A SYSTEMIC STUDY OF CERTAIN NEUROPHARMACOLOGICAL AND ANTIOXIDANTS ACTIVITIES OF NARINGI CRENULATA (ROXB.) NICOLSON LEAVES

Shrikant M. Pundkar Research Scholar School Of Pharmacy Sunrise University, Alwar (Rajasthan)
Dr. Nandu Kayande, Associate Professor, School Of Pharmacy Sunrise University, Alwar (Rajasthan),
E-mail: shripundkar@gmail.com

ABSTRACT

Objective: Neuropharmacological effects of various extracts made from *Naringi crenulata* (Roxb.) Nicolson Leaves is the main objective of this stdy

Materials and methods: The leaves used to authenticate Naringi crenulata (Roxb.) were sourced from Wayanad in Kerala. Throughout the extraction procedure, higher polarity solvents such petroleum ether, chloroform, and methanol were utilised. The methanol extract was also separated with ethylacetate in order to produce ethyl acetate fractions. To ascertain the makeup of the phytoconstituents, all of the extracts and the fraction underwent a phytochemicals screening. Different quantities (5-640 g/mL) of chloroform, methanol, and ethylacetate fractions were utilised for various in-vitro antioxidant assay methods, such as the DPPH scavenging assay, hydroxyl radical scavenging assay, nitric oxide radical scavenging assay, and others. Ascorbic acid (AA) served as the standard.Neuropharmacological screening methods, such as sedative and hypnotic activity, anti-convulsant activity, were conducted on higher and lower dosages of NC. Catalase, SOD, GPx, and other enzymes. The in-vivo antioxidant studies on isolated liver used non-enzymatic antioxidants (GSH) as well. The concentrations of the brain neurotransmitters DA and GABA were also measured in MENC and EAFNC. The methanol extract was also partially purified using column chromatography, and the presence of bioactive compounds was checked by GC-MS thereafter.

Results: Alkaloids, phenolic chemicals, carbohydrates, and flavonoids were all found in Naringi crenulata (Roxb.) after a phytochemical examination. According to in-vitro antioxidant data, the scavenging property also got better as extract concentration did, too. This was followed by a rise in the percentage of inhibition, which revealed reduced IC50 values for all extracts together. The biggest scavenging effect with MENC was found in testing methods. Therefore, it was believed that this extract was advantageous when compared to other antioxidants. When measured against other groups in in vivo antioxidant activities, brain neurotransmitter estimation, and neuropharmacological screening procedures, the increased dose of MENC was shown to be significant. There were 26

bioactive compounds found in the MENC partially purified column fractions, some of which had medicinal promise.

Conclusion: The research revealed that extracts from Naringi crenulata (Roxb.) can be used as an antioxidant and to treat several neurological conditions.

Keywords: Antioxidant, MENC GC-MS, *in-vivo*, and *Naringi crenulata* (Roxb.), *in-vitro.*

INTRODUCTION

The number of receptors affects a neuropharmacological agent's activity by enhancing its selectivity, receptor affinity, and potency. The creation of new medications that can balance out chemical abnormalities in the nervous system is the main focus of neuropharmacology research, which also evaluates the degree of potency and safety of these medications for therapeutic usage.

Studies on how these medications affect other neurologic processes, such as behaviour, memory, emotions, and cognition, are also a part of this field.

They also show certain modification in psychological and psychosocial development in many volunteers in many diseases like as

Inflammatory diseases of brain The wide range of infection-related or alleged autoimmune disorders known as central nervous system inflammatory diseases are defined by immune-mediated tissue injury and inflammatory infiltrates in the CNS and spine areas.

As long as the blood brain barrier is intact, antibodies, with a few notable exceptions, cannot cause a unique inflammation cerebral illness.Even so, theyare crucial for enhancing and modulating inflammatory responses in the central nervous system that are brought on by T cells[1].

Meningitis Bacterial meningitis, which has been known for more than a century, is an inflammation of the meninges, particularly the arachnoid and the pia mater, caused by bacterial invasion of the subarachnoid space.

