

Evaluation Of Anti-Epileptic Activity Of Hydroalcoholic Extract Of *Citrus Maxima* Fruit Peel In Experimental Mice

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Abstract: The antiepileptic activity of *Citrus maxima* (Pomelo) fruit-peel extract (CMPE) was analysed using Maximal Electro-shock and Pentylentetrazole induced convulsion models in Swiss albino mice. The mice were divided into 4 groups with 6 animals each. Group I were treated with vehicle (oral, p.o.) as control, Group II received standard drugs Phenytoin (25mg/kg, i.p.) for Maximal electro-shock model or Diazepam (4mg/kg, intraperitoneal, i.p.) for Pentylentetrazole model, Group III and Group IV consisted of animals treated with 200mg/kg, (p.o.) and 400mg/kg, (p.o.) of the extract. All the treatments were given for 14 days. On the 14th day the convulsions were induced in all the study groups. The hydroalcoholic extract of the fruit-peel of *Citrus maxima* (Pomelo) (CMPE) at both doses (200mg/kg and 400mg/kg, p.o.) demonstrated a significant reduction in Hind Limb Tonic Extension (HLTE) phase duration in MES-induced model. They exhibited a dose-dependent action but with only a slight improvement of activity in the higher dosage group in this model. The extracts showed highly significant, dose-dependent antiepileptic activity in PTZ-induced model by comparing the parameters with the control group, such as delay in onset, reduction in duration of convulsions and decrease in mortality rate. In conclusion, Hydroalcoholic extract of *Citrus maxima* fruit-peel has considerable protective action against Maximal electro-shock and Pentylentetrazole induced convulsions in mice when studied for its antiepileptic potential.

Keywords: Pentylentetrazole, Antiepileptic, *Citrus maxima*, Pomelo, Convulsions, Maximal electro-shock, Hydroalcoholic, Phenytoin, Diazepam.

I. INTRODUCTION

Epilepsy is a disorder of the central nervous system and is characterized by periodic loss of consciousness with or without convulsions associated and with abnormal electrical activity in the brain. Epilepsy is seen as the clinical manifestation of an abnormal and excessive discharge of a set of neurons in the brain [1]. γ -Aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the cerebral cortex, maintains the inhibitory tone that counterbalances neuronal excitation. When this balance is perturbed, seizures may ensue [2]. A "seizure" is defined as a paroxysmal alteration of neurologic function in brain caused by the excessive, hyper-synchronous discharge of neurons [3].

Epilepsy accounts for a significant proportion of the world's disease burden, Epilepsy affects both sexes and all ages with worldwide distribution [4]. The estimated proportion of the general population with active epilepsy at a given time is between 4 and 10 per 1000 people. In high-income countries, there are estimated to be 49 per 100,000 people diagnosed with epilepsy each year. In low- and middle-income countries, this figure can be as high as 139 per 100,000 [5]. It is estimated that there are around 50 million people living with epilepsy (PWE) globally. Around one-sixth of this population resides in India [6]. The problems associated with epilepsy aren't limited to its clinical manifestations, there is an increased risk of mortality in people with epilepsy due to dramatic consequences such as depression, suicide and seizure-related injuries [7].

The treatment of epilepsy is by therapeutic agents such as phenytoin, sodium valproate, carbamazepine etc, which control the excess abnormal electrical activity of brain neurons. These agents act by blocking sodium/calcium channels and balancing the inhibitory and excitatory neurotransmitter system in central nervous system [8]. The draw-back of the available drugs are its adverse effects which can compromise with the quality of life. Megaloblastic anaemia, gastrointestinal irritation, gingival hyperplasia, nervous system dysfunction, rashes, neurotoxic side effects, diplopia, dermatomyositis, blood and respiratory system damages, dizziness, nausea, vomiting, and ataxia are some of the adverse reactions observed in antiepileptic drug treatment [9].

There is a need for the research of new and safe therapeutic agents. The belief that natural products are safer than pure chemicals is quite common. Research based on phytochemical and ethnobotanical characteristics of plants have been conducted based on the assumption that a plant has bioactive compounds that determine the therapeutic effects [10]. Several biochemical hypotheses suggest the involvement of decreased inhibitory GABAergic system and/or increased activity of excitatory amino-acids (glutamate and aspartate) in epilepsy [11].

