

Original article:

Neuropharmacological screening of Ficus Carica Linn; Fruit for Anxiolytic and Antidepressant Activity

Gul S¹, Raza S², Rashid Z³, Ayub M⁴, Sarwar G⁵

Abstract

Background: Rutin and polyphenol which are present in ficus carica linn are responsible for anti-depressant and anxiolytics effect. **Aims:** We have conducted the study to evaluate the anti depressant and anxiolytic effect of ficuscaricalinn on mice and compare its effect with well known prescribed anti depressant and anxiolytic drug alprazolam. **Methods:** Three groups of mice were marked as Control, Reference and Test. Each group comprise of 5 mice. Control group was on normal diet. Reference group was feeded alprazolam at a dose of 0.5mg/60kg while test group were provided two different dilution of ficuscaricalinn, one dilution is 250mg/kg/100ml of water and second dilution is 500mg/kg/100ml of water. We used Light/dark box method and Elevated plus maze method to evaluate the anxiolytic effect of ficus carica linn. To determine the anti-depressant effect of ficus carica linn. **Results:** we was used one method that is Head Dip Method. Results were collected and observed readings and data were clearly indicating the great and pronounced anti depressant and anxiolytic effect of ficus carica linn at a dose of 500mg/kg compare with a widely prescribed drug alprazolam for its anti-depressant and anxiolytic effect. Ficus carica is well known for its numerous biological activities also found to be one of excellent distressing agent. Stress provoking several disorders could be limit by the use of ficus carica fruit in doses 250mg/kg and 500mg/kg. Ficus carica linn as a natural product may prove better therapeutic agent if more study is conducted on it. **Conclusion:** As this study is confined to the mice, there's much possibilities to have similar effect in humans but require more work on it.

Keywords: Ficus caricalinn; Neuropharmacological screening; Fruit; Anxiolytic; Antidepressant

Bangladesh Journal of Medical Science Vol. 17 No. 04 October'18. Page : 606-611
DOI: <http://dx.doi.org/10.3329/bjms.v17i4.38323>

Introduction:

Anxiety & depression are amongst most prevailing mental or psychic disorder currently occurring worldwide. Anxiety is the tense condition with the feeling of displeases, worry and fear¹. One suffers from agitation and nervousness in performing regular affairs of life. The frequently observed sign and symptoms been encounter in such individuals are dyspnea, tachycardia, xerostomia, uneasiness, muscle tightness and stress². Although benzodiazepines are most extensively used and prescribed classes for anxiety and depression,¹ there are so many issues

and complication associated with it. On a long term (regular) use, tolerance and dependence may develop by the body, chances of drug abuse may increase and adverse effects are appeared. The chronic use can also potentiate depression and may lead to suicide attempts in impulsive patient³. Moreover many short acting barbiturates are provided to the anxious patients to gain the benefit of its sedating activity¹. These agents possess strong risk of drug toxicity and needs different methods for the proper evaluation of their plasma levels to subside its harmful toxic effects⁴. These drugs are cytochrome p450 inducer

1. SomiaGul, Faculty of Pharmacy, Jinnah University for women, Karachi, Pakistan, drsomi1983@yahoo.com
2. Sabeen Raza,
3. Zaira Rashid,
4. Maria Ayub
5. Ghulam Sarwar
Faculty of Pharmacy, Jinnah University for women, Karachi, Pakistan

Correspondence to: Somia Gul, Faculty of Pharmacy, Jinnah University for women, Karachi, Pakistan
drsomi1983@yahoo.com

so possess numerous drug-drug interactions and the toxic doses are precipitated to coma¹.

Tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs) are recommended to patients complaining for pressure, anxiety and depression. TCAs are reserved for those individuals who didn't respond well to SSRIs. They owe high potential for decreasing blood pressure, increase in body weight and other anticholinergic effects such as blurred vision; dry mouth etc.³. Sexual dysfunctioning, insomnia, G.I upset and weight gain are typically observed with the use of SSRIs⁵.

According to the Royal Society of Medicine 15% of the global burden of disease is assigned to mental disorders, in high-income countries it is 30%, in middle-income countries its 20% and it is 10% in low-income countries. So probably anxiety is the problem facing all over the globe⁶. In the past centuries so many treatments were provided to get rid of anxiety, the investigation on passion fruit gives out positive results by exerting the antianxiety action at low doses,⁷ similarly another research conducted on a traditional Asian herbal medicine yokukansan for determining its anxiolytic activity on old aged rats is also notable⁸. The literature established comprising of past research on animals and human clinical trials prove many dietary supplements possess mind relaxing and anxiolytic actions⁹. Hence these secondary cures to anxiety are cheap source of earning valuable agents that aims to reduce tension and stress⁹.

