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Behavioural impacts of following administration of *Ficus carica* leaves extract in animal model of acute and chronic unpredictable mild stressed exposed rats

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Abstract: Stress is described as a noxious stimulus that affects the health of an individual and alters body homeostasis resulting in changes the individual behavioural and metabolic condition. Synthesis of drug from plants has main interest due the significant medicinal values. The recent investigation was designed to examine the pharmacological impacts of *Ficus carica* leaves extract on stress. In this experiment, the rodents were randomly distributed as (n=6) control rats were kept at standard condition, second group of rats were exposed with different stressors and Third group of rodents was exposed to stress and treated with extract of *ficus carica* leaves at the dose of 100 mg/kg. Acute behavioural alteration was observed after 7 days and prolonged impact was monitored after the 28 days. The current finding showed that administration of *Ficus carica* leaves extract produced anxiolytic behaviours and decreased depression like symptoms in CUMS treated rats. It also increased stimulatory, ambulatory, locomotor activity and enhanced spatial working memory and recognition memory in CUMS exposed rats. So, it can be concluded from recent study that leaves of *Ficus carica* can be utilized as secure drug for curing physiological stress with less side effect profile.

Keywords: Acute unpredictable mild stress, chronic unpredictable mild stress, anxiety, memory, depression like symptoms, *Ficus carica*,

INTRODUCTION

Stress is considered as, neurological, physical or behavioural alteration due to the reaction to unusual or threatening stimulus. (Koolhaas *et al.,* 2011). Stress executed a significant role in precipitation of depression and causes the alteration in different system of body that happen in depression are resemble to those noticed in stress response (Leanard, 2001). Previous various literatures exhibited that random stress exposure caused innumerable deviations in behaviors (Planchez *et al*., 2019). Prolonged stress triggers drug seeking behavior and causes the variation in impact of drugs abuse (Doyle *et al.,* 2010). Stress can rise the impact of various drug utilization via straight acting on neural track, brain reward passage and it can also rise habituated place preference, self-administration, mesocorticolimbic system of dopamine stimulate the seeking of drug of abuse (Mantsch *et al.,* 2016). In past, human being used certain plants as a source of medicine (Si-Yuan Pan *et al.,* 2014). Today, the whole world's societies possess broad information about herbal drug because of previous gathered knowledge. Chemical investigation revealed that extensive range of secondary metabolites are obtained from plants utilized as medications, agrochemicals, odors, dyes, bio pesticides and cuisine flavors (Al-Snafi, 2016). When speak the word fig leaves, the basic usual point that arises in our mind is the story of Adam and Eve. They were also used by Greek and Romans to adorn the bodies. *Ficus carica* is typically transient plant, belongs to family Moraceae and member of genus *Ficus carica* Linn, and is generally recognized as fig. Throughout the world it is used as a drug for the treatment of various illnesses. The dried fruits of fig plant contained vitamins, minerals, carbohydrates, sugars (Slatnar *et al.,* 2011). Phytochemical Investigation demonstrated that several parts of *Ficus carica* plants possess various bioactive compounds such as phenolic, phytosterols, organic acids, anthocyanin composition, triterpenoids, coumarins and volatile compounds including hydrocarbons, aliphatic alcohols and few different groups of secondary metabolites and the enzymatic components including ascorbate oxidase, ascorbate peroxidase, catalase and peroxidase (Oliveira *et al.,* 2010). *Ficus carica* antioxidant properties were recognized as flavonoids and also to non-enzymatic phenolic compounds like gallic acid and ellagic acid. Some previous research revealed that *Ficus carica* leaves contained elevated level of phenolic substances as compare to stem, bark and fruit (Sirisha *et al*., 2010). Several components of *Ficus carica* plant are utilized with another medicinal plant or used with natural nutrients for therapeutic purpose (Idolo *et al.,* 2010). *Ficus carica* is a potential herbal remedy and traditionally consumed as mild laxative, diuretic, expectorant, aphrodisiac, anti-pyretic, purgative and curing of diabetes, leucoderma and ringworms, inflammation, paralysis as well as for haemorrhage (Vikas and Vijay2011). It also possesses hepatoprotective, hypoglycaemic, antifungal, antispasmodic, anthelmintic,

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antioxidant and antimutagenic activities (Vikas and Vijay 2011). The leaf is consumed as a drug for calcification of the liver and kidneys.