Citrus maxima, the Pomelo also known as Pummelo or Shaddock in the Rutaceae Family is an edible fruit belonging to a perennial tree. The main chemical compositions of Pomelo peel are Vitamin C, flavonoids, and carotenoids, which are strongly associated with antiepileptic activity [12,13]. The extracts such as flowers of *Matricaria chamomilla* and whole plant of *Goodyera schlechtendaliana* containing flavonoids have been studied for its anticonvulsant property. Furthermore, the flavonoids such as apigenin, rutin present in these plants are also found in *Citrus maxima* (Pomelo) peel and have been reported to possess neuroactive properties as these compounds are ligands for GABA_A receptors in the central nervous system (CNS) and act as benzodiazepine-like molecules having the potential to mediate antiepileptic activity [14]. Flavonoids in Citrus peels have been extracted using a hydroalcoholic solvent mixture (ethanol -80% v/v) [15]. Therefore, hydroalcoholic extract of the *Citrus maxima* fruit peel was evaluated for its antiepileptic potential.

Aim of the study are as follows:

1. Authentication and collection of *Citrus maxima* fruit peel.
2. Preparation of Hydroalcoholic extract of *Citrus maxima* fruit peel.
3. Preliminary phytochemical screening.
4. To study the potential antiepileptic effect of *Citrus maxima* fruit peel extract, using experimental animal models,
 - a. Maximal Electroshock (MES) induced seizures.
 - b. Pentylentetrazole (PTZ) induced seizures.

II. METHODOLOGY

Collection and Authentication of Plant Material

The ripe fruits of *Citrus maxima* were collected in the month of March from the local area. The taxonomical characteristics were authenticated by a Taxonomist.

Plant material and extraction

The fruits of Pomelo were washed 2–3 times under tap water, the skin of the fruit was incised with a sharp knife and then peeled off by the fingers. The removed peels of Pomelo were chopped, air dried under shade, powdered by using a mechanical grinder to obtain a coarse powder. The obtained powder was used for the preparation of hydroalcoholic extract. 20g of the powder was packed into Soxhlet extractor with sufficient volume of hydro-alcohol (ethanol-80%) for adequate cycles. The extract was concentrated by evaporation. The final extract was preserved in a refrigerator.

Preliminary Qualitative Phytochemical Analysis

About 50mg of the solvent free extract was stirred with little quantity of ethanol and then filtered. The filtrate was tested for presence of phytochemical constituents in it [16].

Experimental animals

Swiss albino mice (25g to 30g) of either sex was used for this study. They were maintained under standard conditions (temperature $25 \pm 2^\circ\text{C}$, relative humidity $60 \pm 5\%$ and 12 h light/dark cycle) and given free access to standard pellet diet and water *ad libitum*. The animals were housed in sanitized polypropylene cages containing sterile paddy husk bedding. The Institutional Animal Ethics Committee reviewed and approved the experimental protocol (Approval No.: SCP/IAEC/F150/P170/2021 dated 27/08/2021). All the procedures were performed in compliance with Institutional Animal ethics committee constituted as per the direction of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Preparation of stock solution of the extract for dosing

200mg of hydroalcoholic extract of *C. maxima* fruit peel (CMPE) was measured and dissolved in 10ml vehicle (normal saline, 0.9% w/v). Each time fresh preparation of the extract was prepared before administration. The extract was administered orally (p.o.) at a dose calculated according to the body weight of the animal.

Calculation of the dose per body weight

The dose of extract and chemicals to be administered were calculated using the following formula,

$$\text{Dose required (mg/kg), } \mathbf{D} = [\text{body weight of animal} \times \text{dose in mg for 1000g body weight}] \div 1000 \quad (1)$$

$$\text{Volume of dose to be administered (ml), } \mathbf{V} = \mathbf{D} \div \text{concentration of stock solution} \quad (2)$$

V is the dose in ml of extract or chemical to be administered to an animal by a suitable route.

Dose selection

Doses were selected as 200mg/kg and 400mg/kg of the extract as per previous study and were administered post orally [17].

Evaluation of Antiepileptic activity

Maximal Electroshock (MES) induced convulsions in mice [18].

