Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

NEUROPHARMACOLOGICAL SCREENING OF FLAVONOIDS AGAINST MK-801 INDUCED STEREOTYPY AND ANTI ANXIETY ACTIVITY

[1]Supriya.chatla*, [2]SaiSrilakshmi.G;[3] Devalarao.G;[4] Sk.AbdulRahman

Nirmala College of pharmacy; Atmakuru; Guntur Dt; Andhra Pradesh; Pin:522503

Krishna University, Machilipatnam; Andhra Pradesh; Pin:52100.
E.mail.id: supriya.chatla@gmail.com

ABSTRACT:
Objective: The effects of Quercetin and Naringin were investigated on stereotypyes induced by the N-methyl-D-Aspartate (NMDA)-type glutamate receptors agonist MK-801 (Diazocilpine maleate) and Diazepam induced anxiety in SD rats.
Methods: Glutamate/NMDA receptors are located throughout the brain; Glutamatergic models predict widespread cortical dysfunction with particular involvement of NMDA receptors throughout the brain. Further, NMDA receptors are located on brain circuits that regulate dopamine release, suggesting that dopaminergic deficits in schizophrenia may also be secondary to underlying glutamatergic dysfunction.NMDA receptors are widely distributed throughout cortex. MK801- induced stereotypic behaviour was also measured. **Results and conclusion:**The selective flavonoids Quercetin and Naringin exhibited significant antipsychotic activity in a dose dependent manner comparable to the standard drugs, Haloperidol (0.5mg/kg, i.p.) and Diazepam(10 mg/kg, i.p.) at the dose of 100, 50 and 25 mg/kg for Quercetin; 80; 40 and 20mg/kg for Naringin respectively.

KEY WORDS: Quercetin, Naringin, MK-801, Haloperidol, Diazepam

INTRODUCTION

Glutamatergic models are based upon the observation that the psychotomimetic agents such as phencyclidine (PCP) and ketamine induce psychotic symptoms and neurocognitive disturbances similar to those of schizophrenia by blocking neurotransmission at N-methyl-D-aspartate (NMDA)-type glutamate receptors. Further, NMDA receptors are located on brain circuits that regulate dopamine release, suggesting that dopaminergic deficits in schizophrenia may also be secondary to underlying glutamatergicdysfunction.NMDA receptors are widely distributed throughout cortex. In contrast, dopaminergic innervation is much more circumscribed, with relatively sparse innervations of primary sensory cortex[1,2]; Schizophrenia has also been shown to be associated with reduced levels of GSH[3,4,5]; leading to potential dysfunction of NMDA receptors[6]. Second, based upon the observation that NMDA blockade leads to rebound increases in glutamate release that may themselves be pathological[7]it has been proposed that compounds that inhibit presynaptic glutamate release may also be therapeutic [8].Agents that stimulate NMDA receptor-mediated neurotransmission, together with glycine-site agonists and glycine transport inhibitors, have shown encouraging ends up in presymptomatic studies and are presently undergoing clinical development. Overall, these findings counsel that glutamatergic theories may result in new conceptualizations and treatment approaches that might not be attainable based mostly upon dopaminergic models alone. Anxiety is common downside that embrace feeling anxious a couple of employment interview, speech, a primary date, are traditional responses to a nerve-racking scenario. Elevated stress hormones (cortisol, adrenaline) will cause or exacerbate anxiety. Like depression, anxiety will be a learned behaviour.There are many diagnostic classes for anxiety disorders. They include: Generalized mental disturbance (GAD), anxiety disorder (anxiety attacks). Flavonoid glycosides, the most category of flavonoids, are shown to exert CNS-mediated activities, significantly as sedative-hypnotics, analgesics or each, still no studies have evaluated these agents in anxiety. apparently, the consumption of flavonoid-rich foods, specially fruits and vegetables, has been epidemiologically related to a reduced risk of heart condition, neurodegenerative illness, cancer and alternative chronic diseases, most likely thanks to their activity as inhibitors activity.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Citrus plants are an honest supply of flavonoids. Naringin, naringenin, nobelitin, narirutin, and hesperidin are the foremost necessary flavonoids to this point isolated from citrus fruits like orange, lemon, kiwi etc.

MATERIALS AND METHODS:

Male Sprague-Dawley rats,swiss albino mice (National Institute of Nutrition, Hyderabad, India) weighing 150-200g were used. They were kept in metal cages with food and water *ad libitum.* The cages were kept under diurnal lighting cycle and controlled temperature and humidity.The experimental protocol has been approved by the Institutional Animal Ethics Committee and by the Animal Regulatory Body of the Government (Regd. No. 516/01/A/CPCSEA).