Neuronal injury, particularly in hippocampal structures, has recently been recognised as a potential factor in survivors' ongoing cognitive problems. A prompt diagnosis and following treatment are required for bacterial meningitis, which is a medical emergency[2].

Multiple Sclerosis: (MS) is a potentially devastating illness related to brain and spinal cord (central nervous system). Myelin, the protective sheath that protects nerve fibres, is attacked by the immune system, which impairs brain-to-body communication. The condition may eventually result in nerve degeneration or irreversible impairment. A chronic autoimmune condition known as multiple sclerosis

(MS) causes demyelination, gliosis, and neuronal death in the brain.

Neuromyelitisoptica: A condition of the central nervous system called neuromyelitisoptica (NMO) primarily affects the spinal cord and eye nerves (optic neuritis) (myelitis). NMO is sometimes referred to as Devic's disease and neuromyelitisoptica spectrum condition. It happens when the immune system of your body attacks its own cells in the central nervous system, primarily in the spinal cord and optic nerves, but occasionally in the brain as well.

Schizophrenia: Schizophrenia is a severe mental illness in which reality is perceived by sufferers strangely. Schizophrenia may include hallucinations, delusions, and severely irrational thinking and behaviour, which can make it difficult to go about daily activities and be incapacitating.

Autism: Autism, often known as autism spectrum disorder (ASD), is a phenomenal influence which targets both behaviour and communication of an individual. It may feature a variety of signs and abilities.

Epilepsy: Epilepsy is a symptomatic cerebrovascular sinus tachycardia is a group of neurological diseases. It appears as brief periods (convulsions) of altered cognition or absence of awareness, along with or without convulsive, sensory, orpsychological phenomen[3].

Anxiety: Anxiety is a typical psychiatric symptom that frequently coexists with a number of different surgery and clinical conditions. It is a common psychological feeling that is strongly related to appropriate fear and presumably serves as an adaptation mechanism both psychologically and physically.

Furthermore, there is a strong correlation between anxiety symptoms and depression, especially moderately severe chronic depression, panic disorder, agoraphobia, and other specific phobias, as well as eating disorders, obsessive-compulsive disorder, and a range of personality disorders[4]

Depression: Depression, which is a state of sadness, is a psychoneurotic disorder characterised by decreased mental and functional activity, sadness, trouble thinking clearly, trouble concentrating, disturbances in appetite and sleep, as well as feelings of hopelessness and dejection that can lead to suicidal thoughts. Depression has been linked to changes in the amounts of biogenic amines like NE, dopamine (DA), epinephrine, indolamine, serotonin, 5-hydroxytryptamine (5-HT), and two catecholamines in the brain[5].

The genus *Naringi crenulata* (Roxb.) Nicolson. is a member of the Rutaceae family. The trees can grow up to 8 metres tall, with a thorny trunk, smooth, dark grey bark, and a yellowish blaze. Terete, glabrous, and thorny young branchlets. Compound, imparipinnate, alternate, spiral leaves measure 5

cm in length; the rachis has oblanceolate wings and is glabrous. There are 5-7 opposite, sessile leaflets that are 2-4.5 x 1-1.5 cm in size, elliptic to obovate in shape, with an acute or emarginated base and a crenulate or irregularly serrulate margin. The massive tree base, trunk, wood, leaflets, and berries are all utilised as remedies in a variety of illnesses. Dysentery and epilepsy are treated with these leaves[6].

MATERIALS AND METHODS

PLANT MATERIAL

Table no: 1 Plant material

SL. NO	PLANT NAME	PART USED	FAMILY	COLLECTION PERIOD	PLACE OF COLLECTION
1.	*NaringicrenulataRoxb. Nicolson*	Leaves	Rutaceae	November	MS Swaminathan Botanical Garden, Wayanad, India

COLLECTION AND AUTHENTICATION OF *NARINGI CRENULATA (ROXB.)*

The herb was bought as follows.

