in diameter which is filled with fresh water and maintaining normal room temperature. This is a simple test which requires very less of expertise. As the animals were placed in cylinder, immobile phase is noticed for the time when animals stop struggling while mobile phase is when it keeps on moving its limbs. However, strict measures were taken to avoid other kind of stress on animals¹².

Procedure

1. All the animals including test, standard and controlled groups, were induced with depression according to the division by following technique:
2. Depression was induced by hanging the animals daily for 10-15mins in the lab for 10 days daily with the help of a masking tape on slabs also known as "Tail suspension method".
3. After 10 days of induction, the administration of drug/placebo was started in all groups.
4. Control group was given normal saline.

5. Standard group induced for depression study was given Imipramine 25mg/kg.
6. Test group 1 for both depression were given *Citrus paradisi* 100mg/kg strength.
7. Test group 2 for both depression were given *Citrus paradisi* 150mg/kg strength.
8. Test group 3 for both depression were given *Citrus paradisi* 200mg/kg strength.
9. Administration of drugs/ placebo was done between 10am -12pm daily. While readings were observed from 10am to 1pm on the due dates.
10. Readings were observed every 10th day of administration of samples for 30 days.

Statistical analysis

Data was analyzed using SPSS[®] software (version 23.0). ANOVA was used for examining results followed by Tukey's post hoc test for multiple comparisons of test results. Values with $P < 0.05$ were considered as significant.

Results

Test and Standard groups

The results observed at the 10th day of experiment (after induction of depression) showed that most of the animals among the standard and controlled groups had very few phases of immobility, they were mobile most of the time, however, the tests groups were more immobile as shown in Fig. 1a and Fig. 1b. Significant p-values were observed in test group 2 and 3 after 20 days in the immobile phase (Fig. 2a and Fig. 2b). However, by the end of study, at day 30, marked improvement was observed in all the groups as shown in Fig. 3a and Fig. 3b, where the test groups showed remarkable improvement in the mobile phase and keeps on swimming irrespective of the stress and environmental barriers.

Control group

The group which was given only normal feed and no test or standard substance, does not show any significant change in their mobility patterns, they were not reluctant in keep going on and on with swimming from the start of the study till end indicating that since there was nothing being given to alter their mental health, they were not feeling any fear in their movement, see table 1.

ANIMAL	MOBILE	IMMOBILE	MOBILE	IMMOBILE
	(mins. sec)	(mins. sec)	(mins. sec)	(mins. sec)
Control group		Standard group		
1	5.33 ± .12	3.33 ± .14	5.40 ± .17	3.36 ± .14
2	6.50 ± .26	4.33 ± .12	6.33 ± .14	2.26 ± .12
3	7.16 ± .06	3.53 ± .06	6.36 ± .14	2.63 ± .08
4	5.50 ± .11	4.53 ± .12	5.33 ± .12	3.40 ± .15
5	7.53 ± .08	0	5.30 ± .10	3.43 ± .17
6	6.30 ± .11	3.33 ± .12	4.70 ± .05	4.43 ± .17
7	7.63 ± .03	2.20 ± .15	4.33 ± .14	4.26 ± .08
8	5.20 ± .05	3.23 ± .03	6.56 ± .12	2.40 ± .15
9	5.56 ± .17	4.43 ± .12	4.40 ± .15	4.66 ± .06
10	6.56 ± .17	2.40 ± .15	5.40 ± .10	3.36 ± .13

Table 1: Readings of control group and standard group in forced swimming test

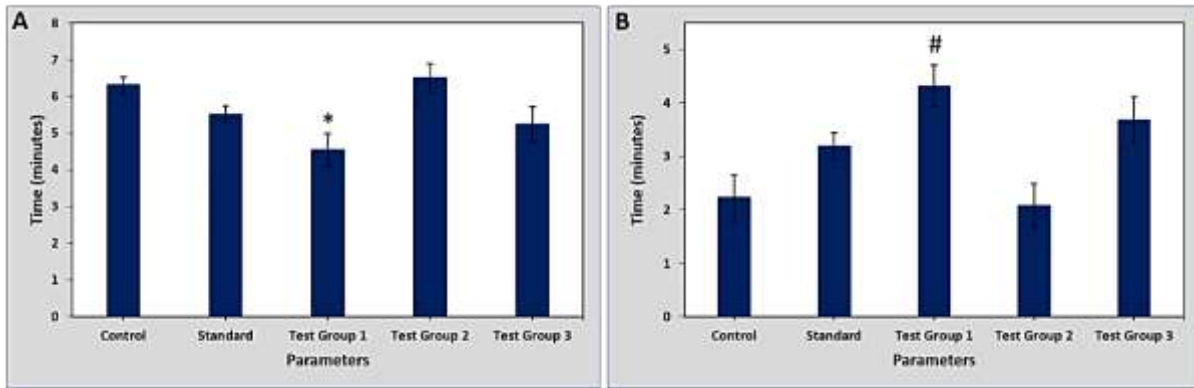


Fig. 1: Combinatorial effect of imipramine and Citrus paradisi on the behavioral activity of mice a) mobile phase after 10 days b) immobile phase after 10 days; * represents significant difference with $P < .05$ as compared to control, # represents significant difference with $P < .005$ as compared to control.