Purpose and rationale

The electroshock assay in mice is used primarily as an indication for compounds which are effective in grand mal epilepsy. Tonic hind limb extensions are evoked by electric stimuli which are suppressed by anti-epileptic drugs.

Experimental design

The Swiss albino mice (25-30g) of either sex were randomly divided into four groups of six each. The different groups were assigned as follows,

Group I: Vehicle Control (0.9% saline, p.o.) + electrical stimulus (50mA;50Hz for 0.2 sec duration).

Group II: Phenytoin (25mg/kg, i.p.) + electrical stimulus (50mA;50Hz for 0.2 sec duration).

Group III: *Citrus maxima* fruit-peel extract (200mg/kg, p.o.) + electrical stimulus (50mA;50Hz for 0.2 sec duration).

Group IV: *Citrus maxima* fruit-peel extract (400mg/kg, p.o.) + electrical stimulus (50mA;50Hz for 0.2 sec duration).

Treatment

From Day 1- 14, Group I and II were treated with vehicle(p.o.) and standard drug Phenytoin (25mg/kg, i.p.) respectively, whereas Group III and IV were treated with respective doses of *Citrus maxima* fruit-peel extract via oral route. On the 14th day, 30 mins after the treatment with standard drug and 60 mins after the treatment with vehicle or extracts, the groups were induced with MES-convulsions resembling the Generalized tonic-clonic seizure/ Grand mal epilepsy by application of electrical stimulus (50mA;50Hz;0.2 sec duration) through ear-clip electrodes using a simulator apparatus.

Evaluation

After inducing MES-convulsions, the animals were observed closely for the delay in onset and reduction in duration of Hind Limb Tonic Extension (HLTE) phase. The suppression of Hind limb tonic extension (HLTE) phase duration was taken as measure of efficacy in this test. Percentage of inhibition of seizures relative to the controls were calculated.

Pentylentetrazole (PTZ) induced convulsions in mice [19].

Purpose and rationale:

This test is used for screening of drugs effective in petit mal epilepsy and absence seizures. GABA antagonist causes direct depolarization of central neurons. It produces jerky type of clonic convulsion in mice.

Experimental design

The Swiss albino mice (25-30g) of either sex were randomly divided into four groups of six each. The different groups were assigned as follows,

Group I: Vehicle Control (0.9% saline, p.o.) + PTZ (80mg/kg, i.p.)

Group II: Diazepam (4mg/kg, i.p.) + PTZ (80mg/kg, i.p.)

Group III: *Citrus maxima* fruit-peel extract (200mg/kg, p.o.) + PTZ (80mg/kg, i.p.)

Group IV: *Citrus maxima* fruit-peel extract (400mg/kg, p.o.) + PTZ (80mg/kg, i.p.)

Treatment

From Day 1- 14, Group I and II were treated with vehicle (p.o.) and standard drug Diazepam (4mg/kg, i.p.) respectively, whereas Group III and IV were treated with respective doses of *Citrus maxima* fruit-peel extract via oral route. On the 14th day, 30 mins after the treatment with standard drug and 45 mins after the treatment with vehicle or extracts, the groups were induced with clonic-type convulsions by intraperitoneal administration of PTZ (80mg/kg).

Evaluation

After administration of PTZ, the animals were observed closely for onset of action (straub's tail, jerky movements of whole body and convulsions). Onset time of the convulsions and duration of convulsions were measured. Delay in onset and reduction in duration of convulsions is calculated in comparison with the control group. Mortality rate was also determined for each group.

Statistical Analysis

The data of all the parameters were analysed using the software Graph pad Prism 5. Analysis of variance (ANOVA); one way ANOVA followed by Dunett's test was performed for comparison with control group. The values were expressed as Mean \pm SEM. For all tests a "P" value of 0.05 or less was considered for statistical significance.

III. RESULTS

Preliminary phytochemical screening of *Citrus maxima*

Preliminary phytochemical analysis was performed and the results confirm the presence of alkaloids, flavonoids, saponin glycosides, tannins, steroids, carbohydrates and phenols.