Stress is recognized as an important issue in basic and clinical neuroscience research (de Kloet *et al*., 2005a; McEwen *et al*., 2015). The anti hyper lipidemic influence of *Ficus carica* has been reported in increased-fat food in animal models (Joerin *et al.,* 2014). Today major health problem that people experienced is unpredictable stress. *Ficus carica* have extensive range of chemical components, its use as a conventional drug for curing several conditions and its biological actions produced wonderful effects in many diseases. No effect of fig leaves extract on stress has been previously reported. Current research was therefore aimed to study the behavioural effects following administration of ethanolic *ficus carica* leaves extract (100 mg/kg) in acute unpredictable mild stress and chronic unpredictable mild stress exposed rats.

MATERIALS AND METHODS

Extract preparation

Ficus carica leaves were collected from the local market and were washed and shade dried for five days. These dried leaves were grounded to powder and then soaked in ethanol for 8 days at room temperature. The soaked material was then filtered with the help of Whatman's No. 1 filter paper and supernatant was collected. Extraction procedure was repeated twice and filtrates were eventually combined earlier than subjecting to evaporation. To take out extract of *Ficus carica* leaves rotary apparatus was used at reduced pressure and stored until required.

Animals

In our experiment eighteen albino Wister rats (140-170g) bought from Agha Khan University Hospital were used. Rats were kept separately in a cage with allowed access to standard food and water. The home cages placed at maintained room temperature under a light on at 6:00 h for 4 days before beginning of the trials so that animals can adjust to the novel surrounding. Whole study was performed by means of procedure approved by IRB of FUUAST Karachi. (FSI/IRB/111/2014).

Experimental Protocol

In this study rats were randomly assigned as (n=6) control, stressed and fig treated stressed animals. Control animal were undisturbed in their cages whereas unpredictable mild stress (UMS) was given to other two test group rats daily for 28 days. The leaves extract of *Ficus carica* were orally given at the dosage of 100 mg/kg (Vasundhara *et al.,* 2013)to drug treated stressed animals regularly for 28 days. Whereas control and stressed animals were injected normal saline orally. The UMS procedure which was illustrated by Mao *et al*. was used with mild changes. Briefly, UMS comprised of a various type, including cold water swim (at 4℃) at least 5 min, shaking cage for 5 min, water deprivation for 24h, 24h food deprivation, hot water swim (at 45◦C) as a maximum 5 min, 24h damp sawdust, predator sound for 2 h. Stressors in unsystematic way was given each day in morning for 4 weeks. CUMS methods overcome the problems of stress familiarization and gender specificity. Such methods have beneficial rational and create authenticity and have given the maximum convenient outcomes in regards of behavioral, neurochemical, neuroendocrine and neuroimmune alterations (Willner, 2017). Control (unstressed) animals were placed at standard condition except daily cage cleaning. Behaviour of rats were monitored after one week to monitor the influence of extract of *Ficus carica* leaves on AUMS and after 4 weeks to observed the influence of leaves extract of *Ficus carica* on CUMS in animals. On day 28th rats were sacrificed after monitoring behavioral activities.

Behavioral procedure

Morris water maze Apparatus

Morris water maze test (MWM) was performed to assess the memory functions of rodents (Haider *et al.,* 2015). The is made up of circular tank. To the depth of 18 cm tank was filled with tap water and milk was mixed in the water so the platform cannot be seen. The platform was submerged about 2-3 cm beneath the water surface. Throughout the experiment, the platform remained in a fix position. During the training period, rats could swim freely in a tank and within 3 minutes they should trace the platform and permitted staying there for few seconds so they remember the position of platform. During training period if they did not discover the platform so they were gently directed towards the platform. After training session, memory was determined after 1 hour for STM and 24 hours for LTM. Time to reach the platform was monitored in training and test sessions.

Forced swimming test (FST)

Force swimming test was accomplished to examine the influence of drugs on depression like symptoms in rats (Siddiqui *et al.,* 2017). In this experiment rats were individually allowed to swim in the glass cylindrical tank which contained tap water (23 ± 2°c) to a depth of 25 cm. This depth was enough to prevent the rat paws and tail to touch the bottom of cylindrical tank. Water was changed after each swim session to remove the occurrence of any alarm substances. Immobility time and number of jumps was monitored for 5 minutes. Decrease immobility time and increase number of jumps showed the anti-depressant effect.