Jithin.M. M. is the lead scientist who certified the leaves of *Naringi crenulata*, which were procured from Wayanad district in Kerala. MS Swaminathan Botanical Garden herbarium received the herbaria with the collection number 3989 and the accession numbers 654 and 655.

Wide spread leaves & flowers of *Naringi crenulata* (Roxb) Nicolson

PREPARATION OF PLANT EXTRACTS

The leaves for the study were prepared as such. Firstly the leaves of *Naringi crenulata* (Roxb.) were shade dried and ground up was extracted in a Soxhlet device using polarity of increasing chemicals, starting with petroleum ether, moving up to chloroform, and ending with methanol. Using a rotating vacuum evaporator, the lower pressure, liquids from the crude extracts were recovered. [7]

The methanol extract of 20 g of plant material was diluted uniformly in water, transferred to a flask with a flat bottom, separated with ethyl acetate, and heated at 50 ^{o}C for 30 min while being swirled till a fixed point .Thereafter the partitioning with ethyl acetate procedure required ten iterations to be successful.

A screening approach was used on the methanol extract and EAF of *Naringicrenulata* (Roxb.) Nicolson.

CALCULATION OF PERCENTAGE YIELD

Using the formula shown below, the percentage yield regarding the raw sample was established for the isolates and primary components.

$$\text{\% yield in relation to the raw plant component} = \frac{\text{Weight in grams of isolate achieved}}{\text{Weight in grams of plant content reserved}} \times 100$$

PRELIMINARY PHYTOCHEMICAL (QUALITATIVE) ANALYSIS OF EXTRACTS OF *NARINGI CRENULATA* (ROXB.)

The chemical experiments were performed individually on the extracts of leaves from *Naringi crenulata* (Roxb.) Nicolson in order to identify the distinct active ingredients [6].

ASSESSMENT OF THE *IN-VITRO* ANTIOXIDANT ACTIVITY OF LEAF EXTRACTS FROM *NARINGI CRENULATA* (ROXB.) NICOLSON

There is a need to estimate the antioxidant property of the herbal extract. Thus different *in-vitro* anti-oxidant parameters were evaluated

A) **DPPH (1, 1 diphenyl 2, picrylhydrazyl)**
B) **HYDROXYL RADICAL SCAVENGING ACTIVITY(HRSA)**
C) NITRIC OXIDE RADICAL SCAVENGING(NORS)

TOXICITY STUDIES OF EXTRACTS OF LEAVES OF *Naringi crenulata* (Roxb.)

ACUTE TOXICITY STUDIES

The examination and evaluation of all substances with hazardous properties often begin with a determination of their acute oral toxicity. Acute, sub-acute, and chronic toxicity are the sorts of toxicity tests that are frequently carried out by pharmaceutical firms in the examination of a new medicine.

Estimating LD_{50}—the dose that has been shown to be deadly (producing death) in 50% of the tested group of animals—involves consideration of acute toxicity. [10]

The Committee for the Purpose of Control and Supervision of Experimental Animals provided the (OECD) draught guidelines 423, which were used for the acute toxicity tests of *Naringi crenulata* (Roxb.) leaves.

ACCLIMATIZATION OF ANIMALS

Female Swiss Albino mice weighing 22–25g and Sprague Dawley rats weighing 150-200gm were kept in a regular laboratory setting at the Cape Bio-Lab & Research Centre, CSI Complex, Marthandam for experimental studies. [8-9]

ADMINISTRATION OF DOSES

The study involved three animals for each phase. Following the period of fasting, animals were forced to go without food and water for three hours before to medication delivery. Starting at a concentration of five milligram per kilo gram, it was subsequently raised to 50, 300, and 2000 mg/kg body composition for the study.[11-12]

EVALUATION OF *IN-VIVO* NEUROPHARAMCOLOGICAL SCREENING OF *Naringi crenulata* (Roxb.) Nicolson leaves.

