Neuropharmacological Activities of Ethanolic Extract of *Citrus macroptera* (Varannamensis) Fruit Peels

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**Abstract:** The objective of present work is to study neuropharmacological activities of ethanolic extract of *Citrus macroptera* (varannamensis) (EECM) fruit peels. Material and Methods: in this study, mice were treated with 250 mg/kg and 500 mg/kg of EECM for seven days and after neuropharmacological activities were assessed using experimental animal models. Anxiolytic activity was assessed using Elevated Plus Maze (EPM) and Light and Dark Model (LDM) in mice. Anti-depressant activity was assessed using Forced Swim Test (FST) and TailSuspension Test (TST) in mice. Anti-epileptic activity was assessed using Maximum Electro Schok (MES) and Pentylenetetrazole (PTZ) induced seizure in mice. Moreover, After treatment period brain anti-oxidant enzyme levels was estimated. Results acute oral toxicity studies of ethanolic extract of *Citrus macroptera* (EECM) fruit peels were carried out according to OECD-423 guidelines in mice and found to be non toxic. Ethanolic extract of *Citrus macroptera* (EECM) fruit peels increases no. of entries and time spent in open arms in EPM and increases no. of entries and time spent in light chamber in LDM in mice. Ethanolic extract of *Citrus macroptera* (EECM) fruit peels FST and TST in mice, decreases duration of immobility. In MES and PTZ induced method, extract potentiate epileptic seizure in mice. Moreover, brain anti-oxidant enzymes levels were found to be improved. Conclusion: ethanolic extract of *Citrus macroptera* fruit peels (EECM) found to posses anti-depressant and anxiolytic but does not possess anti-epileptic rather it found to potentiate epileptic Seizurein mice.

**Key words:** *Citrus macroptera* · Neuropharmacological Activities · Anxiolytic · Anti-Depressant · Anti-Epileptic · Anti-Oxidant Enzymes

**INTRODUCTION**

*Citrus macroptera* (Varannamensis) belongs to the family of Rutaceae and it is native to the regions of Southeast Asia mainly Myanmar, Thailand, Indonesia, Malaysia, Papua New Guinea, Sylhet Division of northeastern Bangladesh and northeastern India mainly Manipur and Assam. Local in Bengali it is called "hatkora" or "shatkora" and in English known as Wild orange [1, 2].

The fruit of *Citrus macroptera* (varannamensis) is edible and popular among the people of Bangladesh, Meghalaya and Assam of India as green matured fruits are used in cooking for flavoring curry mainly meat dishes, pickle preparation and oil is used in perfume production [3].

There are very less literature available for its therapeutic value. It is reported that stem bark of *Citrus macroptera* possesses antioxidant activity [4], Essential oil obtained from leaves possesses antimicrobial activity [5] and traditionally fruits as appetite stimulant and treatment of fever [6]. Essential oil of *Citrus macroptera* leaves contains mainly terpenoids like limonene and aromatic hydrocarbons [5, 7, 8] and Lupeol and Stigmasterol [4].

Most of the literature says plant extracts having anti-oxidant activities have health promoting effects, anti-ageing effects and used for various metabolic and chronic disease like cancer, live diseases, inflammation, diabetic, arthritis, strok [34, 35] etc. There is relatively little published work on the neuroprotective effects of herbal extracts or natural phytochemicals having anti-oxidant
activities. Phytochemicals containing flavonoids, polyphenols and organosulfur compounds have neuroprotective effects, as shown experimentally in cell and animal studies [9, 10].

There are little literature available for neuropharmacological activities Citrus macroptera (Varannamensis) and the present study is a continuation of our previous investigation in which we studied in-vitro anti-oxidant activities of n-Hexane, Chloroform and Ethanol extract of Citrus macroptera (Varannamensis) fruit peels [11]. We found that ethanol extract of Citrus macroptera fruit peels possess highest anti-oxidant activity in-vitro [11]. Therefore, the objective of present work is to study the neuropharmacological activities of ethanolic extract of Citrus macroptera (Varannamensis) (EECM) fruit peels.