MK-801(Dizocilpine Maleate) (Sigma Aldrich, Mumbai), flavonoids Quercetin and Naringin (Sigma Aldrich, Mumbai); were used in the present study.

MK-801(Dizocilpine Maleate) is a highly selective NMDA receptor antagonist. Psychotic behaviour produced Dizocilpine Maleate basically includes locomotion, stereotypy and ataxia(0.05- mg/kg/ to 1 mg/kg ; i.p).Rating of psychotic behaviour was started 15 mins after the injection of MK-801 and continued for another 60 mins (i.e- 15-75 minspostinjection). Three types of behaviour were rated: locomotion, stereotyped sniffing, and ataxia. For locomotor activity, the rating scale described by[9]. Sturgeon and coworkers(1979)was used, and stereotyped sniffing behaviour was rated according to the rating scale described[10]and for ataxia rating was given according to the rating scale described byAndine et.al 1999[11].Rating was given for 30 secs at the end of every 5 min during the 60 min observation period which resulted in 13 observations /rat/experiment. Total cumulative observations for 60 min are recorded and used for the data analysis. Standard drugs used for this model are Haloperidol (0.5 mg/kg, i.p).

The studies were carried out on swiss albino mice. The plus-maze apparatus was made of Plexiglas and consisted of two open (30X5 cm) and two enclosed (30X5X15 cm) arms. The arms extended from a central platform of 5X5 cm. The apparatus was mounted on a Plexiglas base, raising it 38.5 cm above the floor and illuminated by red light. Each mouse was placed individually at the centre of elevated plus maze with its head facing toward an open arm and closed arm, observed for 5 min to record the time spent and number of crossings in each arm.

Vehicle and standard drug

Distilled water + Tween 80 (2%) was used as vehicle for preparing various test doses of Quercetin and Naringin, concentration as to administer a volume ranging Quercetin (25;50and100 mg/kg;o.p) and naringin at (20,40 and 80 mg/kg:o.p) to the rats. mice. Diazepam (Triko Pharmaceuticals, Rohtak, Haryana) was used as standard antianxiety drug at a dose of 10 mg/kg, *i.p*. Haloperidol (Triko Pharmaceuticals, Rohtak, Haryana) was used as standard antipsychotic drug at a dose of 0.3mg/kg, i.p.

Experimental Design

Two experimental protocols were designed. A total of 16 groups of male Sprague Dawley rats were made, and each group comprised 6 animals.

Experimental protocol I, comprising groups I to V was designed to assess antipsychotic activity of Quercetin and Naringin againstMK-801 induced stereotypy.

The Group I was Disease control- MK-801 0.1mg/kg. i.p.
Group II- was the test group - Quercetin 25 mg/kg;o.p+ MK-801 0.1mg/kg. i.p.
Group III- Quercetin 50 mg/kg;o.p+ MK-801 0.1mg/kg. i.p
Group IV - Quercetin 100 mg/kg;o.p+ MK-801 0.1mg/kg. i.p
Group V -Test group - Naringin 20 mg/kg;o.p+MK-801 0.1mg/kg. i.p.
Group V I- Naringin 40 mg mg/kg;o.p+ MK-801 0.1mg/kg. i.p.
Group VII - Naringin 80 mg/kg;o.p+ MK-801 0.1mg/kg. i.p .
Group VIII - Standard drug- Haloperidol (0.5mg/kg, i.p.) suspended in the vehicle.

All the test solutions, were administered orally 30 minutes prior to the experiment before giving an inducer apomorphine 1mg/kg. s.c.

Experimental protocol II, comprising groups I to VIII wasdesigned to assess anti anxiety activity of qQuercetin and Naringin against diazepam induced anxiolytic activity.

The Group I was Control – 2%tween 10ml/kg.
Group II- was the test group - Quercetin 25 mg/kg;o.p+ Diazepam 10 mg/kg; i.p.
Group III- Quercetin 50 mg/kg;o.p+ Diazepam10 mg/kg; i.p.
Group IV - Quercetin 100 mg/kg;o.p+ Diazepam 10 mg/kg; i.p.
Group V - was the Test group - Naringin 20 mg/kg;o.p+ Diazepam 10 mg/kg; i.p.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Group V I- Naringin 40 mg mg/kg;o.p+ Diazepam 10 mg/kg; i.p.
Group VII - Naringin 80 mg/kg;o.p+ Diazepam 10mg/kg; i.p.
Group VIII - Standard drug- Diazepam 10mg/kg; i.p.
All the test solutions, were administered orally 30 minutes prior to the experiment before giving an inducer MK-8010.1mg/kg. i.p.and Diazepam10 mg/kg; i.p.
The first signs of stereotypic behaviour were observed 15 to 60 min after MK-801 administration and Number of entries in to the closed arms is recorded.