Different activities and under each activity two studies were performed in order to analyze the *in-vivo* neuropharmacological screening with precession.[13]

ANTICONVULSANT ACTIVITY

6.5.2.a Pentylenetetrazole (PTZ) induced seizure Test

Table no: 4.5.2.a Effect of MENC & EAFNC on PTZ induced seizures

SL. NO:	THERAPY GROUP	START OF CONVULSIONS (Sec)	EXTENT OF CONVULSIONS (Sec)
1	PTZ control(80mg/kg)(s.c)	533.66±1.72	55.5±0.89
2	Phenytoin+PTZ(25mg/kg)(i.p)+(80mg/kg)(s.c	860.33±2.9[b]	11.33±0.71[b]

	)		
3	MENC+PTZ(400mg/kg)(po)+(80mg/kg)(s.c)	808.5±1.38[b]	18.33±0.42[b]
4	MENC+PTZ(200mg/kg)(po)+(80mg/kg)(s.c)	752.8±1.62[b]	24±0.36[b]
5	EAFNC+PTZ(400mg/kg)(po)+(80mg/kg)(s.c)	698.16±0.60[b]	28.16±0.47[b]
6	EAFNC+PTZ(200mg/kg)(po)+(80mg/kg)(s.c)	601.66±1.35[b]	33.5±1.17[b]

The findings was represented as M±SEM; (n=6). The one-way ANOVA was used to evaluate the findings with the Dunnett's Multiple Comparison test.

When compared to the positive control, b - P<0.01(**).

Table 4.5.2.a displays the PTZ-induced seizures that occurred following oral dosages of MENC and EAFNC in 2 doses.

When compared to control, the onset and duration of the seizures in the MENC (400mg/kg) group were 808.5±1.38 & 18.33±0.42, respectively (P<0.01). The lower dose of MENC revealed a 24±0.36 seizure duration, which is more in comparison to the effective control. The difference between MENC (400mg/kg) and higher and lower doses of EAFNC showed decreased seizure onset (698.16±0.60 and 601.66±1.35), but increased seizure duration (28.16±0.47 and33.5±1.17).

When the mice was treated with Pentylenetetrazole at a dose of 80mg/kg given subcutaneously observed the onset of seizures to be 533.66±1.72 and the duration of seizures was found to be 55.5±0.89 in seconds. Similarly, a combination of Phenytoin at a dose of 25 mg/kg intraperitoneally and PTZ at a dose of 80mg/kg(sc) noted the onset of seizures to be 860.33±2.9 and the duration of seizures was 11.33±0.71. The lower dose of methanolic extract with PTZ delivered an outcome of 752.8±1.62 for the onset of seizures.

