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Psychopharmacological impact of ferulic acid on depressive-like behaviors induced by high fat diet in rats models of depression

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Abstract: Previous studies have been demonstrated that high fat diet can leads to the development of obesity. Obesity is strongly linked with several kinds of neurological and physiological disorders such as type 2 diabetes, and cardiovascular diseases. Furthermore studies also suggested that obesity may cause behavioral changes that mainly deal with less locomotor activity and anxiety obesity linked behavioral changes induced by HFD. By using different parameters like growth rate, food intake, levels of anxiety and locomotor activity the finding of this study showed that, that repeated administration of ferulic acid has great profound effect on impairments that were caused by HFD. In our experiments we have observed that those rats which were on HFD and were treated with water only was seemed to be more depressed, less active, and more anxious than those which were administered by ferulic acid doses. From these results we can also suggest that there must be disturbance in the levels of neurotransmitters in an obese individual that caused such kind of changes in the body. This study has implications in the recovery of the changes in the body that were produced by HFD. And ferulic acid can be used as the drug to cure behavioral consequences that were induced by HFD.

Keywords: High fat diet, neurological disorders, metabolic manifestations, ferulic acid.

INTRODUCTION

Depression is a common mental disorder with symptoms including loss of interest or pleasure (anhedonia), a depressed mood, disturbed sleep or appetite, decreased energy, poor concentration and feelings of guilt or low self-worth (Hankin, 2006). Accumulated evidences demonstrated that chronic stress negatively affects neurogenesis and neural plasticity which produced expressive symptom, impairment in memory and learning processes (Radley *et al.,* 2015 and Sheth *et al.,* 2017). The deleterious effect of chronic stress is modulated by the stress hormone, cortisol/corticosterone (CORT), neurotrophins, and various neurotransmitters (Mizuki *et al.,* 2014, Phillips, 2017 and Schroeder *et al.,* 2018). The use of hyperlipidemic or hyper-chloric diet induced obesity. It is directly related to the development of obesity. High fat diet intake has been responsible to increase adiposity. Human studies shows that high fat diet approximately 30% of energy from fat can easily induce obesity (Jecquer 2002). When the excess energy is stored in body fat particularly in adipose tissues becomes enlarged. Obesity involves either increase in number of adipocytes (hyperplasia) and increase in size of adipocytes (hypertrophy) (Jecquer 2002, Avram *et al.,* (2005). High fat diet induced behavioral changes were accompanied by elevated basal hypothalamic pituitary adrenal (HPA) activity and reactivity in response to stress. The higher mass of dysfunctional adipose tissue in obesity that not only cause metabolic abnormalities which leads to the metabolic disorder but also causes neurobiological impairments which leads to the mood disorder (Hryhorczuk *et al*., 2013). Mood states such as anxiety and depression can affect the food choice and energy metabolism. Overeating and obesity is often associated with anxiety and depression in humans and also in animals (Akubuiro *et al*., 2013). There are some findings shows prolonged high fat feeding leads to negative emotional stress, increase stress sensitivity and also altered the basal corticosterone levels (Sharma *et al.,* 2012). Ferulic acid (4-hydroxy-3-methoxycinnamic acid, FA), which belongs to the broad category of phenols, is a natural phytochemical widely found in vegetables and fruits and is also a major active ingredient in many Chinese medicinal herbs, such as *Angelica sinensis*, *Ligusticum chuanxiong* and *Cimicifuga foetida* (Mancuso and Santangelo, 2014). Ferulic acid is most commonly found in whole grains, spinach, parsley, grapes, rhubarb, and cereal seeds, mainly wheat, oats, rye, and barley. In previous studies, focused on the negative effect of PS on the offspring and the specific mechanism, including the impaired GR and increased HPA axis reactivity. Taken together, the studies suggest that FA improves the depression induced by stress, but the effect and underlying mechanisms remain unclear. FA significantly reduced IL-6, IL-1β and TNF-α concentration and increased IL-10 concentration in male, prenatally-stressed offspring, stimulated by the NF-κB pathway. In addition, FA inhibited interleukin-6 (IL-6), interleukin-1β (IL-1β),

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and tumor necrosis factor-α (TNF-α), and increased interleukin-10 (IL-10) mRNA and protein expression. Furthermore, FA markedly decreased the serum adreno-corticotropin (ACTH) and corticosterone concentration by the increase of GR protein expression. Taken together, the study revealed that FA has anti-depressive-like effects in male, prenatally-stressed offspring, partially due to its anti-inflammatory activity and hypothalamic-pituitary-adrenal (HPA) axis (Xingxing Zheng *et al.,* 2019).

The purpose of the study was to induce depressive like behaviors in mouse model by high fat diet. After the establishment of behavioral deficits in depressive models, the animals' models were treated with ferulic acid to treat behavioral deficits and depression.

MATERIALS AND METHODS

Animals

Male locally bred albino Wistar rats with an average weight of 120-180 grams were purchased from Dow University and Health Science (DUHS) Karachi Pakistan. The animals were housed in individual cages under light dark cycles of 12:12 hours with controlled temperature and humidity environment conditions and maintained on free access to standard rodent diet and tap water for familiarization for 3 days before the experimentation.

Drugs

All chemicals and drugs were purchased from the Sigma Chemical Company (USA) which is used during the study.

Experimental protocol

Twenty four rats were randomly divided into two groups 1) Normal fat diet 2) High fat diet. Animals of high fat diet group received high fat rich diet for 4 weeks to induce an obesity model in rats. After the establishment of obesity animals of both groups were sub divided in to further two groups i.e., Saline and Ferulic acid administrated groups. This resulted in a total of four groups: i) Normal fat diet-Saline ii) Normal fat diet-Ferulic acid iii) High fat diet-Saline iv) High fat diet-Ferulic acid. Animals were administered orally with ferulic acid (10mg/kg/day) or saline for next four weeks. On the next day of 1st doses and then weekly behavioral parameters assessments like food intake, growth rate, locomotor activity in familiar (home cage) as well as in novel (open field) and activities in EPM model were done. On next day of 28th day, blood samples were collected for the estimation of lipid profile of animals.