Effect of Quercetin and Naringin against MK-801 induced stereotypy

The effect of Quercetin against MK-801inducedstereotypy was observed at different doses. The intraperitoneal injections of MK-801(0.1mg/kg) after the administration of quercetin at (25; 50 &100 mg/kg,o.p) and Naringin at (20;40 &80 mg/kg,o.p).
The behavior of Quercetin and Naringin treated rats stereotypy behaviour were significantely decreased rather than control. The behaviour of quercetin and naringin rats consisted mainly of Locomotion,Stereotypy,Ataxia. Most control rats did not show this behavior. Table1 & 2 shows the resultant percentage decrease in stereotypy scores induced by 0.1 mg/kg MK-801as a function of time after quercetinpretreatment. This indicates that the super sensitivity of the MK-801 induced elevation in Quercetin and Naringin treated groups are eventually disappears ($P<0.001$).

Effect of Quercetin and Naringin against Diazepam

The anti anxietyeffect of Quercetin and Naringin after the intraperitonealinjection of Diazepam10 mg/kg is shown in Fig.2.
Test doses produced a significant increase in the % of open arm entries (25mg/kg: $P>0.05$; 50 mg/kg: $P>0.05$, 100mg/kg: $P>0.05$) and the % of time spent in the open arms (25mg/kg: $P<0.001$; 50 mg/kg: $P<0.001$,100mg/kg: $P<0.001$) compared with the vehicle-treated group. In contrast, the number of closed arm entries was only significantly decrease at a dose of 25 mg/kg ($P>0.05$) shown in the fig: 2.

Statistical Analysis:

All data sets were represented as the mean ± standard error of the mean (SEM). Comparisons of findings between groups were made via statistical analysis of data sets using one-way and two-way analysis of variance (ANOVA). A *p*-value of <0.05 was considered as statistically significant. All statistical analyses were performed using Graph Pad Prism version 5.00 for Windows. Significant differences between treatment groups were analyzed with Two-way analysis of variance (ANOVA) followed by Bonferroniposttests test.

Acute Toxicity studies of Quercetin and Naringin:

The main test is performed with the initial dose of 175 mg/kg body weight. The following sequence is followed; 500, 1750 and 5000 mg/kg body weight. First one animal was dose with 175 mg/kg body weight, after 48hrsanimal survived then two more animals were dosed, animals survived. In the similar way 500, 1750 and 5000mg/kg was dosed and animals survived. Then the main test was terminated. High dose and the low dose were selected by $1/10^{th}$ and $1/20^{th}$ of 5000 mg/kg. Oral administration of highest dose 24.0 g/kg of Quercetin and 38.0g/kg of Naringin not showed any acute toxic symptoms, and no deaths occurred in the experiment. There were no significant differences in body weights and physiological or behavioural responses between the flavonoid treated and control group, and there were also no changes in food or water intake. This result indicated that the treatment of Quercetin and Naringin was safe under the maximum dose at 24.0 g Quercetin/kg and 38.0 g of Naringin/kg body.

RESULTS OF NEUROPHARMACOLOGICAL SCREENING OF QUERCETIN AND NARINGIN ON MK-801 INDUCED STEREOTYPIC BEHAVIOUR.

Table 1.1: Effect of Quercetin on MK-801 induced stereotypy

Stereotypic Behaviour	Disease Control MK-801 1mg/kg;s.c	Quercetin 25mg/kg;p.o.	Quercetin 50mg/kg;p.o.	Quercetin 100mg/kg;p.o.	Haloperidol 0.5mg/kg;i.p.
Locomotary	75.17± 2.86	73.17± 1.17	$70.5\pm1.76^{***}$	$69.83\pm 1.33^{***}$	$20.83\pm1.72^{***}$
Stereotypy	25 ± 1.26	22.67± 1.21	$22 \pm 1.41^{*}$	$20 \pm 1.41^{***}$	$11.33\pm2.58^{***}$
Ataxia	51.5 ± 1.87	$46.67\pm1.37^{***}$	$44.33\pm1.63^{***}$	$42 \pm 1.41^{***}$	$21.5 \pm 3.27^{***}$