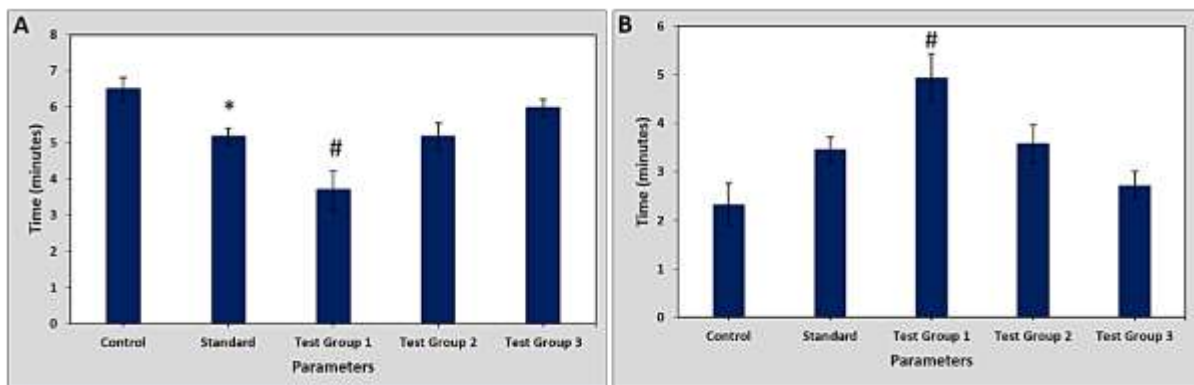


Fig. 2: Combinatorial effect of imipramine and Citrus paradisi on the behavioral activity of mice a) mobile phase after 20 days b) immobile phase after 20 days; * represents significant difference with $P < .05$ as compared to control, # represents significant difference with $P < .005$ as compared to control.

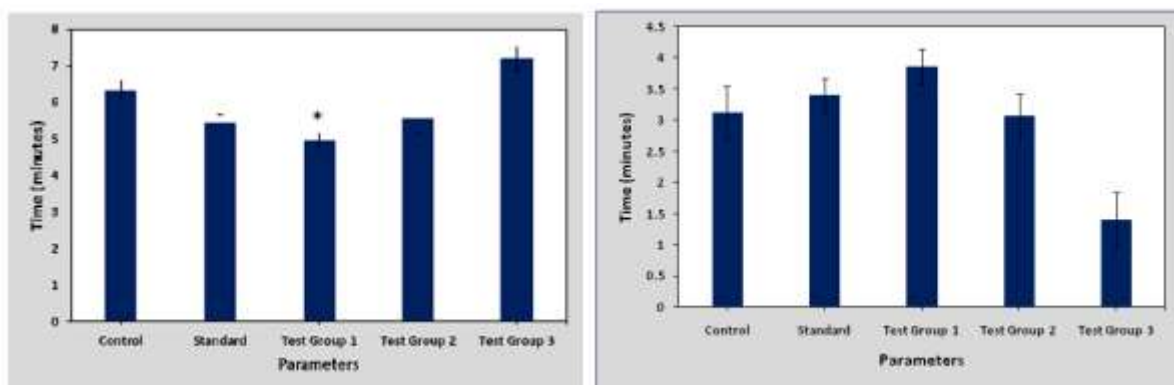


Fig. 3: Combinatorial effect of imipramine and Citrus paradisi on the behavioral activity of mice a) mobile phase after 30 days b) immobile phase after 30 days; * represents significant difference with $P < .05$ as compared to control.