Behavioural assessment

Food intake

Food intake was monitored by giving the measured food in each animal cage. Food intake was measured by weighing the amount of food left in the cage, after 24 hours or weekly as required by the experiment (Rafiq and Farhan, 2015). By subtracting the weight of food left in the cage from the weight provided on the first day of experiment is the amount of food consumed by the rat.

Growth rate

Change in the body weight was monitored daily or weekly as required by the experiment. Changes in the body weight were monitored to find out the effect of specific treatment in the respective chapters. Daily or weekly growth rate changes were calculated as percentage of starting day weight (experiment day body weight/starting day body weight) × 100.

Home cage activity test

Home cage activity is used to monitor the locomotor activity of animals in a familiar environment. Measurement of locomotor activity in rats is an easy and simple way to assess behavior that reflects altered physiology of an animal (Rafi and Farhan 2016). Activity cage apparatus was a square Perspex cage (26×26×26cm) with a saw dust covered floor. Testing was done in a quiet room under white light as described by (Ikram *et al.,* 2011). The rat was placed in the cage and monitor the locomotor activity and the number of cages over the period of 10 minutes (Rafiq and Farhan, 2015).

Open field activity test

Open field activity was done by to monitor the assessment of exploratory locomotor activity in a novel environment. The open field apparatus used in this experiment are much larger than the home cage and it is unfamiliar to the rats (Rafi and Farhan 2016). The open field apparatus was consisted of a square area 76×76cm with opaque plastic walls of 42cm high. The floor of apparatus was divided into 25 equal squares. The rats were individually placed in the center square of the field for the assessment of exploratory activity. The parameters were observed latency time (the time which was taken by the animal for exploring from the center square of area and this time was monitored in seconds). Whereas the number of square crossed (the number of square crossed with all four paws were measured in 5 minutes.

Elevated plus maze test

Elevated plus maze test is one of the most widely used for measuring anxiety-like behavior in rodent models of CNS disorders and to test anxiolytic drugs. The test is based on natural aversion of rats for open and elevated areas. The apparatus is plus shaped and consists of two open arms, two closed arms of 10x50cm and a center passage area. The height of the apparatus is 55cm. The rat is placed on the center passage area and is allowed to move freely in the plus maze. The behavior is recorded that is expressed in terms of number of entries in open arms and time spent in open arms.

Forced swim water

Forced swim test is used for the determination of antidepressant activity. The apparatus is consisting of water filled transparent glass container with diameter 12cm and 22cm height. Each animal allowed swimming in the apparatus containing water with maintained (25±2) temperature. Swimming (struggling) time and the immobility (helpless behavior) time were recorded for the determination of antidepressant activity.

Ethical approval

Experiments were carried out according to a strict procedure and in a well-organized manner, using a detailed guide for the care and management of laboratory animals (Institute of Laboratory Aanimals Resource of Life Science, US National Research Council, 1996).

STATISTICAL ANALYSIS

Results are represented as mean±S.D. All behavioral data were analyzed by three ways ANOVA. Software used for the analysis was SPSS (version 1.7). Individual comparison was made by Newman-Keuls test. P<0, 05 were considered as significant

RESULTS

Effects of ferulic acid on growth rate of HFD treated rats

The fig. 1 shows that the effect of repeated administration of ferulic acid on growth rate of rats which were exposed to HFD for 4 weeks as monitored on next day of first administration and then weekly. Analysis of food intake was done by three way ANOVA (repeated measure design) the effect of days ($F=1.253$; df=1, 32) were found to be non-significant. Whereas the effect of ferulic acid ($F=121.233$; df=1, 32; $p<0.01$) the effect of diet ($F=66.134$; df=1, 32; $p<0.01$) and the interaction between days, drug and diet ($F=28.145$; df=1, 32 $p<0.01$) were found to be significant. Post-hoc analysis by Newman Keuls test showed that administration of ferulic acid increased growth rate in NFD rats but decreased in HFD rats as compared to water administrated rats. Significant decrease was found after 21st and 28thday of administration ($p<0.01$) in NFD and after 2nd, 3rd and 4th ($p<0.01$) weeks of administrations. A compared to similarly administrated ferulic acid rats from 1st day of administration, repeated administration of ferulic acid increase growth rate in NFD rats but decrease was found in HFD treated rats. Significant ($p<0.01$) increase was found after 21st and 28th day of administration in NFD rats. Whereas, growth rate decrease significantly in HFD treated rats after 2nd, 3rd and 4th weeks of administrations.

Effects of ferulic acid on food intake of HFD treated rats

The fig. 2 shows that the effect of repeated administration of ferulic acid on food intake of rats which were exposed to high fat diet for 4 weeks as monitored on next day of first administration and then weekly. Analysis of growth rate is done by three way ANOVA (repeated measure design) the effect of days ($F=88.18$; df=1, 32; $p<0.01$) the effect of diet ($F=121.144$; df=1, 32; $p<0.001$) and the interaction between days, drug and diet ($F=120.198$; df=1, 32; $p<0.01$) were found to be significant. Whereas the effect of ferulic acid ($F=0.213$; df=1, 32) was non-significant. Post-hoc analysis by Newman-Keuls test showed ferulic acid administration decreased food intake in NFD but increased in HFD treated rats as compared to saline treated NFD and HFD rats. Significant decrease was found on 21st and 28th day of administration ($p<0.01$) in NFD rats. Whereas, in HFD treated rats, food intake was increased after 2nd, 3rd and 4th weeks of administrations. Weekly administration of ferulic acid decrease food intake in NFD and increased in HFD rats as compared to 1st day administration. Significant decrease was found after 21st ($p<0.05$) and 28th ($p<0.01$) in NFD treated rats. In HFD rats, decrease were significant after 21st ($p<0.05$), 14th and 28th ($p<0.01$) day of repeated administrations.