**MATERIAL AND METHODS**

**Plant Material and Extraction Procedures:** The fruits of Citrus macroptera Var. annamensis were collected from local areas of Assam state and was authenticated by Prof. Dr.K.Madhavachetty, Taxonomist, SVU University, Chithoor andhra Pradesh (India). The air dried peels were made into coarse powder and extracted with Ethanol. The % yield was found to be 22.4% w/w.

**Preliminary Phytochemical Analysis:** The ethanolic extracts of Citrus macroptera (EECM) Var. annamensis was tested for different Phytoconstituents like alkaloids, glycosides, saponinins, tannins, terpinoids, phenolic compounds, protein, carbohydrates using standard procedures [12, 38].

**Experimental Animals:** Mice of either sex weighing 25-30 g of body weight were used in experiment. Animals were obtained from Anurag Pharmacy College, Kodad. Animals were kept under standard conditions at 23-25°C for 12 hr light/dark cycle and given standard pellet diet and water. The animals were accustomed to the laboratory conditions for a week prior to the experiment. The fresh diet and water for the animals has to be supplied daily to the animals. The condition of the animals has to be supervised daily till the completion of the experiment. Before using animals, IAEC permission was taken as per CPCSEA guideline.

**Acute Oral Toxicity Studies:** Acute oral toxicity studies of ethanolic extract of Citrus macroptera (EECM) fruit peels was carried out according to OECD-423 guidelines in mice using starting dose of 2000 mg/kg, p.o.. The animals exhibited normal behaviour, without any signs of passivity, stereotypy and vocalization.

**Experimental Design:** On the day of the experiment, the animals were divided randomly into six groups of six animals each and treated with drugs for 1 weak. The ethanolic extract of Citrus macroptera (EECM) fruit peels used by dissolving in olive oil.

- **Group I:** Control (Vehicle, Olive oil, p.o)
- **Group II:** EECM (250mg/kg in olive oil, p.o)
- **Group III:** EECM (500mg/kg in olive oil, p.o)
- **Group IV:** Standard (Diazepam; 10mg/kg, in 1% Tween 80, p.o)
- **Group V:** Standard drug (Imipramine; 10mg/kg, p.o in 1% Tween 80)
- **Group VI:** Phenytoin (25mg/kg, in 1% Tween 80, p.o)

Behavioural evaluation was carried out on the last day (7th Day) at 60 minutes post drug/vehicle administration. At end of treatment, on the 8th Day, the animals were sacrificed by cervical dislocation and the whole brain were dissected out, blotted free of blood, transferred to trays maintained at ice-cold conditions by rinsing with ice-cold physiological saline. 50 mg of the brain tissue was weighed and homogenate was prepared in 5 ml tris hydrochloric acid buffer (0.5 M; pH 7.4) at 4°C. The homogenate was then centrifuged for 10 minutes at 10,000 rpm and the resultant supernatant was used for the biochemical determinations of antioxidant enzymes.

**Evaluation of Anxiolytic Activity:** The Anxiolytic activity of ethanolic extract of Citrus macroptera (EECM) fruit peels was evaluated using Elevated Plus Maze (EPM) [13, 37] and Light-Dark Model (LDM) [14, 15] in mice comparing with standard diazepam. All the rodents have aversion for height and open space, they prefer to hide in enclosed arm therefore, spend greater amount of time in enclosed arm. Anxiolytic effect statistically increase in open time or open entries. The plus-maze apparatus, consisting of two open arms (16 x 5 cm) and two closed arms (16 x 5 x 12 cm) having an open roof. The drugs and vehicle were administered orally at their respective doses and compared with standard diazepam. After proper
treatment with drugs each mouse was placed at the center of the maze with its head facing the open arm. During the 5 min experiment, the behavior of the mouse was recorded as the number of entries into the open or closed arms and time spent by the mouse in each of the arms. An arm entry was defined as the entry of all four paws into the arm.

The light-dark model works on the principal that the light/bright environment works as source of anxiety and Anxiolytic effect statistically significant increase in light (Movement) time or number of transition. The mice’s light-dark box (40cm ×20cm ×20cm) consists of two parts, the light-compartment and the dark compartment. The box consists of a hole (5cm×5cm) in the bottom of the clapboard between the two compartments. The mice were treated with drugs and vehicles as respective groups and after one hour of treatment each mice during the test the mice were put into the center of the light compartment with their back to dark compartment and then transition behavior over 5 min was observed. Number of crossings between the light and dark area and total time spent in the illuminated part of the box were calculated. Every time before placing each animal, the maze was cleaned with 5% alcohol to eliminate the possible bias due the odor left by the previous animal.