The ficus plant contains variety of bioactive constituents i.e. Coumarins, flavonoids^{10,11} sterols, triterpenoids, anthocyanins¹⁰ etc. which are very important as far as both nutritional and medicinal merits are concerned. Different parts of the plant could be use for several therapeutic actions including antihypercholesterolaemia¹¹. antidiarrheal¹³, antibacterial¹⁴, antioxidant¹¹, antiinflammatory¹¹, anticancer¹¹, antispasmodic¹⁵, antidiabetic^{12,16}, anthelmintic¹², antiplatelet¹⁵, anti-inflammatory¹¹, antipyretic¹², gastro protective¹¹, immunodulatory¹² and hepatoprotective^{10-12,17,18}

Polyhydroxyphenols commonly known as polyphenols are sub classify into phenolic acids, flavonoids etc. A healthy diet consist of a fine good amount of naturally existing polyphenols render great activity against the oxidative stress which is one of the root cause of anxiety, depression and other central nervous system related diseases¹⁹. Rutin which is present in greatest amount in ficus fruit may act as an anxiolytic and relieves fatigue²⁰.

Rutin found in mulberry leaf extract follows two-compartment model in rats, show rapid absorption and slow decreased in plasma levels²². Here are some phenolic of different concentrations in Ficus carica fruit obtained through HPLC-PDA system; rutin was found chiefly up to 28.7 mg per 100 g FW (fig weight), (+)-catechin chlorogenic acid, (-)-epicatechin, gallic acid, syringic acid were also found in concentrations upto (4.03 mg, 1.71 mg, 0.97 mg, 0.38, 0.10 mg) per 100 g FW, respectively²¹.

The study which evaluates the anxiolytic properties of aqueous acetonetic extracts of Ficus carica L. leaves, we belief that the fruit could also have possibilities of certain central nervous system activities⁶ as well as the presence of high concentration of phenols found might be responsible for anti stress effect. In favor of this assumption we have investigated the two different dilutions of different concentrations of ficus carica fruit by administering orally in mice adopting elevated plus maze method and light and dark box test for determination of anxiolytic action and hole-board apparatus for the determination of antidepressant action of ficus carica fruit.

Methodology:

Animals:

Swiss mice (n=5) of both gender with average weight of 19.02g were caged individually in quiet laboratory at room temperature with 12 hour light dark cycle. Mice have free access to water and food (ad libitum). The wash out of the drugs administered is considered and after each dose the tested animals were given the break of 1 day.

Agents:

Control group was on rodent feed however Reference group was treated with alprazolam dose (0.5mg/60kg). The 2 test group received ficus carica fruit dilution at the doses of 250mg/kg/100ml & 500mg/kg/100ml for their anxiolytic potentials were based on preliminary evidence of ethanolic extract of ficus carica fruit 100 and 200mg/kg body weight of rats being use as a diuretic agent.

Experimental Protocol:

The mice were first taken into elevated plus maze and then into light/dark activity box to induce anxiety and fear in them. The anxiety and activity behavior were noted as control. The forced swim test (FST) is a preclinical test to the screening of antidepressants. The mice were induced depression by this test and then their behavior changes were examined by using hole-board apparatus. After this the mice of each group were given the test and reference drug in order to discover the changes in their mental activity i.e.

anxiolytic and antidepressant action of the drugs.

Anxiolytic screening by Using Light/Dark Box Method

Anxiety and activity corresponding variables in mice were evaluated by submitting the mice in light/dark box for 10min after 40min and 24hours of administration for both test groups. The activity was compared with alprazolam reference dose of 0.5mg/60kg. Mice were submitted for 10min in light/dark box one by one after 40min of drug administration.

Anxiolytic screening by using Elevated plus Maze

Elevated plus maze is an excellent model for determination of antidepressant and anxiolytic effect in mice. It is 50cm above from the base and 10cm wide. The mice were placed in center of the all four arms with its face towards open arm. The behaviors of each group of mice were noted for 5 minutes. The test group mice were treated with two different dilutions of fig and were analyzed one by one after 40min and 24hours. The activity was compared with alprazolam reference dose. Mice were submitted for 10min in light/dark box one by one after 40min of drug administration.