Assessment of The Antiepileptic Activity

Following are the results obtained from the evaluation of antiepileptic activity of hydroalcoholic extract of *Citrus maxima* fruit-peel in experimental mice;

Maximal Electroshock (MES) Induced Convulsions

There was complete abolition of the Hind Limb Tonic Extension (HLTE) in the standard Phenytoin (25mg/kg, i.p.) treated group. In groups treated with the CMPE (200mg/kg and 400mg/kg), the time spent by the animals in the HLTE phase had decreased notably. While it was also observed to produce a delay in the onset-time of HLTE. The results of all the treatment groups were compared with the control as shown in Table. 1 and Fig. 1.

Table. 1: Effect of hydroalcoholic extract of *C. maxima* fruit-peel (CMPE) in MES induced convulsions in mice.

GROUP	TREATMENT	ONSET TIME OF HIND LIMB TONIC EXTENSION PHASE (sec)	DURATION OF HIND LIMB TONIC EXTENSION PHASE (sec)	PERCENTAGE INHIBITION (%)
Control	Normal Saline (0.9% w/v)	4.83 \pm 0.4773	28.50 \pm 1.910	-
Standard	Phenytoin (25mg/kg)	0.00***	0.00***	100%
Extract Dose-1	<i>Citrus maxima</i> peel extract (CMPE) (200mg/kg)	7.00 \pm 0.3651**	24.17 \pm 0.307*	15.12%
Extract Dose-2	<i>Citrus maxima</i> peel extract (CMPE) (400mg/kg)	11.83 \pm 0.401***	22.83 \pm 0.1667**	19.89%

Values are expressed as mean \pm S.E.M, (n=6). Statistical comparison was performed by using one way ANOVA followed by Dunnett's test. *P<0.05, **P<0.01, ***P<0.001 is considered statistically significant when compared with control group.

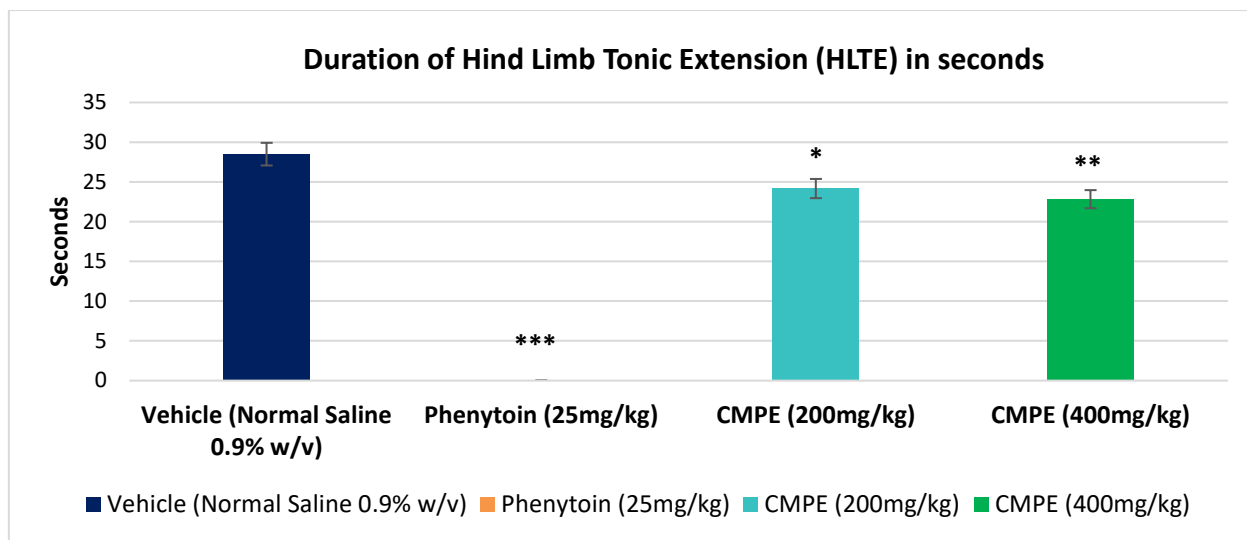


Fig. 1: Effect of hydroalcoholic extract of *C. maxima* fruit-peel on Duration of HLTE in MES induced convulsions in mice. Pentylentetrazole (PTZ) Induced Convulsions

There was complete abolition of the convulsions in the standard Diazepam (4mg/kg, i.p.) treated group. Whereas in the CMPE (200mg/kg and 400mg/kg) treated groups, there was a notable delay in the onset of the convulsions, in addition, the duration of clonic convulsions had distinctly decreased. The results of all the treatment groups were compared with the control as shown in Table. 2 and Fig. 2 & Fig. 3.