Light and dark Box

To determine the anxiolytic and anxiogenic behavior in rats we performed light and dark box activity (Haleem and Mahmood, 2021). It is composed of two identical compartments (26 x 26 x 26 cm) one is black walled (dark

box) and other is illuminated (light box). These two compartments were connected by a door (12cm x12cm) so that the rat could freely explore both compartments. For assessment, animals were put in the light compartment and monitored the time consumed and also no of entries in light compartment for 5 minutes.

Activity box

The assessment of locomotor activity was done in activity box. Procedure was same as described by (Ikram *et al*. (2021). Dimensions of the cage were 26 cm^3 and were made up of Perspex. Activity of the animals was monitored after 10 mins of habituation. Due to this habituation period the environment in this box is familiar environment. Activity was monitored for 5 mins as no. of cage crossing after 10 min of habituation period.

Open field test (OFT)

The impact of leaves extract of *Ficus carica* on ambulatory activity in CUMS exposed rats using open field apparatus (Kaoud *et al.,* 2010). The apparatus comprised of wooden square box. Walls of the apparatus are 35 cm in height which prohibit the escaping of rats. On the floor of the apparatus, 25 squares of equal size were drawn. To observe the activity, rats were placed in the center square and numbers of square crossed were monitored for 5 minutes.

Novel objects recognition (NOR) test

NOR test was done to evaluate the recognition memory in rats. (Batool *et al.,* 2016). The apparatus is made up of red wooden rectangular box and two different objects were needed during this experiment. One was blue painted wooden object which was square in shape and second was yellow painted wood object which was cylindrical. The experiment was conducted into three phase. During the habituation phase, in the absence of objects animal is permitted to freely move in the rectangular box for 5 minutes. Next day after 24 hour of habituation, familiarization phase were performed in the presence of two same objects for 5 minutes. In trail phase animal is exposed to familiar object and a new object at the same time for 5 minutes. Time spent with the novel and familiar object was observed.

STATISTICAL ANALYSIS

All results are represented as mean ±S.D. For analysis the SPSS software version 21 was used. For results we used one-way ANOVA followed by HSD tukey's. P value < 0.05 was considered significant.

RESULTS

Effect of leaves extract of Ficus carica on anxiety in acute unpredictable mild stressed exposed rats

Fig.1 shows that exposure to AUMS (P<0.01, 58.1%) and *Ficus carica* treated stressed rats significantly (P<0.01, 43.4%) produced anxiogenic effect by decreased the time spent in light box in light and dark box apparatus as compared to control rats.

Effect of leaves extract of Ficus carica on locomotor activity in acute unpredictable mild stressed exposed rats

Fig.2 shows that exposure to AUMS significantly (P<0.01, 41.6%) decreased locomotors activity in stressed rats as compared to controls. *Ficus carica* leaves extract administration non-significantly reversed the decrease in locomotor activity exhibited by AUMS exposed rats.

Effect of leaves extract of Ficus carica on stimulatory activity in acute unpredictable mild stressed exposed rats

Fig. 3 shows that a non-significant effect of *Ficus carica* leaves extract on stimulatory activity in AUMS exposed rats.

Effect of leaves extract of Ficus carica on ambulatory activity in acute unpredictable mild stressed exposed rats

Fig.4 shows that exposure to AUMS significantly (P<0.05, 28.7%) decline in ambulatory activity as compared to control rats. Administration of fig leaves extract non-significantly reversed the decrease in ambulatory activity exhibited by AUMS exposed rats.

Effect of leaves extract of Ficus carica on spatial working memory in acute unpredictable mild stressed exposed rats

Fig.5 shows that exposure to AUMS (P<0.01, 81%) and drug administered stressed rats significantly (P<0.01, 77%) impaired SWM (spatial working memory) as compared to control rat.

Effect of leaves extract of Ficus carica depression like symptoms in acute unpredictable mild stressed exposed rats

Fig. 6 revealed a non-significant effect of *Ficus carica* leaves extract on depressive behavior in AUMS exposed rats.

Effect of leaves extract of Ficus carica on recognition memory in acute unpredictable mild stressed exposed rats

Fig. 7 shows that exposure to AUMS significantly (P<0.01, 22%) impaired recognition memory in stressed rats. Administration of *Ficus carica* leaves extract significantly reversed impairment in recognition memory exhibited by AUMS exposed rats (P<0.01, 1.6 folds).

Effect of leaves extract of Ficus carica on anxiety in chronic unpredictable mild stressed exposed rats

Fig. 8 shows that exposure to CUMS significantly (P<0.01, 41%) produced anxiogenic effect as compared to control rats. Administration of *Ficus carica* leaves extract significantly reversed the increase in anxiety exhibited by CUMS exposed rats.

