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Original article

A study the Anti-convulsant activity of 3-methoxyflavone through maximum electroshock and Pentylenetetrazole induced seizures methods and to investigate the mechanism involved in the anti-convulsant activity of 3-methoxy flavone in Swiss Albino Mice

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Abstract

Aim and Background: *The purpose of this study was to assess the anti convulsant activity of 6-methoxy flavone in Swiss albino mice through maximum electroshock (MES) seizure model and pentylenetetrazole (PTZ) induced seizure model. Flavonoids exhibit a strong anti-inflammatory effect through either directly altering the neuro inflammatory pathways or by exhibiting the ability to scavenge free radicals within the brain.*

Materials and Methods: *For research on the mechanism and anti-convulsant activity, mice of both sexes weighing 20–30 g were employed for the anti-convulsant activity and mechanism studies. Maximal Electro shock Seizure model, Pentylenetetrazole Induced Seizure model were used for anti convulsant activity, mechanisms involving adenosinergic system and Serotonergic system were also observed. Statistical analysis was performed using SPSS 16 version. The Institutional Animal Ethics Committee approved the experimental protocol for the study, which adhered to CPCSEA requirements for humane animal care. 3-methoxyflavone from Research Organics in Chennai was utilized.*

Results: *The outcomes which were attained by using pentylenetetrazole and maximum electroshock to cause seizures and imply that 3-methoxyflavone shields experimental animal models from convulsion.*

Conclusion: *The results of this study also show that 3-methoxyflavone's anticonvulsant effects are due to its interactions with GABAA and adenosine receptors rather than serotonergic pathways.*

Keywords*: 3 Methyl flavones, Swiss Albino Mice, Anti convulsant activity, animal experiment*

I. Introduction

Studies show epilepsy as an old brain disorder which has been known to exist for at least 3000 years. The neurological condition affects 1% to 2% of the global population which qualifies it as the most prevalent neurological disorder. The prevalence rates of epilepsy differ between developing nations at 100 cases per 100,000 people and industrialized nations at 50 cases per 100,000 people. Medical science classifies neurone hyperexcitability seizures as epilepsy under neurological conditions. The activity levels of glutamate-mediated neurotransmission appear to be in direct opposition to those of GABA-mediated neurotransmission. Behavioral comorbidities together with cerebral dysfunctions happen regularly as the result.[2]

The occurrence of epileptic convulsions weakens brain antioxidant systems and increases free radical levels that intensify oxidative stress. The scientific definition of free radicals (FR) describes these unstable molecules or fragments because they contain electron pairs which remain unpaired. Various studies have shown evidence of free radicals as causes for epilepsy and lipid peroxidation and brain oedema as well as mortality risks from epilepsy. Many different antiepileptic medications function as treatment options for epilepsy. Both these elements can result in ischaemia and then induce depression while accelerating cognitive decline throughout the body and triggering movement problems. The refractory seizure population amounts to between 20 and 30 percent of all epilepsy sufferers whose seizures show no response to traditional antiepileptic medications[2].

The pharmaceutical development process receives therapeutic treatment from numerous individuals worldwide to create antiepileptic drugs with new structural compounds together with improved safety features and enhanced effects. Phytomedicines with antioxidant properties possess an opportunity to enhance research on antiepileptic pharmacotherapeutic developments. The medical treatments also function as preventative methods against disease development. Across the world established plant medicines treat epilepsy in numerous forms[3]. Flavonoids act upon the GABA-Cl- channel complex according to experimental findings to bring about antiepileptic effects. Flavonoids serve as phenolic compounds which exhibit the ability to alter brain chemical reaction processes thereby contributing to disease modifications affecting neurodegenerative conditions. The development of potent and specific benzodiazepine receptor ligands depends greatly on many flavone derivative compounds. Studies on neuro active flavonoids from herbal medicines open possibilities to create treatments for illnesses linked to GABA receptors[4].