Table. 2: Effect of hydroalcoholic extract of *C. maxima* fruit-peel in PTZ induced convulsions in mice.

GROUP	TREATMENT	ONSET OF CONVULSIONS (sec)	DURATION OF CONVULSIONS (sec)	PERCENTAGE MORTALITY (%)
Control	Normal Saline (0.9% w/v)	65.83 ± 6.700	510.5 ± 5.169	66.66%
Standard	Diazepam (4mg/kg)	0.00***	0.00***	Protected
Extract Dose-1	<i>Citrus maxima</i> peel extract (CMPE) (200mg/kg)	70.83 ± 4.393 ^{ns}	360.0 ± 10.15***	33.33%
Extract Dose-2	<i>Citrus maxima</i> peel extract (CMPE) (400mg/kg)	111.2 ± 4.339***	206.7 ± 10.14***	16.66%

Values are expressed as mean ± S.E.M, (n=6). Statistical comparison was performed by using one way ANOVA followed by Dunett's test. ***P<0.001 is considered statistically significant when compared with control group. ns is non-significant. (Mortality- Control: 4 animals, Standard: nil, Extract Dose-1: 2 animals, Extract Dose-2: 1 animal.)

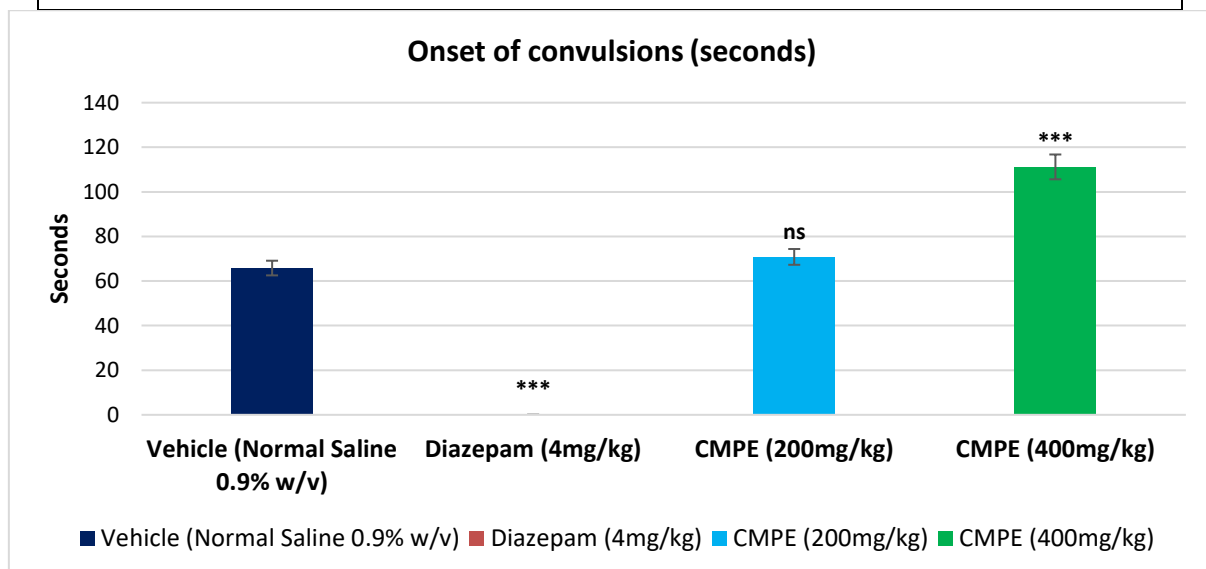


Fig. 2: Effect of hydroalcoholic extract of *C. maxima* fruit-peel on Onset of convulsions in PTZ induced convulsions in mice.