Effect of leaves extract of Ficus carica on locomotor activity in chronic unpredictable mild stressed exposed rats

Fig.9 shows that exposure to CUMS non-significantly increased locomotors activity as compared to controls. Administration of fig leaves extract significantly increased locomotor activity in drug administered stressed rodents as compared to control animals($P<0.01$, 85.7%) and as compared to the CUMS exposed rats ($P<0.01$).

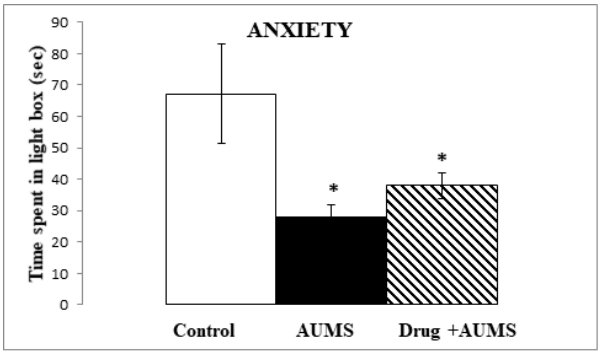

Fig. 1: Effect of leaves extract of *Ficus carica* on Anxiety in acute unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one- way ANOVA (*P<0.01 vs control).

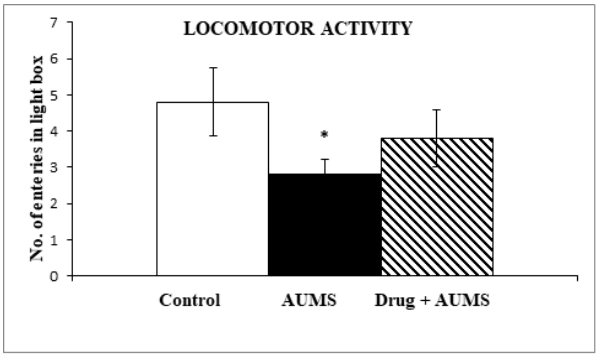

Fig 2: Effect of leaves extract of *Ficus carica* on Locomotor activity in acute unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one -way ANOVA (*P<0.01 vs control).

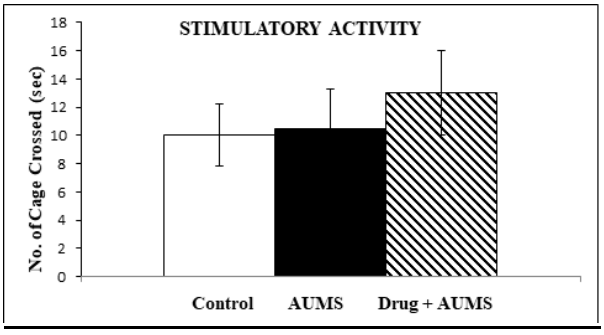

Fig 3: Effect of leaves extract of *Ficus carica* on Stimulatory activity in acute unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one-way ANOVA ($p>0.05$).

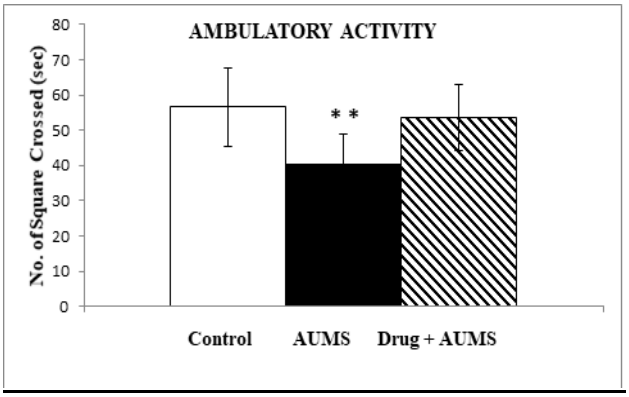

Fig 4: Effect of leaves extract of *Ficus carica* on Ambulatory activity in acute unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one- way ANOVA (**P<0.05vs control).