Quercetin 25mg Ataxia ***p<0.001 Vs Disease control, Quercetin 50mg (Locomotion,Ataxia) ***p<0.001 Vs Disease control and Stereotypy *p<0.05 Vs Disease control, Quercetin 100mg (Locomotion,Stereotypy,Ataxia) ***p<0.001 Vs Disease control, Haloperidol 0.3mg/kg (Locomotion,Stereotypy,Ataxia) ***p<0.001 Vs Disease control.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Table 2.1:Effect of Naringin on MK-801 induced stereotypy

Stereotypic behavior	Disease Control MK-801 1mg/kg;s.c	Naringin 20mg/kg.,p.o.	Naringin 40mg/kg,p.o.	Naringin 80mg/kg,p.o.	Haloperidol 0.5mg/kg,i.p.
locomotion	75.17±2.86	71.33± 1.21**	69.83±1.17***	67.67±1.03***	20.83±1.72***
Stereotypy	25 ± 1.26	21.67± 1.21**	20.67±1.21***	19.5±1.05***	11.33±2.58***
Ataxia	51.5 ± 1.87	42.33± 1.63***	42.67±1.37***	40.33±1.63***	21.5±3.27***

Naringin 20mg (Locomotion,Stereotypy) **p<0.05 Vs Disease control, Ataxia ***p<0.001 Vs Disease control, Naringin 40mg (Locomotion, Stereotypy,Ataxia) ***p<0.001 Vs Disease control, Naringin 80mg (Locomotion, Stereotypy,Ataxia) ***p<0.001 Vs Disease control, Haloperidol 0.3mg/kg (Locomotion,Stereotypy,Ataxia) ***p<0.001 Vs Disease control.

Table 3.1: Elevated plus maze test for Quercetin

Time spent / No of crossings in open/closed arms	Tween 2% 10ml/Kg	Quercetin 25mgkg;p.o.	Quercetin 50mgkg;p.o.	Quercetin 100mgkg;p.o.	Diazepam 10mg/Kg;i.p
open arms time spent	46 ± 2.45	54 ± 1.58***	113.4±3.85***	209±5.43***	152.2±3.63***
open arms crossings	10.8±1.92	9.8 ± 2.17	11 ± 1.22	14.4 ± 1.82	22 ± 1.58***
closed arms time spent	125.8±1.92	101.6±2.41***	87.25±4.27***	72±3.94***	94±2.92***
closed arms crossings	13±1.58	12.6 ± 0.89	10.6 ± 1.14	8.6±1.14*	16.8 ± 1.92

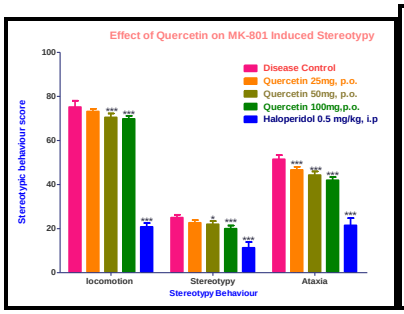
,Quercetin(25mg) open arms time spent ***p<0.001 Vs control, closed arms time spent ***p<0.001 Vs control, Quercetin(50mg) open arms time spent ***p<0.001 Vs control, closed arms time spent ***p<0.001 Vs control, Quercetin(100mg) open arms time spent ***p<0.001 Vs control, closed arms time spent ***p<0.001 Vs control, closed arms crossings *p<0.05 Vs control, Diazepam 10mg/Kgopen arms time spent ***p<0.001 Vs control, open arms crossings ***p<0.001 Vs control, closed arms time spent ***p<0.001 Vs control. Statistical analysis by two-way ANOVA followed by Bonferroniposttests.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Table 4.1: Elevated plus maze test for Naringin

Time spent / No of crossings in open/closed arms	2% Tween 10ml/Kg	Naringin 20mg/kg;p.o.	Naringin 40mg/kg;p.o	Naringin80mg/kg;p.o.	Diazepam 10mg/Kg; i.p
open arms time spent	57.4 ± 6.31	62.82±5.87**	64.46±3.33***	69.84±3.27***	93.66±3.44***
open arms crossings	9.8 ± 3.19	10.9 ± 1.75	9.36 ± 1.94	16 ± 3.39**	24.6±3.21***
closed arms time spent	122.6±1.67	99.8 ± 2.39***	87.6 ± 1.82***	75.2 ± 2.17***	90.6±1.34***
closed arms crossings	13 ± 1	12 ± 1	11.6 ± 1.14	8.8 ± 0.84	16 ± 1.58