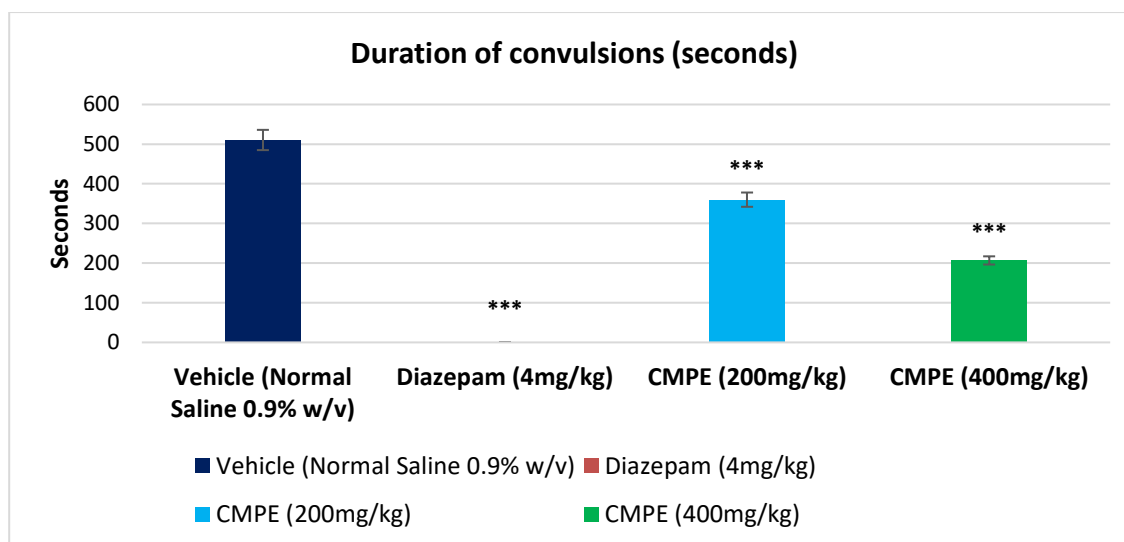


Fig. 3: Effect of hydroalcoholic extract of *C. maxima* fruit-peel on Duration of convulsions in PTZ induced convulsions in mice.

IV. DISCUSSION

Epilepsy is one of the most common neurological disorders. Epilepsy is defined as recurrent unprovoked seizures generated from excessive and abnormal cortical neuronal activity in the brain. An episode of epilepsy is characterized by a convulsive or non-convulsive seizure [20]. Most of the cases of epilepsy are idiopathic though some cases result from brain injury, stroke, brain tumour, severe malaria and drug abuse. Certain genetic mutations have also been implicated as causes of some cases of epilepsy [21,22]. The limited supply, high cost as well as low efficacy and adverse side effects of antiepileptic drugs (AEDs) is a matter of major concern. Herbal medicine has always been traditionally part of treatment of epilepsy due to the therapeutic potential of their bioactive compounds, with Africa and Asia being the continents with most of the users. Herbal medicines are generally well tolerated, with fewer side effects [23].

This study was carried out to investigate the effects of *Citrus maxima* fruit-peel hydroalcoholic extract on Maximal Electroshock (MES) induced convulsions which resemble generalized tonic-clonic seizures and Pentylentetrazole (PTZ) induced convulsions which resemble clonic-type seizure in experimental mice models to evaluate its antiepileptic activity. The MES model permits the evaluation of ability of a substance to prevent seizure spread through neural tissue. Voltage-gated sodium channels play an essential role in the initiation and propagation of action potentials in neurons. Stimulation through ear-clip electrodes activates the brain stem. As the components of tonic seizures have been shown to depend on the brain-stem, trans-auricular stimulation is followed by an immediate severe tonic seizure with maximal extension of the anterior and posterior legs occurs and the body becomes stiffened. There is a high correlation demonstrated between ability of a drug to inhibit MES in rodents and its efficacy in generalized tonic-clonic seizures in humans. Phenytoin, carbamazepine and lamotrigine, for example, act primarily on voltage-dependent Na^+ channels and elevate seizure thresholds in epileptogenic foci [24,25]. Phenytoin is a hydantoin derivative, a first-generation anti-convulsant drug that is effective in the treatment of generalized tonic-clonic seizures, complex partial seizures, and status epilepticus without significantly impairing neurological function. Phenytoin works by blockade of voltage-dependent membrane sodium channels responsible for increasing the action potential. Through this action, it obstructs the positive feedback that sustains high-frequency repetitive firing, thus preventing the spread of the seizure focal point. There are several ADRs associated with phenytoin treatment which potentially include, Rash, Sedation, Peripheral neuropathy, Phenytoin encephalopathy, Psychosis, Locomotor dysfunction, Megaloblastic anaemia, Decreased bone mineral content, gingival hyperplasia, Cardiovascular collapse, Hypotension, Arrhythmias, Hydantoin syndrome in new-borns [26].