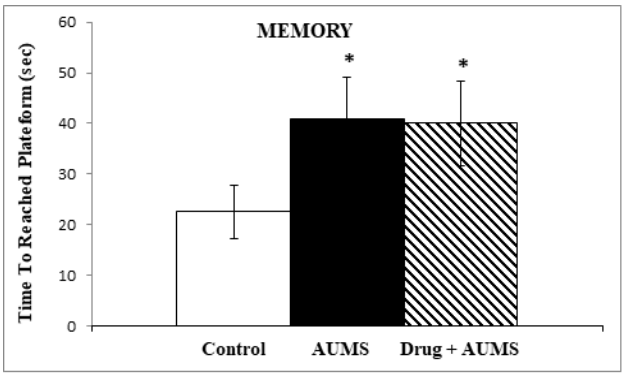

Fig 5: Effect of leaves extract of *Ficus carica* on Spatial working memory in acute unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one-way ANOVA (*P<0.01vs control).

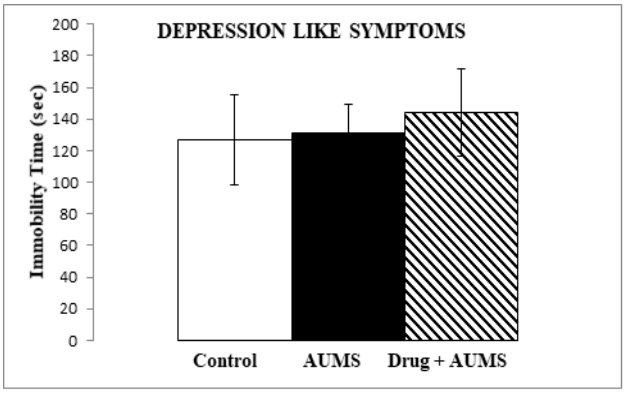

Fig 6: Effect of leaves extract of *Ficus carica* on Depression like symptoms in acute unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one- way ANOVA ($P>0.05$)

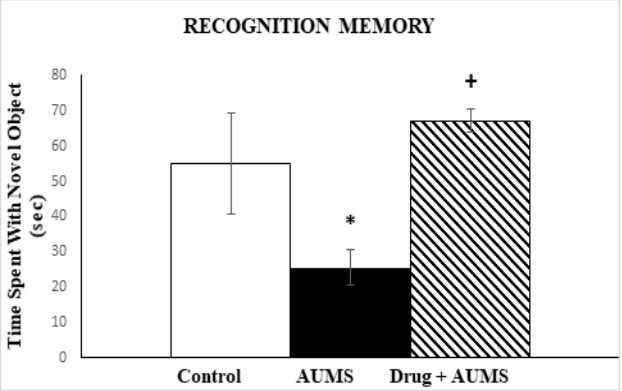

Fig 7: Effect of leaves extract of *Ficus carica* on Recognition memory in acute unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one- way ANOVA (*P<0.01 vs control; +P<0.01vs AUMS).

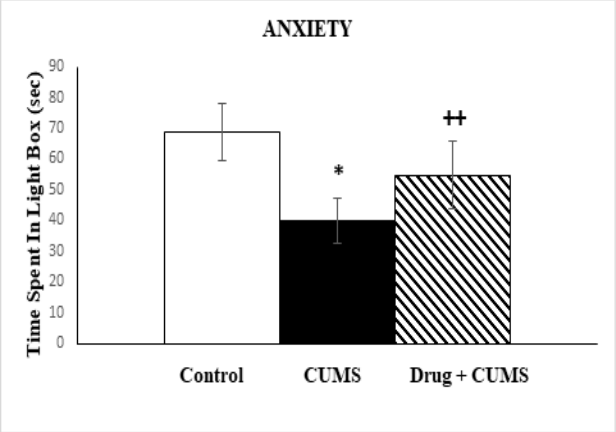

Fig 8: Effect of leaves extract of *Ficus carica* on Anxiety in chronic unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one- way ANOVA (*P<0.01 vs control; ++P<0.05vs CUMS).

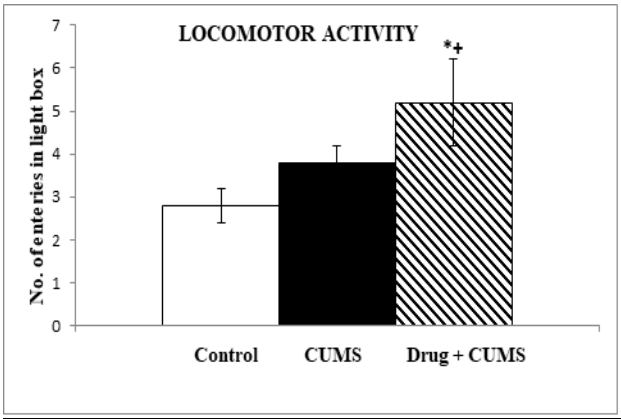

Fig 9: Effect of leaves extract of *Ficus carica* on locomotor activity in chronic unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one- way ANOVA (*P<0.01 vs control; +P<0.01vs CUMS).