Naringin 20mgopen arms time spent **p<0.01 Vs control, closed arms time spent ***p<0.001 Vs control, Naringin 40mgopen arms time spent ***p<0.001 Vs control, closed arms time spent ***p<0.001 Vs control, Naringin 80mgopen arms time spent ***p<0.001 Vs control, open arms crossings **p<0.01 Vs control, closed arms time spent***p<0.001 Vs control, Diazepam 10mg/Kgopen arms time spent ***p<0.001 Vs control, open arms crossings ***p<0.001 Vs control, closed arms time spent ***p<0.001 Vs control. Statistical analysis by two-way ANOVA followed by Bonferroniposttests.



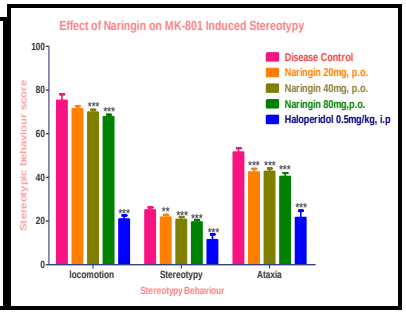
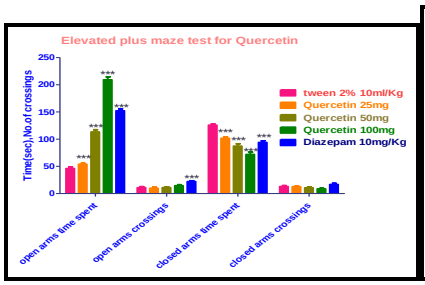


Fig 1.2: Effect of Quercetin on MK-801 stereotypy **Fig 2.1: Effect of Naringin on MK-801 stereotypy**



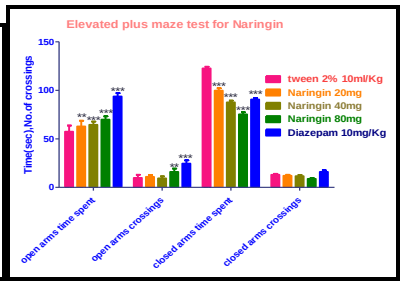


Fig 3.2: Elevated plus maze test for Quercetin4.2: Elevated plus maze test forNaringin

RESULTS AND DISCUSSION

The inhibitory response of the selected Effect of test compounds – Quercetin and Naringin against MK-801 induced stereotypy behavioural scores were represented in **Table & Figure 1.1&1.2; Table& Figure 2.1&2.2** respectively SD rats that received Injection of MK-801 (0.1mg/kg; i.p)caused a significant behavioural activation, consisting of increased locomotion, stereotyped sniffing and ataxia. The first signs of stereotypic

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

behaviour were observed 15 to 60 min after MK-801 administration. This behaviour was dose-dependent (0.05-0.1mg/kg;i.p)and dose was Standardized at 0.1.mg/kg. Fig. 1 shows the behaviour in rats treated with Quercetin at 25mg/kg (Ataxia **p<0.001); 50mg/kg (Locomotion, Ataxia(***p<0.001); 100mg/kg, Locomotion, Stereotypy, Ataxia (***p<0.001) compared to Disease control. The first signs of locomotion and stereotyped sniffing were decreased 20 to 25 min after Quercetinadministration(50mg/kg;i.p), whereas ataxia was decreased in 30to 35 min later. Locomotor activity was decreased more after 45 min and thereafter displayed a major decline over the experimental period. Stereotyped sniffing was minimal after 30 min and persisted at this level throughout the experiment. Fig 2.2 shows rats treated with Naringin (20mg) Locomotion, Stereotypy**p<0.05;Ataxia ***p<0.001, Naringin (40mg) Locomotion, Stereotypy, Ataxia ***p<0.001, Naringin (80mg) Locomotion, Stereotypy,Ataxia**p<0.001and standard Haloperidol (0.3mg/kg) locomotion, Stereotypy, Ataxia ***p<0.001) (6). Vs Disease control. The behavioural scores were significantly decreased from 15-60 minutes in dose dependent manner.Statistical analysis by two-way ANOVA followed by Bonferroniposttests.All values are expressed as mean ±S.D (n=6).