PTZ's mechanism of action is related to inhibition of the function of GABA neurotransmitter. GABA_A receptor complex consists of a number of binding sites for GABA itself, benzodiazepines, barbiturates, ethanol and picrotoxin which is a chloride channel blocker. When GABA binds to its recognition site on the GABA_A receptor complex, an opening of the chloride channel occurs with the subsequent influx of chloride anions into a neuron, resulting in its hyperpolarization. PTZ has a good affinity for the Clonophore of the postsynaptic GABA receptor complex antagonising the GABA mediated inhibition. Administration of PTZ is manifested as Myoclonic jerks and clonic seizures [27]. Benzodiazepine derivatives such as Diazepam, clonazepam etc. increase the frequency of the chloride channel openings, leading to an increased conductance of chloride ions and are used as GABA agonists in treatment of epilepsy [28]. Serious adverse effects of diazepam include, Respiratory depression, Suicidality, Dependency and abuse, Withdrawal symptoms, Cardiovascular collapse, Bradycardia, Hypotension, Syncope, Paradoxical CNS stimulation [29].

Preliminary phytochemical studies of *C. maxima* fruit-peel revealed the presence of Alkaloids, Flavonoids, Saponin glycosides, Tannins, Steroids, Carbohydrates and Phenols. With regard to the presence of Flavonoids in the Pomelo fruit-peel the antiepileptic effect was studied on the basis of its traditional medicinal claim.

Flavonoids are bioactive compounds that are proven to possess neuroactive properties and many of these compounds are ligands for GABA_A receptors in the central nervous system (CNS) and act as benzodiazepine-like molecules. These facts are supported by their behavioural effects in animal models of anxiety, sedation and convulsion [30,31]. Furthermore, studies have shown that flavonoids such as Rutin and Apigenin showed significant antiepileptic activity in experimental

animal models due to its ability to reduce the GABA-activated chloride currents suggesting a selective activity at GABA_A receptor level. These flavonoids which are found in buckwheat, apples, black tea and chamomile are also present in *Citrus maxima* (Pomelo) fruit peel [31,32,33]. Flavonoids in Citrus peels have been reported to be extracted using ethanol 80% v/v [15]. Hence a hydroalcoholic extract of the *Citrus maxima* fruit peel was prepared for this study using ethanol: water (4:1) as solvent.

Many flavonoids have well-established antioxidant and free-radical-scavenging activities, and it was initially believed that their protective effects were as a direct result of these actions. However, it is now accepted that in addition to their ability to prevent damage caused by oxidative stress, flavonoids also exert their biological effects through direct actions on enzymes, receptors and signalling pathways. The CNS actions of flavonoids are primarily associated to their effect on inotropic GABA_A receptors. Flavonoids can bind to the benzodiazepine-binding sites of receptors GABA_A, receptors and consequently alter their activities. This can be credited to their relatively rigid shape. Flavonoids are typically a phenyl benzopyran chemical structure consisting of two aromatic rings and an oxygen containing heterocyclic benzopyran ring. Wide range of natural and synthetic flavonoids were investigated in vitro and in vivo as potential leads for new benzodiazepine ligands. GABA_A receptor is known to be pivotal in the mechanism for antiepileptic drug action. Determination of GABA ratios have shown the impact that ligand binding has on the GABA binding, using this it was established that the flavones exhibited the full spectrum of biological activities at benzodiazepine receptors [34]. The flavones Rutin and apigenin which are abundantly found in Citrus fruit peels such as *Citrus maxima*, made it a potential candidate for the current study [14].

In Maximal Electroshock (MES) model the extract showed moderately significant protective activity against epilepsy at both the doses (200mg/kg and 400mg/kg) in a possible dose dependent manner. There was only a slight improvement seen in the extract Dose- 2 group when compared to Dose-1. The Phenytoin (25mg/kg) treated standard group showed complete abolition of the HLTE phase. Whereas the duration of Hind Limb Tonic Extension (HLTE) phase was notably reduced by the extract in both Dose-1 and Dose-2 when compared to the control group. The percentage inhibition (%) of HLTE was calculated and suggests protective action of the extract doses.