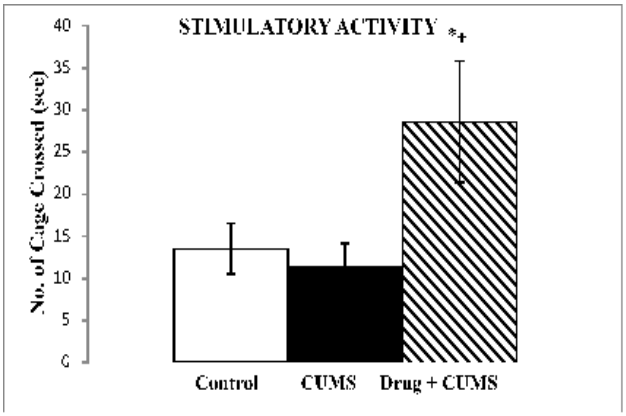

Fig 10: Effect of leaves extract of *Ficus carica* on Stimulatory activity in chronic unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one- way ANOVA (*P<0.01 vs control; +P<0.01vs CUMS).

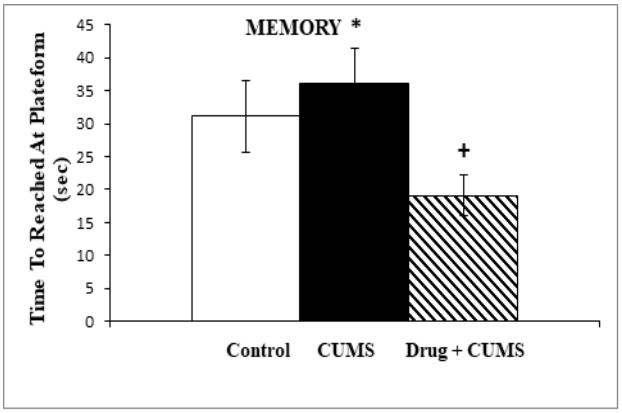

Fig 11: Effect of leaves extract of *Ficus carica* on Ambulatory activity in chronic unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one-way ANOVA (+P<0.01vs CUMS).

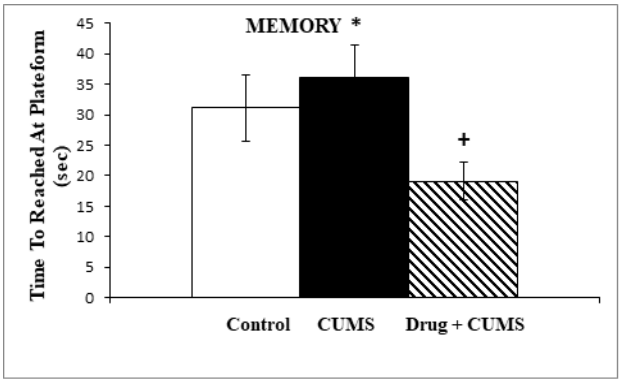

Fig 12: Effect of leaves extract of *Ficus carica* on Spatial working memory in chronic unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one- way ANOVA (*P<0.01vs control; +P<0.01vs CUMS).

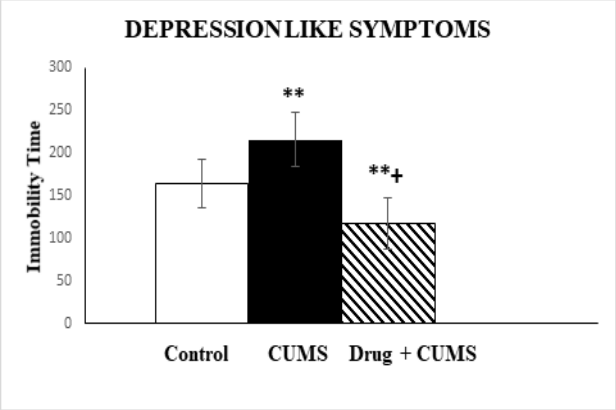

Fig 13: Effect of leaves extract of *Ficus carica* on Depression like symptoms in chronic unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one- way ANOVA (**P<0.05vs control; +P<0.01vs CUMS).