**Evaluation of Anti-Depressant Activity:** The antidepressant activity of ethanolic extract of *Citrus macroptera* (EECM) fruit peels was evaluated using Forced Swim Test (FST) [16, 17] and Tail Suspension Test (TST) [17, 18] in mice by comparing with standard drug Imipramine.

Antidepressant activity was evaluated by using Porsolt’s Forced Swing test in mice [18]. This works on the basic principle of antidepressant effect statistically decrease in immobility and behavioral despair in rodents. The Apparatus consist of a water tub of 60 cm (Inner diameter) and 35 cm (height) was used. It was filled with water (27-29°C) up to a height of 15 cm. For the evaluation of drugs, we used Porsolt’s Forced Swim Test [18]. All the animals were treated for one week with drugs. On day 1, each animal was dropped in water and was forced to swim for 6 min. It was then wiped dry and returned to home cage. On day 7th, mice were treated with drugs as mention in respective groups and control receive only vehicle. After a gap of 1 hour they were subjected to the swim test. In accordance with Porsolt et al., mice were kept in water for 6 min. The duration of immobility was recorded during the last 4 minutes of the observation period because each animal showed vigorous movement during initial 2 min period. The duration of the mouse was considered immobile when it floated motionlessly or made only those moments necessary to keep its head above the water surface. The water was changed after each test. The test was conducted in a dim lighted room and each mouse was used only once in the test.

In Tail Suspension test works on the principle of Antidepressant effect significant decrease in escape oriented movement immobility (Hanging) in rodents. The animals were hung by the tail on a plastic string 50 cm above the surface with the help of an adhesive tape, placed approximately 1 cm from the tip of the tail. Each animal under test was both acoustically and visually isolated from other animals during the test. The duration of immobility was observed for a period of 8 minutes. The duration of immobility was recorded during the last 6 minutes of the observation period. Mice were considered to be immobile only when they hung passively and were completely motionless. The test was conducted in a dim lighted room and each mouse was used only once in the test.

**Evaluation of Anti-epileptic Activity:** The anti epileptic activity of ethanolic extract of *Citrus macroptera* (EECM) fruit peels is evaluated using experimental maximum electric shock (MES) [19, 20] and Pentylenetetrazole (PTZ) [20]induced seizures in mice and compared with standard drug Phenytoin. In MES, after 60 min of treatments on 7th day, each mice were given electro convulsive shock 60m A for 0.2 sec through corneal electrode to induce convulsions. The various phases of convulsion which were produced are flexion, extension, clonus and stupor. Prior to delivery, the current output was checked by multimeter. After the electric stimulation occurrence, the duration of phases were noted.

In PTZ induced seizure 60mg/kg was administrated subcutaneously after 60 min of administration of last dose of drugs on 7th day and various and onset of action and duration of convulsion were noted. Each animal was then placed in to individual plastic cages and were observed initially for 30 min and later up to 24 hrs.

**Estimation of Brain Anti-oxidant Enzymes:** The Superoxide dismutase SOD activity in supernatant was measured by the method of Misra and Fridovich [21] and Modified by Habibur Rahman et al. [22].

Catalase activity was measured by the method of Aebi [23]. Modified by Habibur Rahman et al. [22].
Lipid peroxides (LPO) was estimated by the Thiobarbituric acid reaction method described by Ohkawa et al. [24] modified by Habibur Rahman et al. [22].

**Statistical Analysis:** The data were expressed as mean ± standard error mean (SEM). The data were analyzed by using GraphPad software version-5 by one way analysis of variance (ANOVA). The test was followed by Dunnett’s ‘t’-test, *p* values less than 0.05 were considered as significant.

**RESULTS**

**Preliminary Phytochemical Analysis:** The ethanolic extract of *Citrus macroptera* (EECM) fruit peel extracts were tested for different phytoconstituents using standard procedures and ethanol extract was found to contain like alkaloids, tannins, terpinoids, phenolic compounds, flavanoids and volatile oils.