Behavioural scores were found to be decreased significantly in the rats treated with both test compounds Quercetin and Naringin when compared with the rats treated with the Standard drug(Haloperidol). The test compound has been shown significant reduction in the stereotypic behavioural scores. The MK-801 induced hyperlocomotor, stereotypes and ataxia behaviour was also a valuable animal model to evaluate the anti-psychotic agents. Unlike amphetamine induced model, the MK-801 model exhibits both positive and negative symptoms of the schizophrenia [12.] The N-methyl D-aspartate (NMDA) antagonists have several clinical significances like anxiolytic, ataxic and anticonvulsant effects, but they are also known to affect cognitive and sensory motor function [13.] The literature has been suggested several hypotheses to describe the pathophysiology of psychotic behaviours in the subjects. In the brain glutamate is recognized as the most abundant and important neurotransmitter. One of the hypotheses to describe the pathophysiology of psychosis is the hypo functioning of glutamate neurotransmission in the brain. This hypothesis was evident by the administration of non-competitive antagonists at NMDA receptors like phencyclidine (PCD) and dizocilpine (MK-801) can precipitate psychotic reactions in the human subjects, similar in many aspects of schizophrenia[14.] The role of dopaminergic neurotransmission in the pathology of psychotic symptoms has long been studied and it is known that the dopaminergic agonists can induce psychotic symptoms. These symptoms are thought due to the affinity towards D_2 receptors in the mesolymbic region of the brain(Zahodne 2008).Further, the MK-801 model has been suggested for the elevation of dopamine levels in the brain. The selective NMDA receptor antagonists markedly increased the dopamine levels in the nucleus accumbens and the nucleus caudatus which induces the elements of stereotypical behaviors like grooming and strong hypermotility in the animal models [16.] Scientific data also proposed the role of 5-hydroxytryptamine (5-HT) role in the implication of stereotypic behaviours, in the MK-801 induced animal model. There is substantial research evidence from several lines of research showing the increased turnover of 5-HT found after administration of MK-801 in the induction of stereotypic behaviours in animal models[17.] As the presynaptic $5HT_{1A}$ receptor agonists inhibits the release of 5-HT from the presynaptic neurons leads to decrease in the synaptic levels of 5-HT. So, the $5HT_{1A}$ receptor agonists may have clinical efficacy in the symptomatic treatment of psychotic behaviours. Indeed, there is clinical evidence indicating that the partial agonists of $5HT_{1A}$ receptor, buspirone and ipsapironepossesses antipsychotic activity[18.] There are a number of evidences supporting the oxidative stress role in the pathology of psychosis. The MK-801 model was also proposed to create oxidative stress due to unopposed blocked of NMDA receptors[19.]Thus, the antioxidants may have therapeutic potential in the amelioration of stereotypic behaviours induced by MK-801 model. All these findings proved that the MK-801 model is the best fit model for the induction of positive and negative symptoms of psychosis in animals. In another model, MK-801 induced hyperlocomotion as an indicator for the stereotypical behaviour in rats. In this model the disease control group of animals showed hyperlocomotion. The results are in good agreement with the previous literature [20.21]; The selected flavonoids showed dose dependent decrease in the locomotor activity in SD rats, significantly when compared with the disease control group of animals. Recent scientific reports stated that the antioxidant potential of therapeutic agents might ameliorate the psychotic symptoms induced by the MK-801 animal model, as MK-801 promotes oxidative stress in the animal model [22.] In line with the previous literature, the selected flavonoids showed marked decrease in locomotor activity in MK-801 induced animals, dose dependently. Thus, the anti-psychotic activity of the selected flavonoids might be attributed by their potential anti-oxidant properties. Further, the therapeutic potential of selected flavonoids may be due to modulation of dopaminergic and serotonergic neuronal pathway.

The effects of Quercetin (25 mg/kg, 50 mg/kg,100 mg/kg), diazepam (10 mg/kg) in the plus maze test are displayed in Figs.3.2.for comparison. Diazepam 0.2 mg/kg was used as positive control group.

Figure4.1&4.2.shows the effects of commercial Naringin on the various parameters of the EPM. Naringin at doses of 20and 80 mg/kg significantly increased the % of open arm entries (P>0.05 Fig.4.1) and the

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

# of time in the open arms (P<0.01, Fig. 4.2.). Interestingly, a dose of 20 mg/kg of Naringin was with a slight effect but when injected at 80 mg/kg, Naringin again increased these parameters. However, doses of 80 mg/kg of Naringin also significantly reduced the number of closed arm entries compared to vehicle (P>0.05 Fig.4.2), while all other doses of Naringin significantlyeffect the number of closed arm entries.