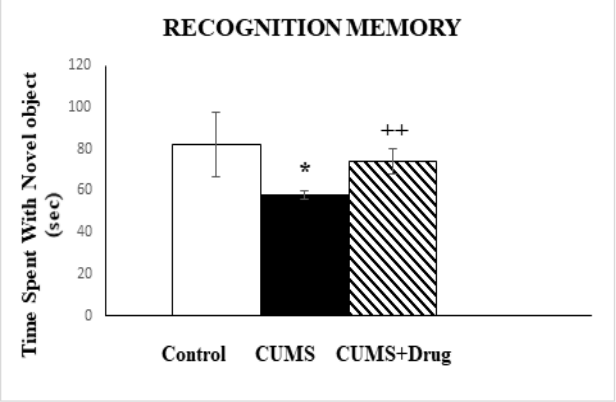

Fig 14: Effect of leaves extract of *Ficus carica* on Recognition memory in chronic unpredictable mild stressed exposed rats.
Values: means ± S.D. Statistics were done via one- way ANOVA (*P<0.01vs control; ++P<0.05vs CUMS).

Effect of leaves extract of Ficus carica on stimulatory activity in chronic unpredictable mild stressed exposed rats

Fig.10 shows that exposure to CUMS produced no effect on stimulatory activity as compared to control rats. Administration of fig leaves extract significantly (P<0.01, 1.1 folds) increased stimulatory activity in drug administered stressed rats as compared to control rats and (P<0.01, 1.5 folds) as compared to stressed rats

Effect of leaves extract of Ficus carica on ambulatory activity in chronic unpredictable mild stressed exposed rats

Fig.11 shows that exposure to CUMS non-significantly decreased ambulatory activity as compared to control rats. Administration of fig leaves extract significantly (P<0.01, 56.8%) reversed the decrease in ambulatory activity exhibited by CUMS exposed rats.

Effect of leaves extract of Ficus carica on spatial working memory in chronic unpredictable mild stressed exposed rats

Fig. 12 shows that exposure to CUMS significantly declined in SWM (spatial working memory) as compared to control rats. Fig leaves extract administration significantly (P<0.01, 38.5%) reversed the impairment in memory functions exhibited by CUMS exposed rats.

Effect of leaves extract of Ficus carica on depression like symptoms in chronic unpredictable mild stressed exposed rats

Fig. 13 shows that exposure to CUMS rats significantly (P<0.05, 31.9%) increased depression like symptoms in stressed rats as compared to control rats. This increased in depression like symptoms exhibited by CUMS exposed rats were significantly decreased in *Ficus carica* leaves extract treated CUMS exposed rats.

Effect of leaves extract of Ficus carica on recognition memory in chronic unpredictable mild stressed exposed rats

Fig. 14 shows that exposure to CUMS significantly (P<0.01, 29.5%) impaired recognition memory in stressed rats. Administration of *Ficus carica* leaves extract significantly increased recognition memory exhibited by CUMS exposed rats (P<0.05, 27.7%).

DISCUSSION

The fig is a blessed tree. From Quran fig is the fruit of Heaven. In the first Quranic verse of Surah at- Teen, ALLAH is swearing by the fruit; Fig (teen). When ALLAH swears on something, it must be of great value. Fig is one of the only 5 plants mentioned in Quran along with grapes, pomegranate, olives and dates. So, this blessed tree has great benefits in various problems, its leaves have great power and medicinally used for diseases as it is used as a safe herbal remedy. In the present study behavioral effects following administration of leaves extract of *Ficus carica* in acute and chronic unpredictable mild stressed exposed rats has been observed. Present study revealed that exposure to AUMS and CUMS significantly impaired recognition memory in rats which was significantly enhanced by the administration of *Ficus carica* leaves extract in AUMS and CUMS exposed rats. Current study also revealed that exposure to CUMS produced anxiogenic effect and increased depression like symptoms which was reversed by the drug administration. *Ficus carica* leaves extract administration increased locomotor, stimulatory, ambulatory activity and increased spatial working memory in CUMS exposed rats.