Plant species show characteristic patterns of flavonoids known as vitamin D in their structures since secondary metabolites serve to protect plants from ultraviolet radiation while providing coloration. Natural occurrences of flavonoids throughout environments lead experts to recommend these compounds in dietary plans since their usage produces limited negative side effects. Multiple dietary products like fruits, vegetables, tea, coffee, juices and red wine naturally contain flavonoids[5]. The properties of these compounds consist of anti-infective abilities together with antioxidant actions which also include vasoprotective and anti-inflammatory features and metal ion chelation activities and hepatoprotective properties and anticancer activities. Neuroprotective mechanisms of flavonoids function against neurotoxic substances and inflammatory processes which result in neurological activity in the body. Evidence indicates that traditional medicine provides cognitive enhancement despite its known limitations. The main factors in folk remedies derive from natural sources. Anti-epileptic properties are found in herbal flavonoids including 4,5,7-trihydroxy-3-methoxyflavone. The plant medicine Valerian produces 6-methylapidigenin (4,5,7-trihydroxy-6-methylflavone or hispidulin with a methyl group at the methoxy position) which decreases drug binding when its concentration reaches 0.5 mm. Observational data demonstrates that this substance can potentially act as a positive GABAA receptor 6 inhibitor. Different mechanisms allow flavonoids to modify signal pathways at cellular level. Researchers examined how 3-methoxy flavone treatment affected maximum electroshock seizures as well as pentylenetetrazole-induced convulsions in Swiss albino mice while analyzing its associated anti-convulsant mechanisms[6].

Researchers have validated through preclinical and clinical investigations that peripheral tissues along with neurones release inflammatory mediators including prostaglandins and cytokines that significantly affect both epilepsy development and seizure onset processes. Flavonoids protect against inflammation by interacting directly with neuro inflammatory cascades as well as eliminating reactive oxygen species. Multiple studies have proven that flavonoids accomplish both anti-inflammatory effects and free radical protection while also controlling receptors linked to epilepsy such as opioid and GABA receptors and NMDA receptors and sodium and calcium ion channels[7].

II. Materials and Methods

Animal

The analysis of anti-convulsant properties with mechanism exploration used a group of mice that contained male and female subjects weighing between 20 to 30 grams. The experimental subjects received unrestricted food and water availability under controlled temperature (20–23°C) and a 12-hour period of light and darkness. The examination was conducted from 10:00 a.m. until 2:00 p.m. to prevent changes in experimental timing conditions which would affect the results. The investigators enthusiastically endorsed the research design protocol through the Institutional Animal Ethics Committee before executing the experiments while adhering to CPCSEA requirements for welfarist treatment of animals.

The research used 3-methoxyflavone obtained from Research Organics in Chennai. Research analysts started the experimental phase by giving rats 30-minute water-resistant 3-methoxyflavone suspensions as a 0.5% carboxymethyl cellulose solution. Research scientists detected induced seizures by giving pentylenetetrazole (Tokyo Chemical Industry Co. Ltd., Tokyo Japan) to subjects. Hindustan Pharmaceuticals from India produced Diazepam which functioned as the reference standard for Pentylenetetrazole-induced seizure model analysis. The maximal electroshock seizure tests used Phenytoin as both standard reference material and produced by Zydus Neurosciences in India. The evaluation of anticonvulsant functioning required either caffeine from Merck Specialities Pvt Ltd.

Maximal Electroshock Seizure Test

An allocation of three mouse groups based on random selection method (vehicle, standard, and test groups) was established. Each group comprises six animals. The pentylenetetrazole (PTZ) required distillation before dissolving it in water then injecting it into the vehicle group animals through an intraperitoneal route at a 90 mg/kg dose level. A period of thirty minutes was established for observing the subjects after their evaluation (Adeyemi, Yemitan, & Adebiyi, 2007)[8]. The observation of various stages of convulsion was documented, encompassing myoclonic jerks, clonic convulsions, tonic flexion, tonic extension, and culminating in the demise of the animal. Thirty minutes prior to the administration of PTZ treatment, the subjects, specifically mice, were systematically allocated into distinct groups and administered with varying dosages of 50, 100, and 200 mg/kg. Administration of 3-methoxyflavone was conducted via the intra-peritoneal route, utilising a suspension in 0.5% carboxymethyl cellulose (CMC). The time when both the first myoclonic jerk and the tonic hind limb extension began was recorded during the 30-minute observation. The researchers kept track of how many test subjects died during this assessment time. During the 30-minute observation period without convulsions the mice demonstrated a state of safety after PTZ treatment. Researchers tested the anticonvulsant properties by how well the sample substance delayed or blocked HLE onset. A standard procedure of diazepam administration at 5 mg/kg intraperitoneally was performed 30 minutes before PTZ delivery followed by systematic monitoring.