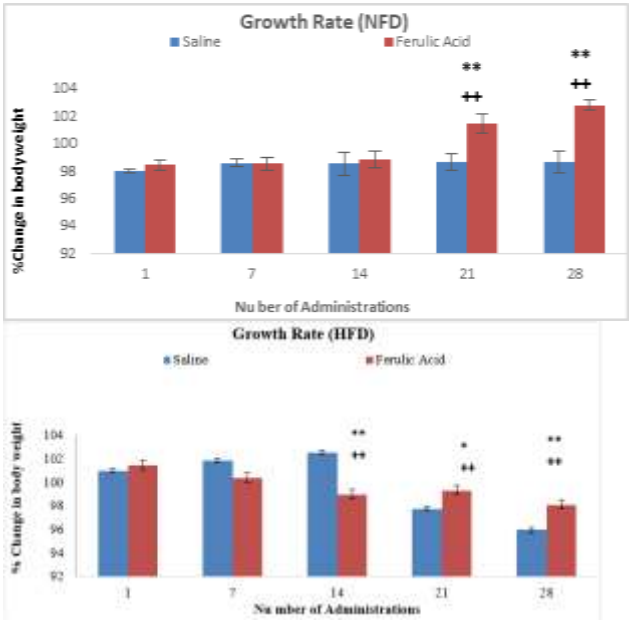

Fig. 1: Effects of Ferulic acid on % Change in body weight of NFD and HFD rats.

Values are means + SD (n=6) as monitored post 24 hrs of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated NFD or HFD rats; +p<0.05, ++p<0.01 from similarly saline or Ferulic acid administrated NFD and HFD rats of 1st day administration following three-way ANOVA (repeated measures design).

Effects of ferulic acid on home cage activity of HFD treated rats

The fig. 3 demonstrated that the effect of repeatedly ferulic acid administration on activity (cage counts) of animals in activity box. High fat diet for 28 days was given to the rats was monitored after 24hrs of the first

administration and then weekly. Three way ANOVA (repeated measure design) was done to analyzed the number of cage crossed in home cage, the effect of days ($F=68.623$; df =1, 32; $p<0.01$) the effect of ferulic acid ($F=125.139$; df=1, 32 $p<0.01$), the effect of diet ($F=78.112$; df 1, 32 $p<0.01$) and the interaction between days, drug and diet ($F=236.714$; df=1, 32; $p<0.01$) were found significant. Post-hoc analysis by Newman-Keuls test showed that administration of ferulic acid increase activity in home cage (number of cage crossings) in both NFD as well as HFD treated rats as compared to similarly treated NFD or HFD saline administrated rats. Significant increase was found after 7th ($p<0.05$) day of administration in NFD rats and 14th, 21st and 28th ($p<0.01$) day of administration in both NFD and HFD treated rats. As compared to similarly repeated administration of ferulic acid of NFD and HFD treated rats from 1st day of administration, greater number of cage crossing were found in NFD and HFD treated rats. Significant ($p<0.01$) increased values were found after 14th, 21st as well as 28th day of ferulic acid administrated NFD or HFD treated rats. After 7th day ($p<0.01$) greater value was found in NFD treated rats.

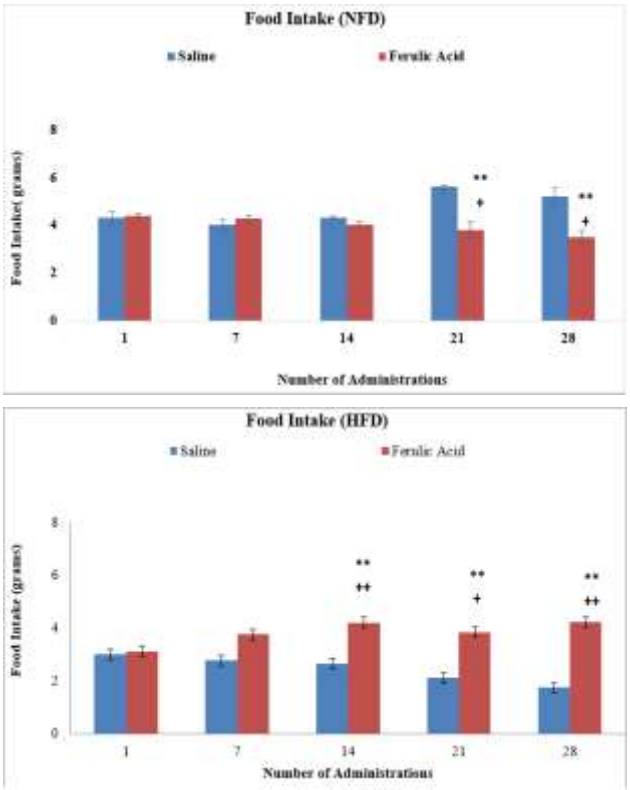

Fig. 2: Effects of Ferulic acid on Food Intake of NFD and HFD rats.

Values are means + SD (n=6) as monitored post 24 hrs of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated NFD or HFD rats; +p<0.05, ++p<0.01 from similarly saline or Ferulic acid administrated NFD and HFD rats of 1st day administration following three-way ANOVA (repeated measures design).