Serotonergic neurons are involved in regulation of numerous biological process including appetite, mood and sleep and cognitive performance (Ray *et al.*, 2011; Meltzer & Roth, 2013).Past literature exhibited that

diverse subtypes of serotonin receptors, including 5-HT 1A, 5-HT2A, and 5-HT2C are involved in anxiety and depression. (Marcinkiewcz *et al.,* 2016). Now a day's herbal medicine are being utilized by 43% persons suffer from various disorders (Alves *et al.,* 2010). Previous study revealed that brain homogenate possesses enhance concentration of 5-HT by the administration of ethanolic extract of *Ficus carica*. Increased endogenous 5-HT produced anxiogenic effect, whereas decreased endogenous 5-HT produced anxiolytics effect. Previous study also revealed that Extract of *Ficus carica* exhibited flavonoids presence which has been currently implicated for countless pharmacological performance and they have been recognized as a novel type of ligand with *in vivo* anxiolytic properties. Similarly, present study showed exposure to CUMS produced anxiogenic effect which was reversed by the *Ficus carica* extract administration. Anxiolytics effect may be due to the increased level of serotonin level or either presence of flavonoids.

In research, the assessment of natural locomotor and exploratory behaviour in rats is generally considered as an essential indication of usual activities of the rats. It has been employed in the analysis of pharmacological agents and in neurobehavioral investigations of the neural regulation of rat performance (Eilam and Golani, 1989). It has been identified that systems of interneurons found within the spinal cord are liable for causing locomotion and interrelate with the definite sensory knowledge to permit for the support along with the alterations in the regulation of locomotor activity. Present study revealed that *Ficus carica* leaves extract administration increased locomotor; stimulatory an ambulatory activity in CUMS exposed rats.

Memory is the process of learning. Deprived memory, low and decelerate memory retention and various cognitive disorders occurs due to certain factors including age and exposure to stress (Desai *et al.,* 2009) which causes learning and memory impairment (Wangkhem *et al.,* 2011). Preceding reviews have publicized that flavonoids and other fruit and vegetable-derived phytochemicals have a positive impact on cognitive functions and also play a part in humans to prevent dementia (Nassiri-Asl*et al.,* 2010). Current study revealed that recognition memory was significantly enhanced by the administration of *Ficus carica* leaves extract in AUMS and CUMS exposed rats. It was also reported that administration of *Ficus carica* leaves extract enhance spatial working memory in CUMS exposed rats. This can be interpreted as presence of antioxidant in *Ficus carica* that may be involved in learning and memory enhancing activity. *Ficus carica* antioxidant properties were attributed to flavonoids and also to non-enzymatic phenolic compounds like gallic acid and ellagic acid (Sirisha *et al.,* 2010) which justifying the result in present study.

Depression is a lethal condition associated with psychomotor retardation symptoms. In old age people, beside with aging, the physical, biological and neurological performance becomes deteriorated. The nervous system metabolism and alteration in various neurotransmitters are the pathophysiological basis of elderly depression (Berntson *et al.,* 2017).

Chronic stress models are comparatively more suitable than acute stress models for investigating depression in experimental models (Katz *et al.,* 1981; Willner *et al.,* 1997). Use of traditional herbs are becoming an emerging trend due to less side effect profile that has gave us a future substitute for the curing of depression (Xia *et al.,* 2007). As well as it has been demonstrated that in rats and human being various polyphenolic compounds produce anti-depressant like effect (Xu *et al.,* 2010; Zhu *et al.,* 2012). Previous report illustrated that polyphenols compounds may possibly involve in the recovery of mental condition. Current study also revealed that exposure to CUMS increased depression like symptoms which was reversed by the *Ficus carica* leaves extract administration.

CONCLUSION

The current investigation revealed that acute and chronic stressors causes various behavioural and biochemical alteration in experimental rats. Different types of stressors produce different effect on behaviours. Acute and chronic stress prompted variable changes in behaviours in experimental rodents. Acute stress induced anxiogenic behaviour and caused memory impairment while depression like symptoms was not produced by acute exposure with the stressors. Spatial working memory and recognition memory was impaired and depression like symptoms was also produced after the exposure with the prolonged stress. In past, different therapy are utilized for the treatment which reduce the disease condition but it also produced severe toxicities so, new remedies are required with less harmful effects. Treatment of acute and chronic stress by the extract of *Ficus carica* leaves produce positive treatment effect such as it reversed the impairment in memory functions exhibited by stressed rats. It also produced anxiolytic effect and decreased depression like symptoms in AUMS exposed rats. Locomotor, stimulatory, ambulatory activity and spatial working memory was also enhanced after the treatment with the *Ficus carica* leaves extract in CUMS exposed rats. Thus, by the observed results it can be said that leaves of *Ficus carica* can be used as safe medicine for the physiological stress treatment with fewer side effects. Further investigation is required to find out the mechanism involved in stress response.

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