Additional research was carried out to understand how 3-methoxyflavone produces its anti-convulsant effect. The maximal electroshock seizure test hind limb extension was completely blocked in all test subjects by giving the intraperitoneal injection of 3-methoxyflavone at 200 mg/kg.

The adenosinergic system

Just before giving 3-methoxyflavone at a dose of 200 mg/kg through i.p. administration researchers administered caffeine at 50 mg/kg through i.p. as a non-selective adenosine antagonist to study the adenosinergic pathway effect. The subjects received 3-methoxyflavone 30 minutes before undergoing maximal electroshock testing for hind limb extension measurement according to Hall, Chebib, Hanrahan, & Johnston (2004)[9].

The serotonergic system

A group of mice received ondansteron (1 mg/kg, i.p.) by intraperitoneal route 15 minutes before getting 6-methoxyflavone (200 mg/kg, i.p.) administered likewise intraperitoneally according to Supriya et al. (2022)[10]. Each animal received electroshock therapy for 30 minutes before researchers recorded the time of hind limb extension in their respective groups.

Statistical analysis

The data are expressed as the mean ± standard error of the mean (S.E.M.). The data underwent statistical analysis utilising SPSS version 16. In the evaluation of the MES and PTZ-induced seizure test, a one-way analysis of variance (ANOVA) was employed, subsequently followed by Dunnett's "t" test to facilitate multiple comparisons. P values below 0.05 were considered to indicate statistical significance. To facilitate comprehension, the results of the various experiments are presented in both tabular and graphical formats. Mice of both sexes were randomly assigned to three groups: vehicle, standard, and test groups. Each group comprises six animals. An electro convulsiometer (MKM, Chennai) was employed to induce seizures in mice. The transauricular stimulation delivered an alternating voltage threshold of 105 mA with a frequency of 50 Hz and a duration of 0.2 seconds through alligator clips placed on mouse ear pins in compliance with previous research methods. Every vehicle-animal exhibited increased locomotor-driven exploration after the current exposure exceeded the predetermined level. Thirty minutes before electroconvulsive shock treatment received an intraperitoneal phenytoin injection at the 25 mg/kg dosage.

Experimental mice received 3-methoxy flavone at doses of 50, 100, and 200 mg/kg through an intraperitoneal injection 30 minutes before electroshock because these subjects received the drug suspension in 0.5% carboxymethyl cellulose solution. For better monitoring of HLE changes after the stimulation the experimental mice needed placement in an opened transparent plastic box. Researchers monitored and recorded the different stages of convulsion that began with tonic flexion followed by extension after clonus before stupor finally led to death. The duration of time served as the endpoint for the experiment which divided mice into three sections after random allocation. Each group comprises six animals. The pentylenetetrazole (PTZ) solution received administration through intraperitoneal injection at 90 mg/kg as distilled water served as the vehicle solution for the group of animals. Thirty more minutes were dedicated for observation during the experiment . The research team documented the movement stages including myoclonic jerks and clonic convulsions with tonic flexion followed by tonic extension until death of the animal. Thirty minutes prior to the administration of PTZ treatment, the subjects, specifically mice, were systematically allocated into distinct groups and administered with varying dosages of 50, 100, and 200 mg/kg.Administration of 6-methoxyflavone was conducted via intra-peritoneal (i.p.) route, utilising a suspension in 0.5% carboxy methyl cellulose (CMC). During the 30-minute observation period, the onset of the myoclonic jerk (initial twitch) and the onset of the tonic hind limb extension were documented. Furthermore, the proportion of animals that succumbed during this period was documented. The data indicate that mice exhibited a protective response when they did not experience convulsions within a 30-minute post-administration period of PTZ therapy. The anticonvulsant activity was established as the ability of the test compound to inhibit or delay the onset of HLE. Administration of 5 mg/kg of intra-peritoneal diazepam was conducted as a standard procedure, administered 30 minutes prior to the administration of PTZ. Observations indicated that the hind limb could be extended to its maximum tonic state, resulting in mortality due to convulsive activity. The animals were considered to be safeguarded in the absence of tonic extension of the hind limb.