**Anxiolytic Activity of ethanolic extract of *Citrus macroptera* (EECM)**

**Effect of EECM for Anxiolytic Activity on EPM in Mice:**
The effect of pretreatment with EECM with (250 mg/kg, p.o and 500 mg/kg,p.o) for 7 days showed increase in no. of entries and time spent in open arm of EPM in mice and the result are shown in Table 1. The effect on no. of entries and time spent in open arm of EPM were compared with Standard (Diazepam; 10mg/kg, p.o) which showed significant increase in no. of entries and time spent in open arm of EPM.

**Effect of EECM for Anxiolytic Activity on Dark-Light Model:** The effect of pretreatment with EECM with (250 mg/kg, p.o and 500 mg/kg,p.o) for 7 days showed increase in spent in light chamber in Dark-light Model in mice and the result are given in Table 2. The effect on spent in light chamber in Dark-light Model in mice were compared with Standard (Diazepam; 10mg/kg, p.o) which showed significant increase in spent in open chamber.

**Anti-Depressant Activity of Ethanol Extract of *Citrus macroptera* (EECM):** The effect of pretreatment with EECM with (250 mg/kg, p.o and 500 mg/kg,p.o) for 7 days showed decreased in duration of immobility both in Forced Swim Test and Tail Suspension Test in mice and the result are given in Table 3. The effect on duration of immobility were compared with Standard (Imipramine; 10mg/kg, p.o) which showed significant decrease in duration of immobility.

**Anti-Epileptic Activity on MES and PTZ Model in rats:** There was no significant effect of percentage protection in MES model in drug treated animals. Moreover, EECM treated group potentiate epileptic seizures and increases duration of tonic hind limb extension in MES method and

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>No. of entries / 5min</th>
<th>Time spent (Sec)/5min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Open arm</td>
<td>Close arm</td>
</tr>
<tr>
<td>Group I</td>
<td>Control (Vehicle, Olive oil, p.o)</td>
<td>4.50±0.3</td>
<td>7.6±0.8</td>
</tr>
<tr>
<td>Group II</td>
<td>EECM (250mg/kg in Olive oil,p.o)</td>
<td>5.37±0.7</td>
<td>8.45±0.45</td>
</tr>
<tr>
<td>Group III</td>
<td>EECM (500mg/kg in Olive oil,p.o)</td>
<td>5.8±0.5</td>
<td>9.80±0.7</td>
</tr>
<tr>
<td>Group IV</td>
<td>(Diazepam; 10mg/kg, in 1% Tween 80, p.o)</td>
<td>7.66±0.2</td>
<td>8.45±0.6</td>
</tr>
</tbody>
</table>

(Values are in Mean±S.E.M (n=6); *p*-Non Significant, *p*<0.05, **p*<0.01, ***p*<0.001 when compared with Control using One way ANOVA followed by Dunnet’s “t” test.)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>Time spent in Dark chamber (Sec) Mean±SEM</th>
<th>Time spent in Light-chamber (Sec) Mean±SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Control (Vehicle, Olive oil ; 10ml/kg, p.o)</td>
<td>220.5±7.85</td>
<td>66±3.99</td>
</tr>
<tr>
<td>Group II</td>
<td>EECM (250mg/kg in olive oil,p.o)</td>
<td>212.56±6.88</td>
<td>76.67±3.95</td>
</tr>
<tr>
<td>Group IV</td>
<td>EECM (500mg/kg in olive oil,p.o)</td>
<td>210.5±6.78</td>
<td>93.83±6.002</td>
</tr>
<tr>
<td>Group V</td>
<td>(Diazepam; 10mg/kg, in 1% Tween 80, p.o)</td>
<td>172.43±7.54</td>
<td>120.2±5.48</td>
</tr>
</tbody>
</table>

(Values are in Mean±S.E.M (n=6); *p*-Non Significant, *p*<0.05, **p*<0.01, ***p*<0.001 when compared with Control using One way ANOVA followed by Dunnet’s “t” test.)
Table 3: Effect of EECM on duration of immobility in Forced Swim Test (FST) and Tail Suspension Test (TST) in mice