Effects of ferulic acid on open field box activity (latency time) of HFD treated rats

Fig. 4 showed the effect of repeated administration of ferulic acid on rats that were provided to high fat diet for 28 days as monitored after 24 hours of 1st drug administration and then monitored weekly. Analysis was done by three way ANOVA of open field test(latency time) which shows the effect of days ($F=45.125$; df=1, 32 $p<0.01$) the effect of ferulic acid ($F=234.562$; df=1, 32; $p<0.01$) the effect of diet ($F=256.134$; df 1, 32 $p<0.01$) and the interaction between days, drug and diet ($F=78.235$; df=1, 32 $p<0.01$) were found to be significant. Post-hoc analysis by Newman-Keuls test showed that time required to move in open field (latency time) decreased with the administration of ferulic acid in NFD as well as HFD rats as compare to their saline administrated control. Significant ($p<0.01$) decreased were found after 14th, 21st and 28th day of administrations in NFD and in HFD treated rats. As compared to similarly administrated ferulic acid rats of NFD or HFD treated rats from 1st day of administrations, repeated administrations of ferulic acid decrease latency time in NFD as well as HFD treated rats. Significant ($p<0.01$) decrease was found after 14th, 21st and 28th day of administration in NFD treated rats and after 4th weeks administration in HFD treated rats.

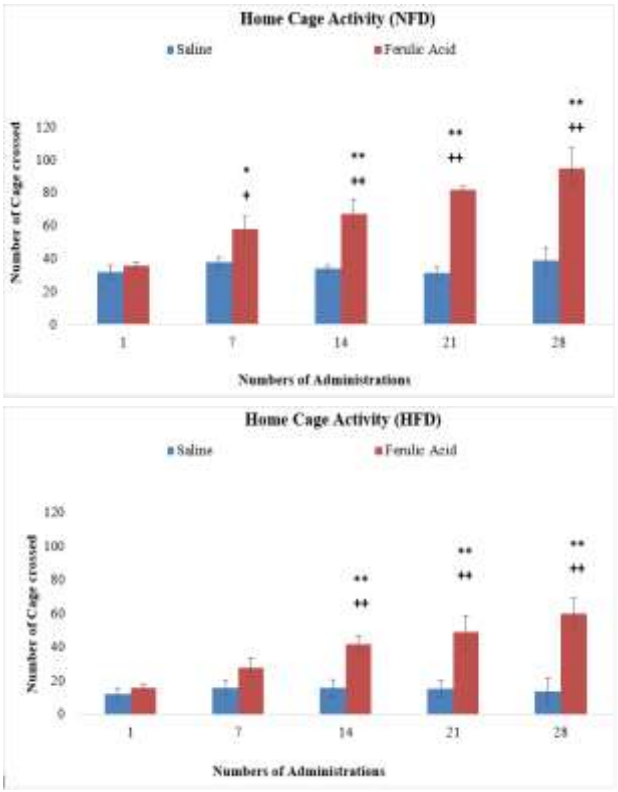

Fig. 3: Effects of Ferulic acid on activity in Home Cage box of NFD and HFD rats.

Values are means + SD (n=6) as monitored post 24 hrs of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated NFD or HFD rats; +p<0.05, ++p<0.01 from

similarly saline or Ferulic acid administrated NFD and HFD rats of 1st day administration following three-way ANOVA (repeated measures design).

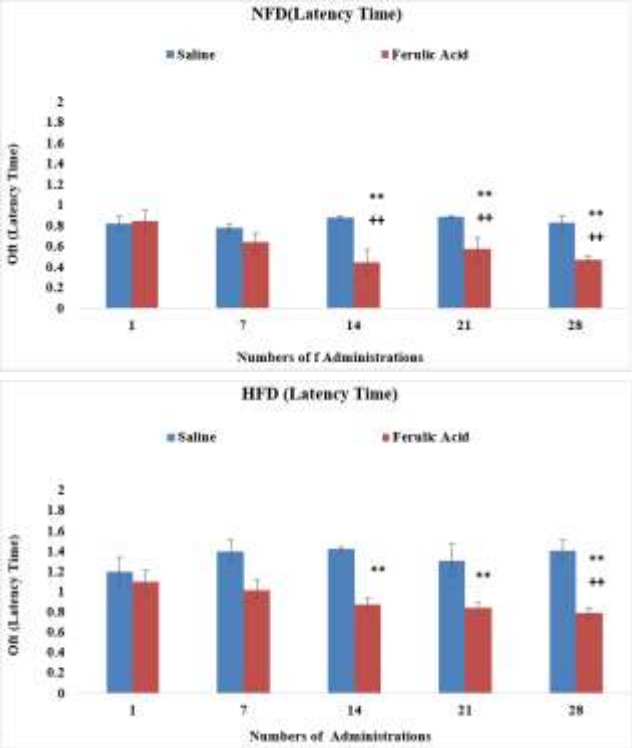

Fig. 4: Effects of Ferulic acid on activity in Open Filed box (Latency Time) of NFD and HFD rats.
Values are means + SD (n=6) as monitored post 24 hrs of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated NFD or HFD rats; +p<0.05, ++p<0.01 from similarly saline or Ferulic acid administrated NFD and HFD rats of 1st day administration following three-way ANOVA (repeated measures design).

Effects of ferulic acid on open field box activity (square counts) of HFD treated rats

Analysis of data fig. 5 on number of square count by three way ANOVA shows that the effect of repeated administration of ferulic acid on rats which was exposed to high fat diet for 4 weeks as monitored by post 24 hours of the 1st administration and then weekly. The effect of days (F=201.576; d/f=4, 21; p<0.01) the effect of ferulic acid (F=124.451; df=1, 32; p<0.01) the effect of diet (F=178.135; df=1, 32; p<0.01) and the interaction between days, drug and diet (F=140.563; df=1, 32; p<0.01) were significant. Post-hoc analysis by Newman-Keuls test showed administration of ferulic acid increased square count in NFD as well as HFD rats from their respective control. Significant (p<0.01) increased were found in NFD rats after 14th, 21st and 28th day of administration in HFD rats and after 21st and 28th day of administrations in NFD treated rats. From 1st day of administration, ferulic acid repeated administration increase square counts in NFD and HFD rats. Significant (p<0.01) greater number of square counts were found after 3rd and 4th of NFD and after 2nd, 3rd and 4th weeks of administrations in HFD treated rats.