Antidepressant screening by using Head Dip Method/ Hole-Board Apparatus

This Hole Board apparatus is used to evaluate antidepressant effect in mice after inducing depression by the aid of force swim method. Variation in the psychological state of mice were examined by observing changes in exploratory activity, i.e. numbers of head-dip after depression being induced in mice and then when the reference and fig dose are provided. The numbers of head dips by mice were observed 40min and 24hours post administration of the test doses respectively and 40min post reference dose. The mice were submitted to hole-board apparatus for 5min.

Result

The experimental data obtained from light/ dark box test, head dip method and elevated plus maze test clearly reveals antidepressant & anxiolytic activity of ficus carica fruit. The results showed that on lower doses 250mg/kg/100ml the antidepressant and anxiolytic action of the fruit appears to be significant and by increasing the dose to 500mg/kg/100ml, marked and pronounce anxiolytic and antidepressant effects were noted in mice. This effect was comparable with a well-known drug alprazolam shown in Table 1, 2 & 3.

Table 1. Anxiolytic effect of fig 250mg/kg/100ml & 500mg/kg/100ml intake after 40min & 24hours, and its comparison with alprazolam 0.5mg/60kg for 40min on time spend in light and dark compartment.

Light/Dark box Test		
Groups	Time Spend In Light Compartment (Sec)	Time Spend In Dark Compartment (Sec)
Control Mean \pm S.D	153.6 \pm 0.21	446.4 \pm 0.32
Reference Mean \pm S.D	221.2 \pm 1.11	378.8 \pm 1.21
Test 250mg/kg/100ml (After 40min) Mean \pm S.D	225.6 \pm 0.95	374.4 \pm 0.25
Test 250mg/kg/100ml (After 24hours)	189 \pm 0.85	411 \pm 0.24
Test 500mg/kg/100ml (After 40min) Mean \pm S.D	235.8 \pm 52	364.2 \pm 75
Test 500mg/kg/100ml (After 24hours) Mean \pm S.D	190 \pm 0.86	410 \pm 0.48

The mean time spend by mice in close compartment were 389.8sec and 208.6sec (control group i.e. stress induced), 378.8sec and 182.6sec (reference group), 374.4sec and 173.8sec (test group 1 after 40min), 411sec and 182.4sec (test group 1 after 24hours), 364.2sec and 138.2sec (test group 2 after 40min) & 410sec and 169.2sec (test group 2 after 24hours) in light/dark box and elevated plus maze apparatus, respectively [Table 1 & Figure 1].

The control group mice hesitate to explore the field and remain confined to the close chamber upon application of both the method to check anxiety and anxiolytic effects but mice of reference and test groups showed great interest to explore both the fields [Table 2 & Figure 2].



Figure 1: Anxiolytic screening by using light/dark box method

Table 2. Anxiolytic effect of fig 250mg/kg/100ml & 500mg/kg/100ml intake after 40min & 24hours, and its comparison with alprazolam 0.5mg/60kg for 40min by using Elevated plus Maze apparatus.

Elevated Plus Maze		
Groups	Time Spend in Open Field (Sec)	Time Spend in Close Field (Sec)
Control Mean ± S.D	91.4±0.85	208.6±0.26
Reference Mean ± S.D	117.4±0.89	182.6±1.26
Test 250mg/kg/100ml (After 40min) Mean ± S.D	126.2±0.83	173.8±0.75
Test 250mg/kg/100ml (After 24hours) Mean ± S.D	117.6±0.91	182.4±0.25
Test 500mg/kg/100ml (After 40min) Mean ± S.D	161.8±0.36	138.2±0.49
Test 500mg/kg/100ml (After 24hours) Mean ± S.D	130.8±0.73	169.2±0.46

The mean time spend by mice in open compartment were 210.2sec and 91.4sec (control group), 221.2sec and 117.4sec (reference group), 225.6sec and 126.2sec (test group 1 after 40min), 189sec and 117.6sec (test group 1 after 24hours), &235.8sec and 161.8sec (test group 2 after 40min) &190sec and 130.8sec (test group 2 after 24hours) in light/dark box and elevated plus maze apparatus, respectively.

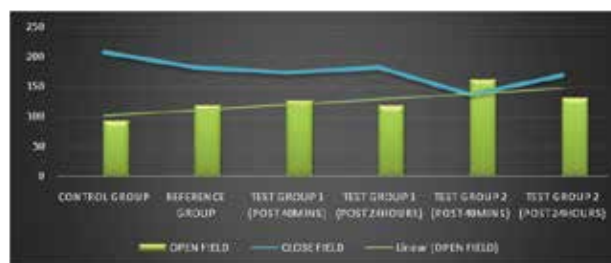


Figure 2: Anxiolytic Screening By Using Elevated Plus Maze

The average (round of) number of head dips were 14 (Depression induced), 19 (Reference), 17 (test group 1 after 40min), 15 (test group 1 after 24hours), 20 (test group 2 after 40min) and 19 (test group 2 after 24hours) [Table 3 & Figure 3].