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug Treatment</th>
<th>Forced Swim Test</th>
<th>Tail Suspension Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Control (vehicle, olive oil, p.o)</td>
<td>116.5±4.18</td>
<td>136.2±5.12</td>
</tr>
<tr>
<td>I</td>
<td>EECM (250mg/kg in olive oil, p.o)</td>
<td>91.67±5.48</td>
<td>97.17±4.83</td>
</tr>
<tr>
<td>III</td>
<td>EECM (500mg/kg in olive oil, p.o)</td>
<td>67.83±3.31</td>
<td>86.17±5.71</td>
</tr>
<tr>
<td>V</td>
<td>Standard (Imipramine; 10mg/kg, p.o in 1% Tween 80)</td>
<td>82.33±4.70</td>
<td>74.33±4.47</td>
</tr>
</tbody>
</table>

Values are in Mean ±S.E.M (n=6); ns - Non Significant, *p<0.05, **p<0.01, ***p<0.001 when compared with Control using One way ANOVA followed by Dunnetts multiple “t” test

Table 4: Effect of EECM on MES and PTZ induced convulsions in mice

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>Maximum Electric Shock (MES)</th>
<th>PentyleneTetrazole (PTZ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Onset time (Sec)</td>
<td>Duration of tonic hind limb extension (sec)</td>
</tr>
<tr>
<td>Group I</td>
<td>Control (Vehicle, olive oil, p.o)</td>
<td>1.50±0.34</td>
<td>7±0.73</td>
</tr>
<tr>
<td>Group II</td>
<td>EECM (250mg/kg in olive oil)</td>
<td>0.86±0.08</td>
<td>16.33±0.95</td>
</tr>
<tr>
<td>Group III</td>
<td>EECM (500mg/kg in olive oil)</td>
<td>0.75±0.11</td>
<td>20.5±1.72</td>
</tr>
<tr>
<td>Group VI</td>
<td>Phenytoin (25mg/kg, in 1% Tween 80, p.o)</td>
<td>No extension</td>
<td>0</td>
</tr>
</tbody>
</table>

*= Inhibition, †= stimulation

Table 5: Effect of EECM on In-vivo anti-oxidant enzymes in mice brain

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>SOD (unit/mg wet tissue)</th>
<th>Catalase (unit/mg tissue)</th>
<th>LPO (unit/mg wet tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Control (Vehicle, olive oil, p.o)</td>
<td>1.65±0.02</td>
<td>2.13±0.02</td>
<td>136±±6.75</td>
</tr>
<tr>
<td>Group II</td>
<td>EECM (250mg/kg in olive oil)</td>
<td>1.815±0.03</td>
<td>3.11±0.04</td>
<td>206±±3.94</td>
</tr>
<tr>
<td>Group III</td>
<td>EECM (500mg/kg in olive oil)</td>
<td>2.12±0.03</td>
<td>3.35±0.04</td>
<td>216±±4.64</td>
</tr>
</tbody>
</table>

duration of convulsion in PTZ method. Standard drug Phenytoin significantly protected in MES method but non significant in PTZ method. The results were given in Table 4.

**Effect of EECM on In-vivo Anti Oxidant Enzymes Levels:**

In-vivo antioxidant studies of isolated brains from mice were estimated by using standard procedure and results are given in Table 5. EECM found to improved anti-oxidant enzyme levels in treated group compared to normal groups.

**DISCUSSION**

The fruit peels of *Citrus macroptera* were made coarse powder and extracted with using n-hexane, chloroform and ethanol as solvents using standard procedure and found ethanolic extract have highest percentage yield [11]. *Citrus macroptera* fruit peels extract tested for different phytoconstituents like alkaloids, glycosides, saponinins, tannins, terpinoids, reducing sugars, phenolic compounds, flavanoids, protein, carbohydrates and volatile oils. The Knowledge of the chemical constituents of plants is desirable because such information will be valuable for synthesis of complex chemical substances and to screen for biological activities [25, 26]. The phenolic and flavanoids are widely distributed secondary metabolites in plants having anti-oxidant activity and have wide range of biological activities as anti-apoptosis, anti-aging, anti-carcinogen, anti-inflammation, anti-atherosclerosis, cardiovascular protection and improvement of endothelial function, as well as inhibition of angiogenesis and cell proliferation activities [27].