Discussion

Depression, like other diseases, is not a simple disease which affects a particular part of the body and gets treated with appropriate drugs and/or lifestyle modification techniques. It affects everything in a person, from their basic and normal daily routines to response towards all kind of life events. Patient stops feeling happiness in things which previously used to make him/her happy, patient or person suffering from depression starts losing confidence in themselves, starts fearing about and from any ordinary thing, there is a very disturbed pattern of sleep and eating, either they sleep too much or doesn't feel like having a good relaxing sleep at all, there is no feeling of hunger or an unstoppable crave for having food all the time which is usually not including healthy options even, patients feel like they are going to be attacked by someone, or sometimes try to even harm others without even realizing how bad their condition is getting with every passing day. They start laughing which often ends on tears, starts crying that might lead to locking themselves in an isolated place, most of the times the patients try to avoid social interactions, feel unable to explain themselves. Depression is a mental condition which has nothing to do with patient's financial status, it does not discriminate between rich and poor, everybody gets affected. Usually, the more educated and advanced people get it more because of the extra pressure they face from society and people around, and worst part is that the more a person is educated or rich or have any kind of worldly facilities, they are supposed to be happy¹³. It is now proven via multiple studies that herbal or phytochemical products are having better effect on altering the neurotransmitters which helps in managing depression and other psychological issues along with established mechanisms of actions as compared to classical drugs where the mechanisms are still unknown. The allopathic medicines as compared to herbal medicines are usually costlier and have more unwanted effects which is why people feel more comfortable in taking herbal medicines¹⁴. In this study, we make sure that all the animals were in properly controlled environment to make sure that the effects observed were purely due to the drugs given to them and not because of the other external factors. Most of the patients suffering from chronic depression or anxiety also suffer from body aches and it needs simultaneous treatment for giving patient a complete relief¹⁵. A recent study has been conducted to analyse the age-related outcomes on elderly when treated with anti-depressants including Imipramine also suggests that the results were not satisfactory with use of these drugs in such patients due to age related comorbidities¹⁶. Multiple studies have been done to explore the possible mechanism through which it exerts its action as anti-depressant but there is no study that suggests that use of SSRIs like Imipramine can produce anti-depressant effect without any side effect. In fact, studies suggest that the use of these drugs can further worsen the condition of the patient due to undesirable outcomes, the prescriber must keep an eye on overdosing as well¹⁷. It is due to these unwanted and harmful effects that the herbal drugs are getting more acceptances by both healthcare practitioners and patients. Various kinds of naturally occurring herbs are now being investigated for their possible facilitation in managing patients suffering from any kind of psychological issues because of the having less undesirable and little or more desirable effects¹⁸. There is a wide range of Chinese herbs also that are being under thorough investigation for managing depression and other psychological issues. Studies suggests that these Chinese products are exerting highly significant impact on mental illness¹⁹. Patient's feel more confidence in using these herbal or natural options as compared to conventional drugs. It has also been observed that patients even stop taking the prescribed drugs after some time due to lack of compliance and side effects²⁰. *Citrus paradisi* has a world of healthcare benefits hidden in all parts of it like leaves,

bark, fruit etc. Previously, it was stated the beneficial effects of leaves of this plant in managing psychological issues²¹. How our diet can influence our mental health and how herbs like Citrus fruits can help in combating multiple organs including our behavioural status is also proven by many scholars and studies where consumption of a healthy diet and use of herbs were found to be effective in managing patients²². In Fast Swimming Test (FST), the animals were in a continuous state of stress due to water and enclosed surrounding, also the animals were induced with depression that is the reason they were unable to perform in the mobile phase at the start. However, with the passage of time as the test sample which was *Citrus paradisi* (grapefruit juice) starts producing its anti-depressant effects, the animals overcome the external stimuli and showed more struggle in the mobile phase with significant p values showing the efficacy of test sample on psychological system of mice^{23, 24}. It can be clearly observed that the animals that were on *Citrus paradisi* have shown most significant outcomes. Test group 3 which received the highest dose of sample, showed highest degree of improvement in the psychological pattern with advancement in the research trials. Similar kind of results about effectiveness of herbal drugs in depression have been observed in other studies as well^{25,26,27}. The standard group which received Imipramine, one of the drugs of choice for managing depression, showed marked improvement with significant p-values in the behavior of animals as the study progressed which coincides with another study also²⁸. The animals which were previously not struggling to continue swimming, started being more mobile by the end of the study and completion of dosing representing positive effect of test sample on the behavior of animals. Clinical studies are needed to observe these effects on human subjects to co-relate the effects observed in animal models since the animal models cannot represent the exact response as we observe in clinical settings.

Conclusion

The established facts about the unwanted and undesirable effects of most of the commonly present drugs for management of illness related to mental health, herbal alternatives present a better, safer, and cheaper option. *Citrus paradisi* along with its multiple other healthcare benefits, can also be used as a more reliable tool for helping the humanity in fighting their internal and external demons.

Future Recommendation

This study can be taken as a pilot study to be used in future on clinical settings after taking informed consent from the patients to compare the results obtained in our study on animals with the clinical data.

AUTHORS' CONTRIBUTION:

The following authors have made substantial contributions to the manuscript as under:

Conception or Design: *Syeda Hafiza Afsheen Zafar Dr. Riffat Farooqui,*

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Manuscript Writing & Approval: *Ifragh Jawaaid, Syeda Afroze*

All authors acknowledge their accountability for all facets of the research, ensuring that any concerns regarding the accuracy or integrity of the work are duly investigated and resolved.

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