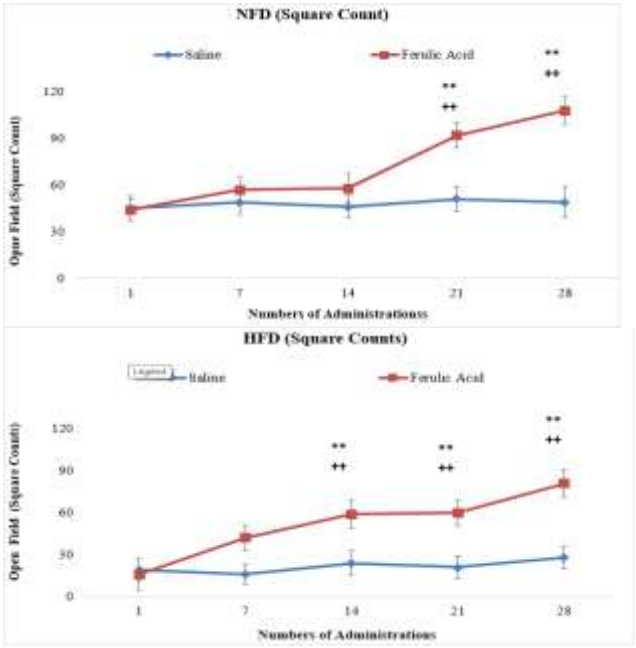

Fig. 5: Effects of Ferulic acid on activity in Open Filed box (Square crossed) of NFD and HFD rats.
Values are means + SD (n=6) as monitored post 24 hrs of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated NFD or HFD rats; +p<0.05, ++p<0.01 from similarly saline or Ferulic acid administrated NFD and HFD rats of 1st day administration following three-way ANOVA (repeated measures design).

Effects of ferulic acid on EPM activity (entries counts) of HFD treated rats

Fig. 6 showed the effect of repeated administration of ferulic acid on rats that were provided to high fat diet for 1-28 days as monitored after 24hrs of 1st drug administration and then monitored weekly. Analysis was done by three way ANOVA of number of entries in open arm which shows the effect of days (F=45.125; df=1, 32 p<0.01) the effect of ferulic acid (F=234.562; df=1, 32; p<0.01) the effect of diet (F=256.134; df 1, 32 p<0.01) and the interaction between days, drug and diet (F=78.235; df=1, 32 p<0.01) were found to be significant. Post-hoc analysis by Newman-Keuls test showed that numbers of entries in an open arm of EPM increase with the administration of ferulic acid in both NFD and HFD treated rats as compared to similarly NFD and HFD treated saline administrated controls. Significant (p<0.01) increase were found after 21st and 28th day of administration in NFD and HFD treated rats. As compared to similarly ferulic acid administrated NFD and HFD treated rats from 1st day of administrations, daily administration of ferulic acid for 4 weeks increase number of entries in both NFD and HFD rats. In NFD rats, significant greater value were found after 21st and 28th day

of administration in NFD ($p<0.05$) and HFD ($p<0.01$) treated rats.

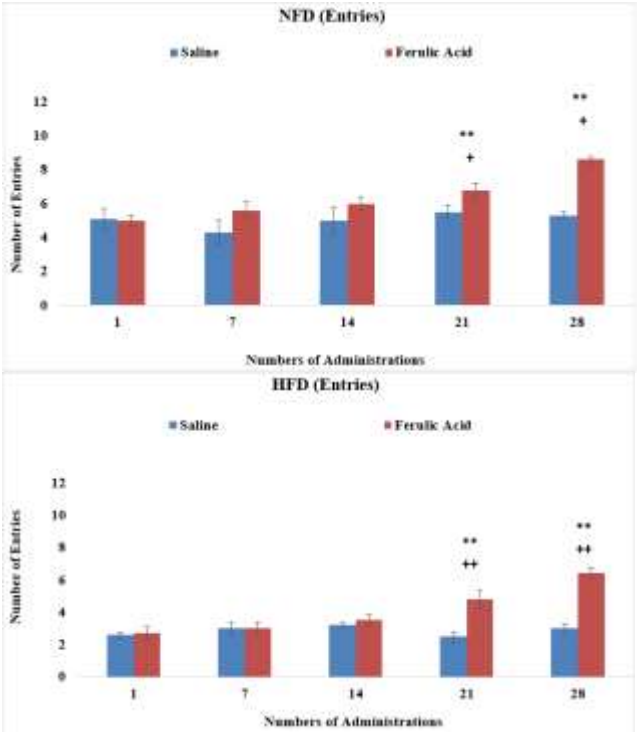

Fig. 6: Effects of Ferulic acid on activity in EPM (Entries) of NFD and HFD rats.

Values are means + SD (n=6) as monitored post 24 hrs of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated NFD or HFD rats; +p<0.05, ++p<0.01 from similarly saline or Ferulic acid administrated NFD and HFD rats of 1st day administration following three-way ANOVA (repeated measures design).