In Pentylentetrazole (PTZ) model the extract showed strongly significant antiepileptic activity at both the extract doses (200mg/kg and 400mg/kg) in a dose-dependent manner. There was a good suppressive activity seen against the duration of PTZ induced convulsions by both the extract doses when compared to the control group. The delay in onset of convulsions was significant at Dose-2 of extract in comparison to control. The Diazepam (4mg/kg) treated standard group showed complete abolition of the convulsions and 100% protection against mortality. Protection against mortality was observed in a dose-dependent manner with regards to the extract treated groups.

The results obtained in the present study suggest that the hydroalcoholic extract of *Citrus maxima* fruit peel was found to be effective against both the Maximal Electroshock (MES) and Pentylentetrazole (PTZ) induced convulsion models for epilepsy in mice. And the antiepileptic activity was of high statistical significance in PTZ-induced convulsion model than MES-induced convulsion model suggesting that the bioactive compounds of the hydroalcoholic extract of *Citrus maxima* fruit peel may primarily act through the GABA_A receptor mediated mechanism of action of antiepileptic agents by overcoming the PTZ's GABA antagonistic effect on GABAergic function hence potentiating the GABA_A-benzodiazepine receptor complex mediated inhibitory action which results in an increase in the permeability of the membrane to the chloride ion (Cl⁻), which reduces the cellular excitability. Secondly, the results from MES model suggest that the bioactive compounds may also possess the ability to prevent seizure spread through neural tissue by reducing the excitability of the electrical cell membranes, in particular by blocking the voltage-dependent sodium ion (Na⁺) channels that are responsible for the inward current that generates an action potential [35].

However, the exact mechanism of antiepileptic potential is still unclear and can be further investigated. Further studies are needed to isolate, characterize the active principles and to find out the exact mechanism responsible for the antiepileptic activity. Nonetheless this study provides a good lead on the antiepileptic potential of the *Citrus maxima* fruit peel.

V. CONCLUSION

Many herbal medicines have been recommended for the treatment of Epilepsy. In the present study the fruits of *Citrus maxima* (Pomelo) were procured, their peels were collected and subjected to extraction process to form the hydroalcoholic extract (CMPE). The test compounds of CMPE given at 200mg/kg and 400mg/kg body weight by oral route was studied for its antiepileptic potential by using the Maximal Electroshock (MES) induced and Pentylentetrazole (PTZ) induced convulsion models in experimental mice. The preliminary phytochemical screening of the hydroalcoholic extract of *Citrus maxima* (Pomelo) fruit-peel revealed the presence of Alkaloids, Flavonoids, Saponin glycosides, Tannins, Steroids, Carbohydrates and Phenols. The observed anti- epileptic activity might be due to the presence of these phytoconstituents with emphasis to the flavonoids by virtue of their scientifically established neuroactive properties. From experimental data it can be concluded that the CMPE showed a plausible protective activity against epilepsy at both the extract doses in MES-model. A dose-dependent action is seen but with only a slight improvement of activity in the 400mg/kg treated group compared to 200mg/kg treated group. Whereas the CMPE showed a more distinct, dose-dependent protective activity against epilepsy at both extract doses in PTZ- model.

The possible mechanism of action might be primarily due to the GABA_A agonistic activity, potentiating the GABA_A-benzodiazepine receptor complex mediated inhibitory action resulting in reduction of the cellular excitability due to chloride ion (Cl⁻) mediated hyperpolarization; as depicted by the results from PTZ model. Secondly, the ability to prevent seizure spread through neural tissue by reducing the excitability of the electrical cell membranes, such as by blocking the voltage-dependent sodium ion (Na⁺) channels responsible for action potential generation; as depicted by the results from MES model.

From this study it can be concluded that the hydroalcoholic extract of *Citrus maxima* (Pomelo) fruit-peel does have antiepileptic potential. Though the results showed significant protection against epilepsy, further investigation needs to be carried out to isolate the bioactive compounds, precise mechanism(s) of action, and the safety profile of the plant as a medicinal remedy for epileptic disorders.

VI. ACKNOWLEDGMENT

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