II. Results

Scientists used both maximal electroshock (MES) seizures and pentylenetetrazole (PTZ)-induced seizures on mice to measure 3-methoxyflavone (3MF) anticonvulsant activities. The researchers used caffeine and flumazenil to evaluate the role of adenosine and serotonin receptors in understanding the anticonvulsant actions of 6MF.

1. Effect of 3MF on Maximal Electroshock-Induced Seizures

A breakdown of 3-methoxyflavone effects on maximal electroshock seizure development exists in Table 1. The vehicle group showed THLE lasted for 18.37 ± 0.44 seconds while half of the animals died in this condition. The administration of 25 mg/kg phenytoin through intraperitoneal injection completely terminated THLE (0.00 ± 0.00 seconds; *$p < 0.001$) while blocking all deaths. The distribution of THLE (17.16 ± 0.25 seconds) along with mortality rate at 50% remained unchanged following 3MF administration at 50 mg/kg. When administered at 100 or 200 mg/kg dosage 3MF produced THLE durations that measured 14.18 ± 0.13 seconds and 8.69 ± 1.02 seconds respectively (*$p < 0.001$) while the treatment led to zero observed deaths at 200 mg/kg.

2. Effect of 3MF on PTZ-Induced Seizures

The experimental mice exposed to vehicle solution began displaying myoclonus contractions at 66.92 ± 0.78 seconds before transitioning to tonic extension seizuring at 7.01 ± 0.23 minutes with complete mortality rates. 5 mg/kg i.p. Diazepam provided full protection against seizures together with mortality reduction ($p < 0.001$). 3MF showed a positive relationship between its dosage and the time to myoclonus development coupled with decreased mortality rates. A single dose of 50 mg/kg 3MF prolonged the onset of myoclonic seizures to 162 ± 1.57 seconds with **$p < 0.001$ significance yet failed to stop deaths from occurring. The drug administration at 100 mg/kg elevated the time to myoclonic seizures to 160.92 ± 1.24 seconds while lowering death rates to 50% (**$p < 0.001$). The highest dosage of 200 mg/kg resulted in complete cessation of tonic extension along with a total elimination of mortality ($p < 0.001$).3. Interaction of 3MF with flumazenil in MES-Induced Seizures

Table 1 illustrates the effect of flumazenil, a 5-HT3 receptor antagonist, on the anticonvulsant activity of 3MF. Flumazenil (5 mg/kg, i.p.) alone did not affect the duration of THLE (18.25 ± 0.17 seconds). Treatment with 3MF (200 mg/kg) significantly reduced THLE duration to 8.69 ± 1.02 seconds (*$p < 0.001$). Co-administration of ondansetron and 3MF slightly attenuated the anticonvulsant effect of 3MF (THLE: 9.3 ± 0.35 seconds), though the reduction remained significant compared to the vehicle-treated group.

Table 1: Effect of 6-Methoxyflavone on Maximal Electroshock (MES) andPentylenetetrazole(PTZ)-Induced Seizuresin Mice

Treatment (mg/kg, i.p.)	Maximal Electroshock (MES) Test	Pentylenetetrazole (PTZ) Test
	Duration of THLE (sec)	Onset of Myoclonus (sec)
Vehicle	18.37 ± 0.44	66.92 ± 0.78
Phenytoin/Diazepam	0.00 ± 0.00**	0.00 ± 0.00**
3MF 50 mg/kg	17.16 ± 0.25	162.00 ± 1.57**
3MF 100 mg/kg	14.18 ± 0.13*	160.92 ± 1.24**
3MF 200 mg/kg	8.69 ± 1.02**	129.40 ± 0.86*

Data are expressed as mean ± S.E.M (n = 6 animals per group); *p < 0.01 and **p < 0.001 compared to vehicle-treated control (ANOVA, Dunnett's test); THLE: Tonic Hind Limb Extension.