Effects of ferulic acid on EPM activity (time) of HFD treated rats

Fig. 7 showed the effect of repeated administration of ferulic acid on rats that were provided to high fat diet for 1-28 days as monitored on next day of 1st drug administration and then monitored weekly. Analysis was done by three way ANOVA of open field test(latency time) which shows the effect of days ($F=45.125$; df=1, 32 $p<0.01$) the effect of ferulic acid ($F=234.562$; df=1, 32; $p<0.01$) the effect of diet ($F=256.134$; df 1, 32 $p<0.01$) and the interaction between days, drug and diet ($F=78.235$; df=1, 32 $p<0.01$) were found to be significant. Post-hoc analysis by Newman-Keuls test showed that administration of ferulic acid increased time spent in open arm of EPM in both NFD and HFD treated rats as compared to similarly treated saline controls. Significant ($p<0.01$) increase in time spent were found after 21st and 28th day of administration in NFD and HFD treated rats. As compared to similarly administrated rats of NFD and HFD treated rats from 1stday of administration, ferulic acid repeated administration increase activity in NFD and HFD treated rats. Significant ($p<0.01$) greater increase in activity were found after 3rd and 4th weeks of administrations in both NFD as well as HFD treated rats.

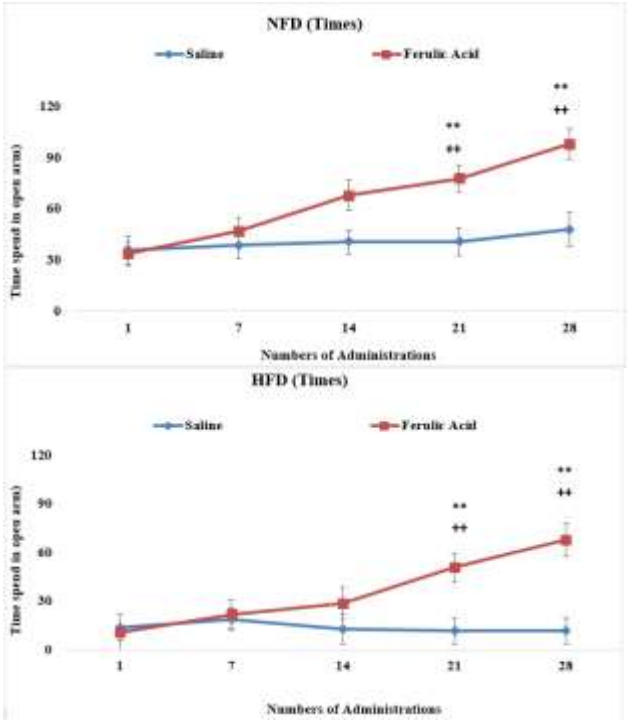

Fig. 7: Effects of Ferulic acid on activity in EPM (Time) of NFD and HFD rats.

Values are means + SD (n=6) as monitored post 24 hrs of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated NFD or HFD rats; +p<0.05, ++p<0.01 from similarly saline or Ferulic acid administrated NFD and HFD rats of 1st day administration following three-way ANOVA (repeated measures design).

Effects of ferulic acid on FST activity (immobility) of HFD treated rats

Fig. 8 showed the effect of repeated administration of ferulic acid on rats pretreated with high fat diet for 28 days as monitored on next day of 1st drug administration and then monitored weekly. Analysis was done by three way ANOVA of FST (immobility time) which shows the effect of drug ($F=51.68$; df=1, 32 $p<0.01$) the effect of repeated monitoring ($F=45.21$; df=1, 32; $p<0.01$) the effect of HFD ($F=81.48$; df 1, 32 $p<0.01$) were significant and the effects of the interaction between days, drug and diet ($F=3.27$; df=1, 32) was non-significant. Inistrations. Post hoc analysis by Newman Keuls test showed that administration of ferulic acid in NFD as well as HFD pretreated rats decrease the immobility time as compared to similarly NFD and HFD pretreated saline administrated rats respectively. Significant decrease was found after 7th ($p<0.05$) and after 21st and 28th ($p<0.01$) day of administration in NFD and in HFD pretreated rats, significant decreased value were found after 7th ($p<0.05$) and after 14th, 21st and 28th ($p>0.01$) day of administrations. As compared to similarly ferulic acid administrated rats of NFD and HFD pretreated rats

from1st day, repeated administration of ferulic acid decrease activity (immobility time in FST). Significant decrease was found after 2nd week ($p<0.05$) and after 3rd as well as a 4th weeks ($p<0.01$) in NFD rats. However, in HFD pretreated rats, activity decreased significantly after 1st week ($p<0.05$) and after 2nd, 3rd and 4th weeks ($p<0.01$) of administrations.

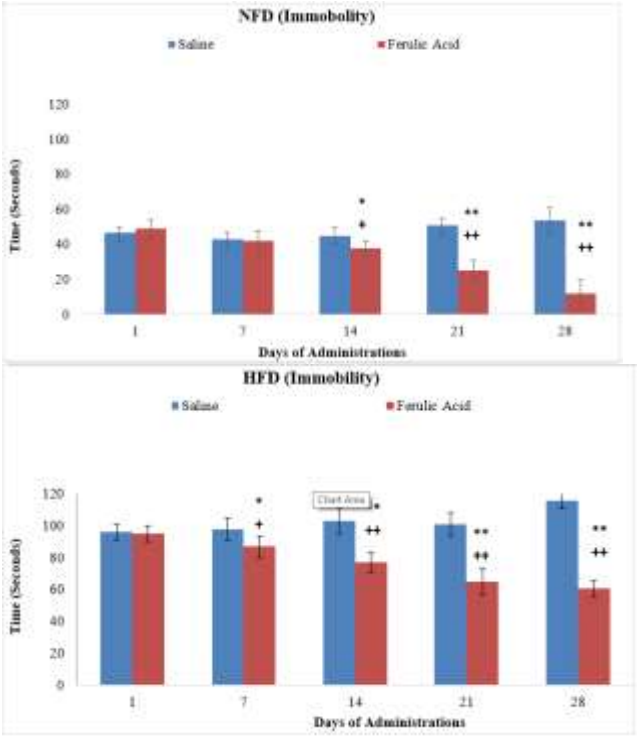

Fig. 8: Effects of Ferulic acid on activity in FST (Immobility Time) of NFD and HFD rats.