Benzodiazepines extensively used for the last 30 years to treat several forms of anxiety, but due to their unwanted side effects, alternative treatment strategies with favourable side-effect profiles, benefits with moderate costs are of interest.The flavonoids have considerable properties because of their potential beneficial effects on human health. Flavonoids may give protection against these diseases by contributing along with antioxidants vitamins and enzymes .Quercetin is a type of flavonol[23]and Naringin (flavanone) were used in the present study; an attempt was made to evaluate the antianxietyproperty. The elevated plus maze is one of the widely used models of animal anxiety, the test was carried out on the exposure of animal to an elevated maze array evokes an approach-avoidance conflict that is considerably stronger than that evoked by exposure to an open maze array. The animals being exposed to the new environment tend to avoid open entries[24] and prefer to stay in the closed arm due to fear. As expected standard diazepam significantly increased time spent in open arm [25]. Mice pretreated with Quercetin at the dose of 25, 50 and 100 mg/kg.p.o;Naringin 20,40,80 mg/kg.p.o shows significantly increased the time spent in open arm and decreased the time spent in the closed arm compared to the control group[26] indicating the test drugs could reduce the fear and anxiety in the mice[27.]The effects of Quercetin at 100 mg/kg on the EPM, light–dark test, were almost equivalent to that of 2 mg/kg diazepam.These observations clearly indicate that these two flavonoids have an anxiolytic activity in a dose dependent manner.Mechanism of action by which Quercetin and Naringin shows anxiolytic activity may be similar to that of diazepam (that acts via the gamma-aminobutyric acid $(GABA)_A$ receptor complex) as flavonoids and diazepam are structurally similar.

CONCLUSION:

Significant Neuropharmacological protective action was observed with both the bioflavonoids namely Quercetin and Naringin in normal and psychosis inducedrats.At a dose level of 100 mg/kg, for Quercetin and 80mg/kg of Naringin has offered complete Neuroprotection against MK-801 induced stereotypy and anti-Anxiety. The probable mechanisms involved might be anti-oxidant, and modulator influence at dopaminergic and serotonin receptors.

ACKNOWLEDGEMENTS

The author is verymuch thankful to our guide Dr.Ch.Siva Reddy, Dr.G. DevalaRaoand Management of Nirmala college of pharmacy for their valuable support and Guidance in this research.

REFERENCES:

1.Lewis DA, Campbell MJ, Foote SL, Goldstein M, Morrison JH.1987. Thedistribution of tyrosine hydroxylase-immunoreaction fibers in primate neocortex iswidespread but regionally specific. *J Neurosci.*7(6):279-290.

2. Lewis DA, Sesack SR, Levey AI, Rosenberg DR.1998. Dopamine axons in primateprefrontal cortex: Specificity of distribution, synaptic targets, and development.*AdvPharmaco.* 42(6):703-706.

3. Do KQ, Trabesinger AH, Kirsten-Kruger M, Lauer CJ, Dydak U, Hell D,2000.Schizophrenia: Glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo.*Eur J Neurosci.*12(9):3721-3728.

4. Matsuzawa D, Obata T, Shirayama Y, Nonaka H, Kanazawa Y, Yoshitome E, et al.Negative correlation between brain glutathione level and negative symptoms inschizophrenia: a 3T 1H-MRS study2008.*PLoSOne* ;3:e1944.

5.Yao JK, Leonard S, Reddy R. Altered glutathione redox state in schizophrenia.Disease Markers 2006;22(5):83-93.

6.Steullet P, Neijt HC, Cuenod M, Do KQ. Synaptic plasticity impairment andhypofunction of NMDA receptors induced by glutathione deficit: Relevance toschizophrenia, 2006. *Journal ofNeuroscience*;137(7):807-819.

7. Moghaddam B, Adams B, Verma A, Daly D. Activation of glutamatergicneurotransmission by ketamine: A novel step in the pathway from NMDAreceptor blockade to dopaminergic and cognitive disruptions associated with theprefrontal cortex. 1997. *Journal of Neurosci.*17(8):2921-2927.

8.Moghaddam B. Targeting metabotropic glutamate receptors for treatment ofthe cognitive symptoms of schizophrenia.2004.*Psychopharmacology (Berl)* 174(13);39-44.