Table 3. Antidepressant effect of fig 250mg/kg/100ml & 500mg/kg/100ml intake after 40min & 24hours, and its comparison with alprazolam 0.5mg/60kg for 40min by using Head Dip Method.

Head Dip Method	
Depression Induced Mice Mean ± S.D	14±0.99
Reference Mice Mean ± S.D	19±0.81
Ficus Carica 250mg/Kg/100ml (After 40min) Mean ± S.D	17±1.89
Ficus Carica 250mg/Kg/100ml (After 24hours) Mean ± S.D	15±1.74
Ficus Carica 500mg/Kg/100ml (After 40min) Mean ± S.D	20±0.28
Ficus Carica 500mg/Kg/100ml (After 24hours) Mean ± S.D	19±0.95



Figure 3: Antidepressant screening by using head dip method

Discussion

The above study on mice was conducted to explore antidepressant and anxiolytic activity of fig employed by administering dilution of two different doses of fig (250mg/kg/100ml of water and 500mg/kg/100ml of water). The anxiety related behaviors were defined by using light/dark box and elevated plus maze method. The Depression related behaviors were defined by using head dip method. Table 1 shows anxiolytic effect of fig 250mg/kg/100ml & 500mg/kg/100ml intake after 40 minutes and 24hours, and its comparison with alprazolam 0.5mg/60kg after 40min on time spend in light and dark compartment. We can observed that with increased dose of fig i.e. from 250mg to 500mg the time spend in light compartment was found to be more pronounced. The anxiolytic activity of fig, when compared to a reference drug alprazolam, turned out to be quite enhanced.

Whereas, in Table 2 anxiolytic effect of fig 250mg/kg/100ml & 500mg/kg/100ml intake after 40 minutes and 24hours, and its comparison with alprazolam 0.5mg/60kg after 40min by using Elevated plus Maze apparatus is shown. The control group manifest great pressure and anxiety. The number of entries in open arm (anxiety index) and close arm (activity index) are important parameters to notice anxiolytic potential of drugs. The mice of control group passed most of the time in close arm in immobile state and have serious fear from open space induce anxiety. The test group who were treated with 250mg consume less time

in close arm than control group. It displays that the mice were having lower degree of anxiety because they explore the field more confidently.

The mice of fig dose 500mg stayed most of the time in open field (anxiety index) even more than the mice of reference group. The mice of these two groups have alleviated level of tension and stress. The mice spend time in close arm of test group 2 and reference group are far more shorten than the control group. Table 3 demonstrates the antidepressant activity of mice by using head dip method. After performing force swim test, the mice were induced depression and they showed greater latency but when the test doses and fig dose were provided the mice showed improved motor activity. By observing these tables we can say that the high amount of polyphenols present in fig bears powerful action against fear, anxiety and depression in dose of 500mg/kg/100ml of water. It claims to have more antidepressant & anxiolytic action than a widely prescribed drug alprazolam. It has been reveal from this study that a slight higher dose of fig could improve its anxiolytics well as antidepressant capabilities.

Conclusion

Ficus carica linn as a dried fruit easily available & have remarkable source of nutrients, proven to have active anxiolytic and antidepressant activity. Since this study was purely confined to the mice, there's much probability and possibilities to have similar effects in humans too but it will required further research.

References:

1. Michelle A. Clark, Richard Finkel, Luigi X Cubeddu. Lippincott's Illustrated Reviews Pharmacology. 4th ed. Wolters Kluwer (2011). Chapter 09. Pg 105.
2. Christopher Gale, Mark Oakley-Browne (2004). Generalised anxiety disorder. *Evid Based Mental Health*. Volume 7. Issue. Pg 32-33.
3. S.Bleakley, D.Baldwin. Clinical Pharmacy and Therapeutics. 5th ed. Edited by Roger Walker and Kate Whittlesea. Published by Churchill Livingstone (2012). Chapter 28. Pg 459 & 461.
4. Piero Perucca, Dr Frank G Gilliam (2012). Adverse effects of antiepileptic drugs. *The lancet neurology*, volume 11, issue 9, pg.739-834.
5. James M. Ferguson (2001). SSRI Antidepressant Medications: Adverse Effects and Tolerability. *Primary Care Companion Journal of Clinical Psychiatry*. Volume 3. Issue 1. Pg 22-27.
6. Mittal M. Bhanushali, Dinesh T. Makhija, and Yadunath M. Joshi (2014). Central Nervous System Activity of an Aqueous Acetonic Extract of Ficus Carica L. in Mice. *Journal of Ayurveda Integrative Medicine*. Volume 5. Issue 2. Pg 89-96.
7. Jun Deng, Yujuan Zhou, Mengmeng Bai, et.al (2010). Anxiolytic and Sedative Activities of Passiflora edulis f.flavicarpa. *Journal of Ethnopharmacology*. Volume 128. Issue 1. Pg 148–153.
8. Kazushige Mizoguch, Yayoi Tanaka, Takeshi Tabira (2010). Anxiolytic Effect of a Herbal Medicine, Yokukansan, in Aged Rats: Involvement of Serotonergic and Dopaminergic Transmissions in the Prefrontal Cortex, *Journal of Ethnopharmacology*. Volume 127. Issue 1. Pg 70–76.
9. Benjamin S. Weeks (2009). Formulations of Dietary Supplements and Herbal Extracts for Relaxation and Anxiolytic Action: Relarian. *Med Sci Monit*. Volume 15. Issue 11. Pg 256-262.
10. Anshul Chawla, Ramandeep Kaur, Anil Kumar Sharma (2014). Ficus Carica Linn. A Review on its Pharmacognostic, Phytochemical and Pharmacological aspects. *International Journal of Pharmaceutical and Phytopharmacological Research*. Volume 1. Issue 4. Pg 215-232.
11. N.Sirisha, M.Sreenivasulu, K.Sangeeta, et.al (2010). Antioxidant Properties of Ficus Species – A Review. *International Journal of PharmTech Research*. Volume 2. Issue 4. pg 2174-2182.
12. Vikas V Patil, Vijay R Patil (2011). Evaluation of anti-inflammatory activity of Ficus carica Linn. Leaves. *Indian Journal of Natural Products and Resources*. Volume 2. Issue 2. Pg 151-155.
13. Vikas V Patil, Shandavi C, et.al (2012). Evaluation of the antidiarrheal activity of the plant extracts of ficus species. *Journal of Chinese Integrative Medicine*. Volume 10. Issue 3. Pg 347.
14. Mi-Ran Jeong, Hye-Young Kim, Jeong-Dan Cha (2009). Antimicrobial Activity of Methanol Extract from Ficus carica Leaves against Oral Bacteria. *Journal of Bacteriology and Virology*, Volume 39. Issue 2. Pg 97-102.
15. Anwarul Hassan Gilani, Malik Hassan Mehmood, Khalid Hussain Janbaz et.al (2008). Ethnopharmacological studies on antispasmodic and anti-platelet activities of Ficus carica, *Journal of Ethnopharmacology*, Volume 119, Issue 1, and Pg 1–5.
16. C.Perez, E. Dominguez, J.R. Canal (2011). Hypoglycaemic Activity of an Aqueous Extract from Ficus Carica (Fig Tree) Leaves in Streptozotocin Diabetic Rats, Taylor Francis Online, Volume 38, Issue 3, pg 181-186.
17. N. Y. Gond and S. S. Khadabadi (2008). Hepatoprotective Activity of Ficus carica Leaf Extract on Rifampicin-Induced Hepatic Damage in Rats. *International Journal of Sciences*. Volume 70. Issue 3. Pg 364–366.
18. Mohan G.K., Pallavi E., Ravi Kumar B., et.al (2007). Hepatoprotective activity of Ficus carica Linn leaf extract against carbon tetrachloride-induced hepatotoxicity in rats, *DARU journal of Pharmaceutical Sciences*. Volume 15. Issue 3. Pg 162–166.
19. Bouayed, Jaouad. Current Nutrition & Food Science. Bentham Science Publishers (2010). Polyphenols: A Potential New Strategy for the Prevention and Treatment of Anxiety and Depression. Volume 6. Issue 1. Pg. 13-18(6).
20. Su KY, Yu CY, Chen YW, et.al (2014). Rutin, a flavonoid and principal component of saussurea involucreta, attenuates physical fatigue in a forced swimming mouse model. *International Journal of Med Sciences*. Volume 11. Issue 5. Pg 528-537.
21. Robert Veberic, Mateja Colaric, Franci Stampar (2008). Phenolic acids and flavonoids of fig fruit (Ficus carica L.) in the northern Mediterranean region. *ELSEVIER*. Volume 106. Issue 1. Pg 153–157.