Values are means + SD (n=6) as monitored post 24 hrs of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated NFD or HFD rats; +p<0.05, ++p<0.01 from similarly saline or Ferulic acid administrated NFD and HFD rats of 1st day administration following three-way ANOVA (repeated measures design).

Effects of ferulic acid on FST activity (swimming) of HFD treated rats

Fig. 9 showed the effect of repeated administration of ferulic acid on rats pretreated with high fat diet for 28 days as monitored on next day of 1st drug administration and then monitored weekly. Analysis was done by three way ANOVA of FST (Swimming time) which shows the effect of days ($F=85.49$; $df=1, 32$ $p<0.01$), the effect of HFD ($F=41.51$; $df=1, 32$; $p<0.01$) the effect of ferulic acid administrations ($F=72.67$; df 1, 32 $p<0.01$) and the effects of the interaction between all factors ($F=47.43$; $df=1, 32$; $p<0.01$) was found significant. Post hoc analysis by Newman Keuls test showed that administration of ferulic acid in NFD and HFD pretreated rats increase the swimming time in FST as compared to similarly saline administrated controls. Significant ($p<0.01$) greater value were found after 2nd, 3rd and 4th weeks of administration in NFD. However, in HFD pretreated rats, swimming time increased significantly ($p<0.01$) after 1st, 2nd, 3rd and 4th of administrations. Repeated administration of ferulic acid for28 days increases activity (swimming time) in FST rats of NFD and HFD pretreated rats as compared to similarly administrated rats from 1st day of administrations. Significant ($p<0.01$) increased value were found from 1st to 4th weeks of administrations in HFD and from 2nd to 4th weeks in NFD pretreated rats.

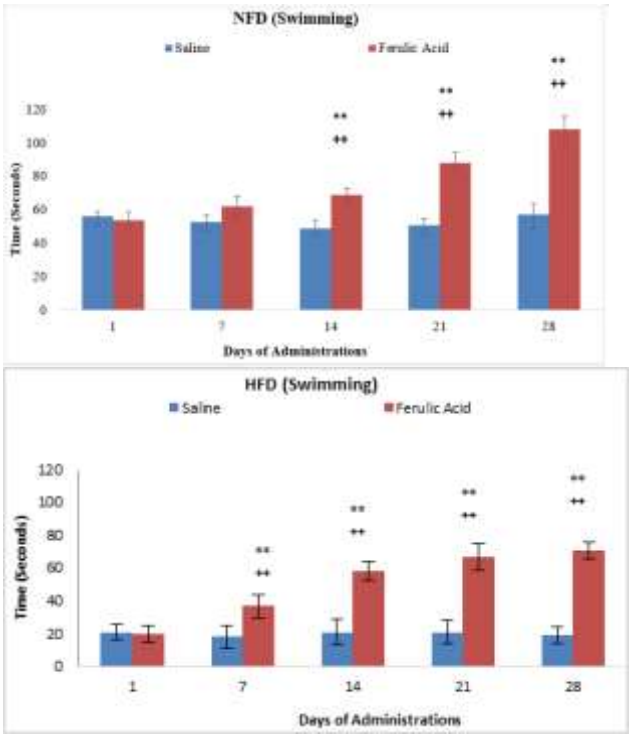

Fig. 9: Effects of Ferulic acid on activity in FST (Swimming Time) of NFD and HFD rats.

Values are means + SD (n=6) as monitored post 24 hrs of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated NFD or HFD rats; +p<0.05, ++p<0.01 from similarly saline or Ferulic acid administrated NFD and HFD rats of 1st day administration following three-way ANOVA (repeated measures design).

DISCUSSION

The present study was design to investigate that whether ferulic acid administered repeatedly at dose (100mg/kg /day) could reverse the behavioral deficits induced by high fat diet in rats models of depression., as previous literature has been showed that dietary profile plays a crucial role in body response to different activities (Rafiq and Farhan, 2015) and may lead to several pathologies including physiological and neurological disorders. To carry out this study total of 24 rats were taken which were divided into two groups (12 in each) on basis of dietary profile (NFD and HFD) and within each group further grouping was done as each group of 6 rats were treated

with water while the other one was administered by ferulic acid, this procedure was done for 28 days.

The results of our study confirmed the outcome of previous studies and demonstrated that HFD causes obesity impaired several behavioral changes, but our results also specifically showed that the supplementation of HFD along with repeated administration of ferulic acid cause less behavioral impairment as compared to HFD rats that were treated with water only.

As for growth rate it has been seen in our experiment that the rats that (both NFD and HFD group). On repeated administration of ferulic acid, growth rate was decreased in HFD rats as compared to similarly administered HFD rats of 1st day administration. In previous studies conducted in our laboratory also proved that the food that is high in fat cause disturbance in metabolism and normal morphology and undergoing mechanism (Hamna and Farhan. 2015). Our studies demonstrated that the repeated administration of ferulic acid has effective role in decrease growth rate in the body that was subjected to High fat diet.

