**International Journal of Current Advanced Research**
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 7; Issue 12(C); December 2018; Page No. 16524-16528
DOI: http://dx.doi.org/10.24327/ijcar.2018.16528.3058

**Research Article**

# NEUROPHARMACOLOGICAL SCREENING OF FLAVONOIDS AGAINST APOMORPINE AND QUIPAZINE INDUCED STEREOTYPY

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**A R T I C L E I N F O**

***Article History:***
Received 13th September, 2018
Received in revised form 11th October, 2018
Accepted 8th November, 2018
Published online 28th December, 2018

***Key words:***
Apomorphine, Quipazine, Haloperidol, Resperidone.

**A B S T R A C T**

The effects of Quercetin and Naringin were investigated on stereotypys induced by the 5HT-2A and 5HT-3 agonist Quipazine and Dopamine (D1 and D2) receptor agonist Apomorphine in SD rats. Apomorphine-induced stereotypic behaviour and quipazine induced head twitches were also measured. The selected flavonoids quercetin and naringin exhibited significant antipsychotic activity in a dose dependent manner comparable to the standard drugs, Haloperidol (0.3mg/kg, i.p.) and Resperidone (0.1mg/kg, i.p.) at the dose of 100, 50 and 25 mg/kg for quercetin; 80; 40 and 20mg/kg for Naringin respectively.



## INTRODUCTION

There have been numerous reports in which chronic blockade of synaptic transmission, by lesion of the presynaptic neurones or by pharmacological antagonism of the transmitter substance, resulted in enenhancement of the observed effects associated with synaptic transmission. This has been interpreted evidence for the development of postsynaptic receptor super sensitivity. Recent studies also indicate the occurrence of this phenomenon in dopaminergic neuronal systems in the CNS. After chronic lesion of the dopaminergic nigro neostriatal pathway. There is an increase in the stereotypic response to the direct ting dopaminergic agonist, Apomorphine. Chronic treatment with neuroleptic agents, which have dopaminergic antagonistproperties, also result in increased stereotype is induced by Apomorphine ($D_1$,$D_2$receptor agonist) given after withdrawal of the neurolepticagent (Klawans and Rubovits, 1972; Tarsy and Baldessarini, 1974; Sayers, Biirki, Ruth and Asper,1975; Smith and Davis, 1975, 1976). In addition to stereotypic movements, striatal acetylcholine (ACh) concentration is another parameter of dopaminergic nigro-neostriatal transmission that can be studied. Numerous studies indicate that there seems to be an inverse relationship between Ach levels and cholinergic neuronal activity, and that the dopaminergic nigro-neostriatal neurones act to inhibit cholinergic interneurones in the striatum (for review, see Roth and Bunney, 1976).

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Thus, Apomorphine ($D_1$,$D_2$ receptor agonist) treatment results in an increase in striatal ACh levels (Consolo, Ladinsky and Garattini, 1974; McGeer, Grewaal and McGeer, 1974; Sethy and Van Woert, 1974) and a decrease in ACh turnover (Trabucchi, Cheney, Racagni and Costa, 1975) Apomorphine treatment resulted in a greater increase in striatal ACh level on the lesioned side as compared to the intact side. Their study provided neurochemical evidence for denervation supersensitivity. The hypothesis that the LSD psychosis and by inference schizophrenic psychoses are related to dysfunctions in central serotonergic systems, formulated by woolley and Shaw in the early 1950s was the first testable theory of modern biological psychiatry. Initially, it did not get the scientific attention it deserved. The antipsychotics were discovered and they are acting by blocking dopaminergic transmission and hence dopaminergic system occupied center stage in biological schizophrenia research. The relation between serotonin and schizophrenia has been revived, due to the development of serotonin blocking agents that appears to exert therapeutic effects in schizophrenia. Serotonergic dysfunction leads to the pathogenesis of schizophrenic psychosis. The quipazine (5-HT2A and 5HT-3 receptor agonist) is induces psychosis by a stereotypic behavior like headtwiches.