9.Sturgeon and coworkers (1979) ; Psychosis induction by animal models: 1979.*Journal of psuchology*; 16(7) - 2719-2723

10.Hoffman DC. Typical and atypical neuroleptics antagonize MK-801-inducedlocomotion and stereotypy in rats.1992.*Journal of Neural Transmission/General Section JNT*.;89(1-2):1-0.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

11.Andiné, Nina Widermark, Rolf Axelsson, Gösta Nyberg, Ulla Olofsson, Erik Mårtensson and Mats Sandberg: Characterization of MK-801-Induced Behavior as a Putative Rat 1991.*Model of Psychosis Journal of Pharmacology and Experimental Therapeutics;* 290 (3) 1393-1408.

12.Mathé JM, Nomikos GG, Hildebrand BE, Hertel P, Svensson TH. Prazosininhibits MK-801-induced hyperlocomotion and dopamine release in the nucleusaccumbens.1996.*European journal of pharmacology.* 309(1):1-1.

13.Ouagazzal A, Nieoullon A, Amalric M. Effects of dopamine D 1 and D 2receptor blockade on MK-801-induced hyperlocomotion in rats.1993.*Psychopharmacology*;111(4):427-34.

14. Hoffman DC. Typical and atypical neuroleptics antagonize MK-801-induced locomotion and Stereotypy in rats.1992.*Journal of Neural Transmission/General Section JNT.* 89(1-2):1-0.

15.Zahodne LB, Fernandez HH. Pathophysiology and treatment of psychosis inParkinson's disease.2008.*Drugs & aging*. ;25(8):665-82.

16. Imperato A. NMDA receptors and in vivo dopamine release in the nucleusaccumbensand caudatus. 1990 *Eur J Pharmacol*. 187:555-6.

17.Löscher W, Hönack D. The behavioural effects of MK-801 in rats: involvementof dopaminergic, serotonergic and noradrenergic systems.1992.*European journal of pharmacology.*215(2-3):199-208.

18. Löscher W, Hönack D. The behavioural effects of MK-801 in rats: involvementofdopaminergic, serotonergic and noradrenergic systems.1992.*European journal of pharmacology*. 215(2-3):199-208**.**

19. Löscher W, Annies R, Hönack D. The N-methyl--aspartate receptor antagonistMK-801 induces increases in dopamine and serotonin metabolism in several brainregions of rats.1991.*Neuroscience letters.* 128(2):191-4.

20. Ouagazzal A, Nieoullon A, Amalric M. Effects of dopamine D 1 and D 2 receptor blockade on MK-801-induced hyperlocomotion in rats.1993.*Psychopharmacology.* 111(4):427-34.

21. Ouagazzal DC. Typical and atypical neuroleptics antagonize MK-801-inducedlocomotion and stereotypy in rats.1992.*Journal of Neural Transmission/GeneralSection JNT*. 1;89(1-2):1-0.

22. Ozyurt B, Ozyurt H, Akpolat N, Erdogan H, Sarsilmaz M. Oxidative stress inprefrontal cortex of rat exposed to MK-801 and protective effects of CAPE.2007.*Progress in Neuro-Psychopharmacology and Biological Psychiatry*9;31(4):832-8.

23. Trehan N, Verma N. HPLC analysis of methanolic extract of herbs forquercetincontent.2013.*J PharmacogPhytochem*. 2(1):159-162.

24. Tiwari et al AshutoshMishra1 , Ganesh Bhatt2 and Anil Chaudhary; Anti-stress Activity of a Bioflavanoid: Quercetin from Euphorbia hirta;BJPR.2015. *Journal of sciences*, 6(2): 68-75.

25. Viswanatha GL, Nandakumar K, Shylaja H, Ramesh C, Rajesh S, Srinath R.Anxiolytic and anticonvulsant activity of alcoholic extract of heart wood ofCedrusdeodararoxb in rodents.2009.*J Pharm Res Health Care.* 1(2):217-239.

26. Kinthada PMMS, Naidu PVS, Kalyani P, Muralidhar P. Characterization andbiological activities of Quercetinthiosemicarbazone derivatives: Potentialanticancer drugs.2012.*Int J Pharm Biomed Sci*..3(2):24-27.

27. Gowda KPS, Arora AK, et al. Stress evaluation of anxiolytic activity of aqueousandalcoholic extracts of leaves of crataegusoxycantha in mice.2011.*Int J PharmBiomed Sci.* ;2(s3):86-91.