4. Interaction of 3MF with Caffeine in MES-Induced Seizures

A study evaluated the involvement of adenosine receptors in 3MF anticonvulsant activity through combined administration of caffeine which functions as a non-selective adenosine receptor blocker (Table 5.4). The single administration of caffeine at 50 mg/kg through i.p. did not produce a substantial impact on THLE values (17.01 ± 0.18 seconds). The administration of 6MF (200 mg/kg) reduced the THLE value to 8.69 ± 1.02 seconds (**p < 0.001). When 3MF was combined with caffeine, it proved to defeat the antiepileptic properties of 6MF by extending the THLE to 14.33 ± 0.15 seconds (*p < 0.001). The action of adenosine A1 receptors plays a vital role in the anticonvulsant mechanisms which 6MF employs in the body

Table 2: Interaction of 3-Methoxyflavone with Flumazenil and Caffeine in Maximal Electroshock (MES) Test

Treatment (mg/kg, i.p.)	Duration of THLE (sec)	Effect
Vehicle	18.37 ± 0.44	-
Flumazenil (5 mg/kg)	18.25 ± 0.17	No effect
3MF 200 mg/kg	8.69 ± 1.02**	Significant anticonvulsant activity
3MF 200 mg/kg + Flumazenil(5 mg/kg)	9.3 ± 0.35*	Slight attenuation of anticonvulsant effect
Caffeine (50 mg/kg)	17.01 ± 0.18	No effect
3MF 200 mg/kg + Caffeine	14.33 ± 0.15*	Partial attenuation of anticonvulsant effect

Data are expressed as mean ± S.E.M (n = 6 animals per group).
*p < 0.01 and **p < 0.001 compared to vehicle-treated control (ANOVA, Dunnett's test).
THLE: Tonic Hind Limb Extension.

Table 3: Effect of 3-Methoxyflavone on Behavioral Changes and Recovery Time in MES and PTZ-Induced Seizures

Treatment (mg/kg, i.p.)	MES Test: Recovery Time (min)	PTZ Test: Recovery Time (min)	Behavioural Observations
Vehicle	>30	Not recovered	Severe tonic-clonic seizures, respiratory distress
Diazepam	<5	<5	Normal behavior, no observable seizures
3MF 50 mg/kg	25 ± 2.4	18 ± 1.8	Mild convulsions, reduced locomotor activity
3MF 100 mg/kg	15 ± 1.6	12 ± 1.5	Significant reduction in seizure intensity and duration
3MF 200 mg/kg	8 ± 1.2**	6 ± 0.8**	Normal grooming behavior, no tonic-clonic seizures

Note: Data are expressed as mean ± S.E.M (n = 6 animals per group); **p < 0.001 compared to vehicle-treated control (ANOVA, Dunnett's test).

The results demonstrate that 3MF demonstrates a gradient dose-response pattern which corresponds to phenytoin and diazepam in both MES and PTZ testing. Results indicate that the anticonvulsant properties of 3MF depend heavily upon adenosine A1 receptor activity because it becomes less effective with caffeine intake yet remains unaffected by Flumazenil use. The research demonstrates how 3MF stands as a potential leading anticonvulsant agent which operates through distinct pathways in the body.

III. Discussion

Epileptic seizures emerge because of abnormal electrical discharge after brain cells activate predefined regions of the brain. Present-day seizure management through medication accomplishes therapeutic control of epilepsy symptoms in greater than 70% of epileptic patients who use these pharmaceutical agents to modulate transmission of GABAergic or glutamatergic signals alongside membrane channel activity. GABA functions as the primary inhibitory neurotransmitter of the central nervous system because it produces inhibitory signals towards postsynaptic neurones. Multiple epilepsy forms relate to signaling disruptions affecting GABA-mediated transmission according to research in experimental animal models (Treiman, 2001)[11].