The herbal medicines are effective in the treatment of various ailments. The herbal drugs are unscientifically exploited and or improperly used. Therefore these plant drugs deserve detailed studies in the light of modern science. The detailed investigation of plants used in local health traditions and pharmacological evaluation of these plants can lead to the development of invaluable plant drugs for many deadly

diseases. Flavonoids which have high therapeutic profile and which are abundantly present in different dietary sources like onion, apple, grapes and oranges. The selection of the flavonoids was based on the literature sources found to posses anti-ischemic (Rump *et al*., 1995), antiplatelet (Belinky *et al*. 1998), antineoplastic (Lin *et al*., 1997), anti-inflammatory (Read 1995), antiallergic (Yamamura *et al*., 1998), antilipoperoxidant (Terao *et al*. 1994), gastro-protective (Mojzis 1999) properties and other effects have also been described. In the present study we have selected Quercetin and Naringin to study the antipsychotic activity against two different psychotic induction models like Apomorhine ($D_1$,$D_2$receptor agonist) induced stereotypy and Quipazine induced head twitches (5-HT2A and 5HT-3 receptor agonist).

## MATERIALS AND METHODS

Male Sprague-Dawley rats (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. Apomorphine and Quipazine (Sigma Aldrich, Mumbai), flavonoids Quercetin and Naringin (Sigma Aldrich, Mumbai);

Apomorphine induced stereotypy behavior: Stereotyped behavior induced by Apomorphine hydrochloride (0 .1-1.0 mg/kg i.p) 15 min previously; Sigma) was scored in six animals at each dose of Apomorphine from each drug treatment group as follows: (asleep-0, awake and quite-1, locomotary activity-2, head bobbing(Perrault *et al*., 1997) -3, licking-4, sniffing-5, and gnawing-6) were counted and recorded. The dose was standardized at1mg/kg.

Quipazine induced head twitches (Seeger *et al*., 1995): Quipazine is a 5-HT2A and 5HT-3 receptor agonist. Head twitch response is mainly mediated by 5-HT-2A receptors. Quipazine maleate in saline as subcutaneous injection at (0.01 to1mg/kg) shows Head twitch response. Observation of head twitches are made for 45 minutes for every five minutes. Total cumulative observation for 45 min are recorded and used for the data analysis. The dose was standardized at 0.1mg/kg.

### *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 2 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 VIII was designed to assess antipsychotic activity of Quercetin and Naringin against Apomorphine induced stereotypy.

The Group I was Disease control-Apomorphine 1mg/kg. i.p.
Group II- was the test group - Quercetin 25 mg/kg;o.p+ Apomorphine 1mg/kg. i.p.
Group III- Quercetin 50 mg/kg;o.p+ Apomorphine 1mg/kg. i.p
Group IV - Quercetin 100 mg/kg;o.p+ Apomorphine 1mg/kg. i.p.
Group V - was the Test group - Naringin 20 mg/kg;o.p+ Apomorphine 1mg/kg. i.p.
Group V I- Naringin 40 mg mg/kg;o.p+ Apomorphine 1mg/kg. i.p.
Group VII - Naringin 80 mg/kg;o.p+ Apomorphine 1mg/kg. i.p.
Group VIII - Standard drug- Haloperidol (0.3mg/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 was designed to assess antipsychoticactivity of quercetin and naringin against Quipazine induced head twiches.

The Group I was Disease control – Quipazine 0.1mg/kg. s.c.