In-vitro antioxidant studies are widely carried to screen various plant containing phenolic and flavanoids constituents [36, 38]. Plant derived antioxidant compounds, flavonoids and phenolics have received considerable attention because of their physiological effect like antioxidant, anti-inflammatory, antitumor activities and low toxicity compared with those of synthetic phenolics antioxidant such as BHA (ButylatedHydroxyanisole), BHT (Butylated Hydroxytoluene) and Propyl Gallate (PG) [28, 29].
The Total phenolic contents of Ethanolic extract of *Citrus macroptera* (EECM) fruit peels were estimated using standard Gallic acid equivalent of phenols and found 142.5mg/g equivalent of Gallic Acid [11] and total Flavanoid content 333.00 mg/g equivalent of Quercetin [11]. Ethanolic extract of *Citrus macroptera* (EECM) fruit peels posses highest anti-oxidant activities in-vitro methods [11].

Anxiety and depression form commonest stress-induced psychiatric disorders. To combat the biochemical changes which occur as a result of stress, there is antioxidant defence in the biological system. The role of anti-oxidant phytoconstituents widely screened for various diseases, such as cardiovascular disease, cancer, inflammation and allergy. But very less literature suggest the evidence for CNS diseases. A few studies available which suggest that antioxidant supplement therapy like vitamins A, C and E as an adjuvant therapy is useful in patients with stress-induced psychiatric disorders and the results have been discussed [30].

Anxiolytic activity was evaluated using Elevation of Plus Maze and Light-Dark Transition Models were used. The elevated plus maze is a well-established animal model for testing anxiolytic drugs [31]. It was found that dose dependent way theethanolic extract of *Citrus macroptera* (EECM) increases no. of entries and time spent in open arms but was less effective then standard diazepam.

In Light-Dark Transition test, the apparatus contains two compartments i.e. light and dark. Animals always try to spend more time in dark compartment because of fear about new environment. The light-dark test may be useful to predict the anxiolytic like activity of drugs in mice. Transitions have been reported to be an index of activity exploration because of habituation over time and the time spent in each compartment to be a reflection of aversion[32]. It was found that dose dependent way theethanolic extract of *Citrus macroptera* (EECM) increases no. of entries and time spent in light chamber but was less effective than standard diazepam.

Anti-depressant activity was evaluated using Forced Swim Test(FST) and Tail Suspension Test (TST) in mice. Ethanolic exact of *Citrus macroptera* (EECM) fruit peels showed dose dependent decreased duration of immobility but lower than standard imipramine. The decreased duration of immobility in Forced Swim Test reveals antidepressant activity [16].

Tail Suspension Test (TST) is a simple, rapid and reliable method to screen antidepressants and other class of psychotropics. TST induced immobility is reduced by a large no of clinically active and atypical antidepressants [33]. The ethanolic extract of *Citrus macroptera* (EECM) fruit peels showed dose dependent decreased duration of immobility but lower than standard imipramine. The decreased duration of immobility in reveals antidepressant activity of the plant.

Ethanolic extract of *Citrus macroptera* fruit peels (EECM) was evaluated for anti-epileptic activity in MES and PTZ induced Seziure in mice. It is found that extract does not have anti-epileptic activity rather it found to potentiate epileptic Seizure in animal models.

In-vivo antioxidant studies of isolated brains from mice reveals that protection of the EECM against the free radicals which are generated during oxidative stress. The in-vivo studies were performed for Superoxide dismutase, catalase and lipid peroxidation activity. The enzyme levels unit/mg wet tissue values were increased significantly in EECM treated animals.

**CONCLUSION**

Ethanolic extract of *Citrus macroptera* fruit peels (EECM) was evaluated for neuropharmacological activities found to have anti-depressant, anxiolytic but does not have anti-epileptic rather it found to potentiate epileptic Seizure in animal models.

EECM found to protect from oxidative stress in brain and it was found to protect brain antioxidant enzyme levels in in-vivo.

Finally, it can be concluded that neuroprotective activity of *Citrus macroptera* fruit peels may due to protection from oxidative stress and it may prove the tradition uses of *Citrus macroptera* fruit peels for anxiety and depression in Assam.

**REFERENCES**