In the case of food intake, our results revealed that, ferulic acid administered rats that were on normal fat diet increases their food intake as compared to high fat diet rats, which showed a decrease in consumption of food as well as water treated rats of HFD groups also decreases their intake of food as compared to the start of the study. As high fat diet leads to less activity that leads to less energy expenditure and may impaired normal food intake and hence rats with high fat diet showed less interest in the food consumption as compared to normal fat diet rats. On the other hand previous experiments also showed that another major reason to not to take adequate diet is depression, as it has been observed that depressed people always made poor choice of food or completely quiet on to not to take a enough diet (Rao, *et al.*, 2008). But if we talk about ferulic acid administered HFD rat in the comparison of water treated HFD rats, ferulic acid treated rats showed that the consumption was far more than water treated HFD rats., proving that ferulic acid is effective in intake of food in HFD rats by reserving behavioral changes that were causing less food intake. These results are further suggested that the rats were probably in depression. Home cage test was used to determine that how rats will behave in their known environment by determining the number of cage crossing. In the present study ferulic acid administered NFD rats showed increase in number of cage crossing after 1stday, and this increase was further increases after day 7th and 14th. In water treated HFD rats the number of crossing was decreased by the time and at the end of the study the activity was lower as compared to the 1st day. Proving HFD causes such kind of changes that enhance rats' anxiety level. While in ferulic acid treated HFD rats the activity was increased after 1st and 14th day of administration from the present study results we can suggest that ferulic acid proved to be effective in lowering the anxiety levels. To determine the locomotor activity and anxiety level Open field test was used in this study. Our results findings showed that in ferulic acid administered HFD rats the latency time was gradually decreases as compared to the beginning of the study, while number of square crossing was increased in HFD administered rats. In HFD water treated rats the results were opposite, increases latency time and decrease in number of square. These results suggested that HFD causes behavioral impairment that cause less in activity as previous studies showed that obesity is associated with less locomotor activity because in obese individual fat starts to accumulate within the adipose tissues (Schrauwen *et al.,* 2000). From all the present study results, findings, outcome and in the light of previous studies we can concluded that HFD is highly associated with behavioral consequences and lead to anxiety and depression. Through this study we can further suggest that ferulic acid is effective in the treatment of physiological and neurological changes that is brought by High fat diet. From the present study it is concluded that the repeatedly administrated ferulic acid attenuate the behavioral deficits induced by HFD in depressive induced psychiatric manifestations. Furthermore studies required on clinical and molecular level for the establishment of mechanisms to understand the ferulic acid to produce its pharmacological impact.

REFERENCES

Akubuiro A, Bridget Zimmerman M, Boles Ponto LL, Walsh SA, Sunderland J and Mccormick L and Singh M (2013). Hyperactive hypothalamus, motivated and non-distractible chronic overeating in ADAR2 transgenic mice. *Genes Brain Behav.*, **12**(3): 311-322.

Avram MM, Avram AS and James WD (2005). Subcutaneous fat in normal and diseased states - 1. Introduction. *J. Am. Acad. Dermatol.*, **53**(4): 663-670.

Friedewald WT, Levy RI and Fredrickson DS (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin. Chem.*, **18**(6), 499-502.

Hankin BL (2006). Adolescent depression: Description, causes and interventions. *Epilepsy Behav*., **8**(1):102-114.

Hryhorczuk C, Sharma S and Fulton S (2013). Metabolic disturbances connecting obesity and depression. *Front. Neurosci.*, **7**(7): 177.

Ikram H, Ahmed S and Haleem DJ (2011). Effects of apomorphine on locomotor activity and monoamine metabolism: A dose related study. *Pak. J. Pharm. Sci*., **24**(3): 315-321.

Jequier E (2002). Pathways to obesity. *Int. J. Obes.*, **26** (Suppl 2): S12-S17.

Mancuso C and Santangelo R (2014). Ferulic acid: Pharmacological and toxicological aspects. *Food Chem. Toxicol*., **65**: 185-195.

Mizuki D, Matsumoto K, Tanaka K, Lex T, Fujiwara H, Ishikawa T and Higuchi Y (2014). Antidepressant-like effect of *Butea superba* in mice exposed to chronic mild stress and its possible mechanism of action. *J. Ethnopharmacol*. **156**: 16-25.

PhillipsC (2017). Brain-derived neurotrophic factor, depression, and physical activity: Making the neuroplastic connection. *Neural Plast*. **8**: 7260130.

Radley J, Morilak D, Viau V and Campeau S (2015). Chronic stress and brain plasticity: mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders. *Neurosci. Biobehav. Rev*., **58**: 79-91.

Rafiq H and Farhan M (2015). Height fat diet induced obesity. Stimulate depressive behavior in rats. *Curr. Psychopharmacol.,* **4**(2):125-132

Rafi H and Farhan M (2016). Dapoxetine: An innovative approach in the therapeutic management in animal model of depression. *Pak. J. Pharm. Res.,* **2**(1): 15-22.

Schrauwen P and Westerterp KR (2000). The role of high-fat diets and physical activity in the regulation of body weight. *Br. J. Nutr.*, **84**(4): 417-427.

Schroeder A, Notaras M, Du X and Hill RA (2018). On the developmental timing of stress: Delineating sex-specific effects of stress across development on adult behavior. *Brain Sci*., **8**(7): 121.

Sharma S, Hryhorczuk C and Fulton S (2012). Progressive-ratio responding for palatable high-fat and high-sugar food in mice. *J. Vis. Exp.* **63**: e3754 10.

Sheth C, McGlade E, Yurgelun-Todd D (2017). Chronic stress in adolescents and its neurobiological and psychopathological consequences: An RDoC perspective. *Chronic Stress* (Thousand Oaks), **1**: 2470547017715645.

Zheng X, Cheng Y, Chen Y, Yue Y, Li Y, Xia S, Li Y, Deng H, Zhangand J and Cao Y (2019). Ferulic acid improves depressive-like behavior in prenatally-stressed offspring rats via anti-inflammatory activity and HPA Axis, *Int. J. Mol. Sci*., **20**(3): 493.