Group II- was the test group - Quercetin 25 mg/kg;o.p+ Quipazine 0.1mg/kg. s.c.
Group III- Quercetin 50 mg/kg;o.p+ Quipazine 0.1 mg/kg. s.c.
Group IV - Quercetin 100 mg/kg;o.p+ Quipazine 0.1mg/kg. s.c.
Group V - was the Test group - Naringin 20 mg/kg;o.p+ Quipazine 0.1 mg/kg. s.c.
Group V I- Naringin 40 mg mg/kg;o.p+ Quipazine 0.1mg/kg. s.c.
Group VII - Naringin 80 mg/kg;o.p+ Quipazine 0.1mg/kg. s.c.
Group VIII - Standard drug- Resperidone (0.1mg/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.i.p and Quipazine 0.1mg/kg.

After Apomorphine induction, rats were allowed setup for few seconds and then count the Apomorphine induced stereotypy scores such as locomotion (head bobbing), continuous sniffing, licking and gnawing (vacuous chewing), asleep, awake. The behavioral scoring was given as follows: 0-asleep, 1-awake and quiet, 2-locomotion (head bobbing), 3-sniffing,4-licking, 5-gnawing (vacuous chewing) for 25 minutes.

### *Effect of Quercetin and Naringin against Apomorphine induced stereotypy*

*The* effect of Quercetin against Apomorphine induced stereotypy was observed at different doses. The intraperitoneal injections of Apomorphine (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 stereotypic scores were significantely decreased rather than control. The behaviour of quercetin and naringin rats consisted mainly of sniffing, with occasional grooming, licking and gnawing. Most control rats did not show this behavior. Table1 & 2 shows the resultant percentage decrease in stereotypy scores induced by 1 mg/kg. APO as a function of time after quercetin pretreatment. This indicates that the super sensitivity of the APO-induced elevation in Quercetin and Naringin treated groups are eventually disappears ($P<0.001$).

### *Effect of quercetin and naringin against quipazine induced headtwiches*

The effect of Quercetin and Naringin against quipazine induced head twitches were obsereved for 45 min after the sub cutaneous injection of quipazine 0.1mg/kg is shown in Fig. 2. Significantly higher stereotypy scores were recorded in quipazine treated rats than for controls ($P<0.01$). This

difference occurred throughout the 45 minutes duration of the experiment. The behavior of the quipazine treated rats consisted mainly of head twitches. Count of head twitches were significantly decreased for Quercetin and Naringin (P<0.001) treated groups is shown in Fig:3&4. The standard drug Resperidone (0.1mg/kg, i.p.) showed significant effect when compared to control (P<0.001). Low dose of drug (25 mg/kg) did not show any significant effect.

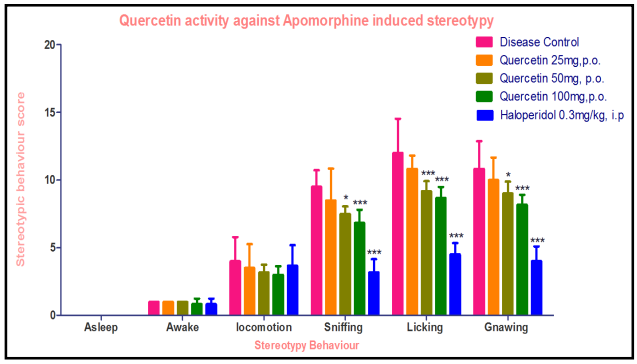


**Figure 1** Quercetin activity against Apomorphine induced stereotypy

All values are expressed as mean ± S.D (n=6), Quercetin (50mg) Sniffing *p<0.05 Vs Disease control, Licking ***p<0.001 Vs Disease control, Gnawing *p<0.05 Vs Disease control, Quercetin(100mg) Sniffing ***p<0.001 Vs Disease control, Licking ***p<0.001 Vs Disease control, Gnawing ***p<0.001 Vs Disease control, Haloperidol 0.3mg/Kg Sniffing ***p<0.001 Vs Disease control, Licking ***p<0.001 Vs Disease control, Gnawing ***p<0.001 Vs Disease control. Statistical analysis by two-way ANOVA followed by Bonferroni posttests.