Pharmaceuticals with neuroactive properties such as benzodiazepines find their binding sites at GABAA receptors' benzodiazepine region to activate hypnotic as well as anxiolytic and anticonvulsant outcomes. Neuronal excitability in seizures requires the influence of multiple neurotransmitter systems which includes dopamine together with serotonin and norepinephrine as well as GABA (Rogawski & Löscher, 2004)[12]. Experimental research shows that adenosine works as an anticonvulsant through its A1 receptor actions in animal epilepsy studies (Etherington & Frenguelli, 2004)[13].

Preclinical studies prove the anticonvulsant properties of natural products particularly flavonoids which exhibit effectiveness in various testing models. Flavonoid compounds show evidence of working as GABAA receptor ligands due to their benzodiazepine-like structure. Studies show flavonoids at least partially affect GABAA–chloride channel activity just like anticonvulsant drugs do according to research presented by Marder and Paladini (2002)[14].

Studies using animals as experimental models of anxiety and sedation and convulsion serve to support these actions. Experimental analysis demonstrated that 3-methoxyflavone (3-MF) which derives from flavonoids acted as a depressant in the central nervous system of mice and rats. Scientific studies investigated anticonvulsant properties of this compound by using both maximal electroshock (MES) and pentylenetetrazole (PTZ)-induced seizure models according to Eunice et al. (2015)[15].

Tests in the MES model demonstrated that 3-MF showed anticonvulsant effects at par with phenytoin although phenytoin functions by blocking voltage-dependent sodium channels. The data shows that 3-MF can either modify sodium channel function or NMDA receptors since these components are essential for seizure development. The medical research using PTZ models to study absence and myoclonic seizures showed that 3-MF given by intraperitoneal injection lengthened seizure onset time and reduced mortality rates in a dose-related way. At a dosage of 200 mg/kg 3-MF provided complete seizure protection and mortality prevention which showed similar results to diazepam at its 5 mg/kg dosage according to Herrera-Ruiz et al. (2008)[16].

Research on mechanisms demonstrated that adenosine receptors play an important role in achieving anticonvulsant effects from 3-MF. The anticonvulsant protection from 3-MF required the blockade of adenosine A1 receptors by caffeine based pretreatment in accordance with other model study findings (Detlev Boison, 2013)[17]. The protective effects of 3-MF remained unchanged after patients received ondansetron before their treatment to block 5-HT3 receptors in the serotonergic system during this condition.

Experimental research on animals has demonstrated that 5 of the most studied flavonoids like luteolin, wogonin, chrysin, apigenin, and vitexin show anticonvulsant effects by either modifying GABAA receptor activity or reducing oxidative cellular damage. The GABAA receptor benzodiazepine binding site becomes the target of anticonvulsant properties displayed by Baicalein which scientists derive from Scutellaria baicalensis (Paladini et al., 1999)[18]. Laboratory findings suggest that flavonoids especially 3-MF demonstrate suitable characteristics to develop new anticonvulsant drug candidates.

Additional studies need to determine the exact molecular approaches that 3-MF utilizes for its effects on sodium and calcium channels. Further clinical advancement depends on studies explaining 3-MF's blood-brain barrier permeability and its combined effects with existing anticonvulsant medications and detailed pharmacokinetic

analysis. The current research determines flavonoids have potential as an important starting point for future anticonvulsant therapy developments.

IV. Conclusion

The present research supports the use of 3-methoxyflavone as an anticonvulsant treatment for absence seizures as well as generalized tonic-clonic seizures in human subjects. Animal experimental models confirmed that 3-methoxyflavone serves to protect against seizures after researchers subjected animals to maximal electroshock and PTZ administration. This study shows that anticonvulsant effects of 3-methoxyflavone do not involve serotonin pathways because the substance interacts with adenosine and GABAA receptors.

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