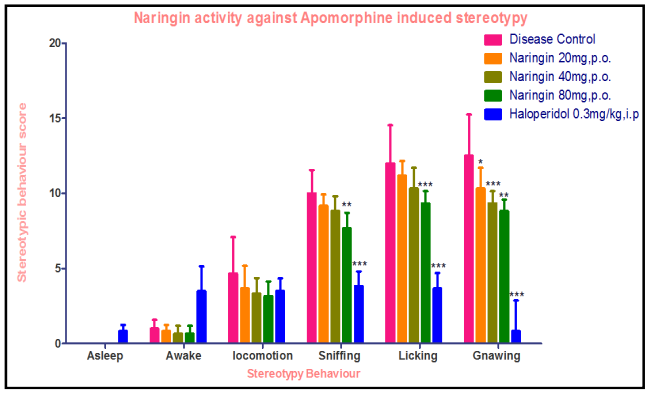


**Figure 2** Naringin activity against Apomorphine induced stereotypy

All values are expressed as mean ± S.D (n=6), Naringin(20mg) Gnawing *p<0.05 Vs Disease control, Naringin(40mg) Gnawing **p<0.01 Vs Disease control, Naringin(80mg) Sniffing **p<0.01 Vs Disease control, Licking **p <0.01 Vs Disease control, Gnawing ***p<0.001 Vs Disease control, Haloperidol 0.3mg/kg Sniffing ***p<0.01 Vs Disease control, Licking ***p <0.001 Vs Disease control, Gnawing ***p<0.001 Vs Disease control. Statistical analysis by two-way ANOVA followed by Bonferroni posttests.

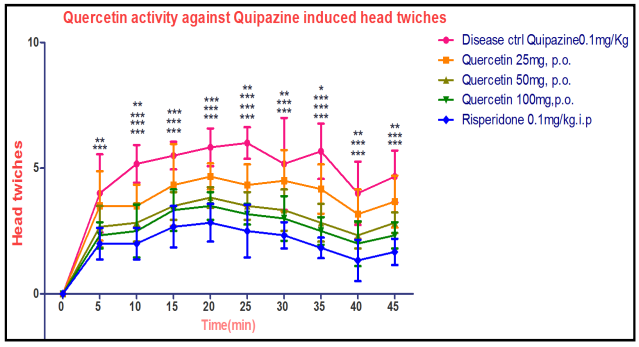


**Figure 3** Quercetin activity against Quipazine induced head switches

All values are expressed as mean ± S.D (n=6), Quercetin25mg (10-15min,25-30min) **p<0.01 Vs Disease control, 35-40min *p<0.05 Vs Disease control, Quercetin50mg (10-15min,15-20min,20-25min,25-30min,35-40min) ***p<0.001 Vs Disease control,(30-35min,40-45min,45-50min) **p<0.01 Vs Disease control, Quercetin(100mg) 5-10min **p<0.01 Vs Disease control, (10-15min,15-20min,20-25min,25-30min,30-35min, 35-40min,40-45min,45-50min) ***p<0.001 Vs Disease control, Risperidone 0.1mg/kg (5-10min,10-15min,15-20min,20-25min,25-30min,30-35min,35-40min,40-45min,45-50min) ***p<0.001 Vs Disease control. Statistical analysis by two-way ANOVA followed by Bonferroni posttests.

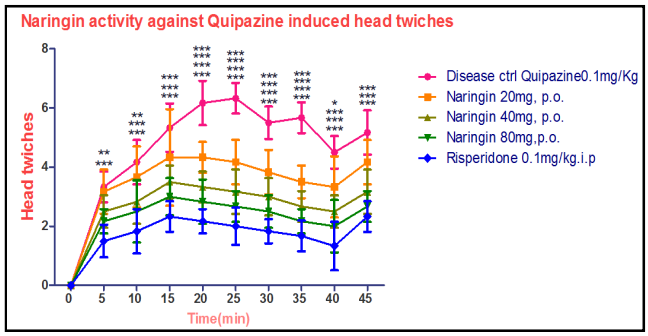


**Figure 4** Naringin activity against Quipazine induced head switches

All values are expressed as mean ± S.D (n=6), Naringin 20mg (25-30min,30-35min,35-40min) ***p<0.001 Vs Disease control, 40-45min *p<0.05 Vs Disease control, Naringin40mg 10-15min **p<0.01 Vs Disease control ,(15-20min,20-25min,25-30min,35-40min,40-45min,45-50min) ***p<0.001 Vs Disease control, Naringin80mg 5-10min *p<0.05 Vs Disease control, (10-15min,15-20min,20-25min,25-30min,30-35min,35-40min,40-45min,45-50min) ***p<0.001 Vs Disease control, Risperidone 0.1mg/kg (5-10min,10-15min,15-20min,20-25min,25-30min,30-35min,35-40min,40-45min,45-50min) ***p<0.001 Vs Disease control. Statistical analysis by two-way ANOVA followed by Bonferroni posttests.

## RESULT AND DISCUSSION

In the present study two selective flavonoids Quercetin and Naringin were studied against Apomorphine and Quipazine induced psychotic induced animal models such as stereotypic behavior includes asleep, awake, sniffing, licking, gnawing and head twitches. The results indicate that, Quercetin and Naringin influences general behavioural profiles, as evidenced by decrease in the stereotypic scores. The Quercetin and Naringin significantly dose dependently reduced the stereotypic behavior induced by Apomorphine and head twitches of quipazine. The inhibitory response of the selected

flavonoids on apomorphine induced stereotype may be attributed due to their antioxidant potentials (Kensler *et.al*;2007, Chanet *et al*; 2012), as the oxidative stress has a greater implication in the stereotypic behaviors (Ozyurt *et.al*;2007). Further, the anti-stereotypic activity may be due to its modulator influence at dopaminergic receptors. The results propose the role of flavonoids in the inhibition of head twitch, may be attributed by the modulation of serotonin receptors (Malick *et.al*; 1977). The quipazine induced head twitch response was also evaluated against selected flavonoids in rodents. In our study, quipazine produced higher incidence of head twitch at different time intervals in quipazine alone treatment group. The results are in good agreement with the previous reports (Malick *et.al*; 1977). The selected flavonoids showed significant inhibitory response against quipazine induced head twitches in rodents, dose dependently. The results propose the role of flavonoids in the inhibition of head twitch, may be attributed by the modulation of serotonin receptors (Malick *et.al*; 1977).

All these findings support the potential therapeutic benefits of the selected flavonoids in the symptomatic treatment of psychosis. But, further studies are needed to confirm the role of dopamine, serotonin and the oxidative defensive system in the anti-psychotic activity of the selected flavonoids.

## CONCLUSION

Based on the results of the present study of quercetin and naringin on psychopharmacological tests, we conclude that the quercetin at 100 and 200mg/kg and Naringin at 40 and 80mg/kg possess strong CNS depressant activity. The selected flavonoids showed the Anti-psychotic activity in dose dependent manner. The reduction in exploratory behaviour in animals is similar with the action of other CNS depressant agents. A significant decrease in stereotypic behavior and head twitches were also noted in animals treated with flavonoids. All these findings support the potential therapeutic benefits of the selected flavonoids in the symptomatic treatment of psychosis. However, further studies are necessary to confirm the role of dopamine, serotonin and the oxidative defensive system in the anti-psychotic activity of the selected flavonoids.

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**How to cite this article:**

Supriya CH., Siva Reddy CH and Basaveswara Rao M.V (2018) 'Neuropharmacological Screening of Flavonoids Against Apomorpine and Quipazine Induced Stereotypy', *International Journal of Current Advanced Research,* 07(11), pp. 16524-16528. DOI: http://dx.doi.org/10.24327/ijcar.2018.16528.3058

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