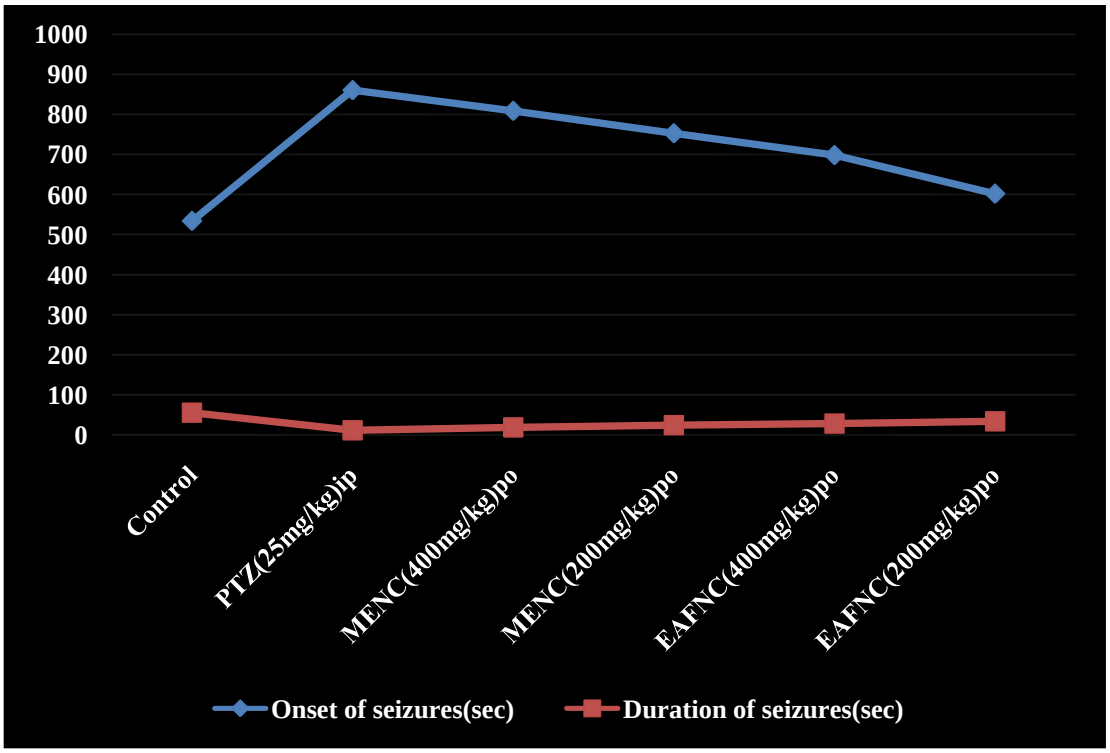

Fig.no:6.5.2.a PTZ induced seizure on MENC and EAFNC

4.5.2.b Maximum Electric Shock Induced Seizure

Table no: 4.5.2.b Effect of MENC and EAFNC on Maximum Electric Shock Induced Seizure

SL. NO:	TREATMENT GROUP	TIME IN VARIOUS PHASES OF CONVULSIONS(SEC)				
		FLEXION	EXTENSION	CLONIC	STUPOR	RECOVERY/DEATH
1	MES Control	8±0.36	20.83±0.87	28±0.93	58.16±4.30	138.66±6.12
2	Phenytoin(25mg/kg)(i.p) + MES	4±0.51[b]	5.66±4.47[b]	19.33±2.55[b]	32.5±1.25[b]	92.33±1.47[b]

3	MENC(400mg/kg)(p.o)+MES	1.33±0.21^{b}	7.33±0.55^{b}	14±0.85^{b}	30±0.57^{b}	101.33±1.78^{b}
4	MENC(200mg/kg)(p.o)+MES	2.66±0.21^{b}	11.5±0.42^{b}	19.16±0.60^{b}	46.5±1.17^{b}	111.16±0.47^{b}
5	EAFNC(400mg/kg)(p.o)+MES	5±0.36^{b}	14.33±0.55^{b}	19.16±0.79^{b}	51.83±1.16^{b}	120.5±0.45^{b}
6	EAFNC(200mg/kg)(p.o)+MES	6.5±0.22^{c}	16.83±0.60^{b}	21.83±0.65^{b}	56±1.23^{b}	129.5±1.14^{b}

The findings was represented as M±SEM; (n=6). The one-way ANOVA was used to evaluate the findings with the Dunnett's Multiple Comparison test.

When compared to the positive control, b - P<0.01(**).

C - P<0.05(*) in comparison to the normal

Table 4.5.2.b illustrates the MES-induced convulsion that occurred following oral administration of two dosages of MENC and EAFNC. It is clear that mice administered with 400 mg/kg of MENC had a significant (p<0.01) effect on MES-induced convulsion in comparison to mice given 200 mg/kg of methanol extract during all stages.

Relative to mice given 200 mg/kg of methanol extract, it showed a reduced time for MES-induced convulsion in all episodes.

It showed a shorter time frame in each step of the convulsion as compared to the control. Comparing higher and lower doses of EAFNC to higher and lower doses of methanol extracts, however, revealed enhanced reactions during various periods of convulsion.

Less significant (p<0.05) was the lower dose of EAFNC (6.5±0.22 toward flexion).The clonic phase of convulsion for the lower methanolic extract of NC and the higher ethylacetate fractions of NC was almost found to be similar as (19.16±0.60 and 19.16±0.79).

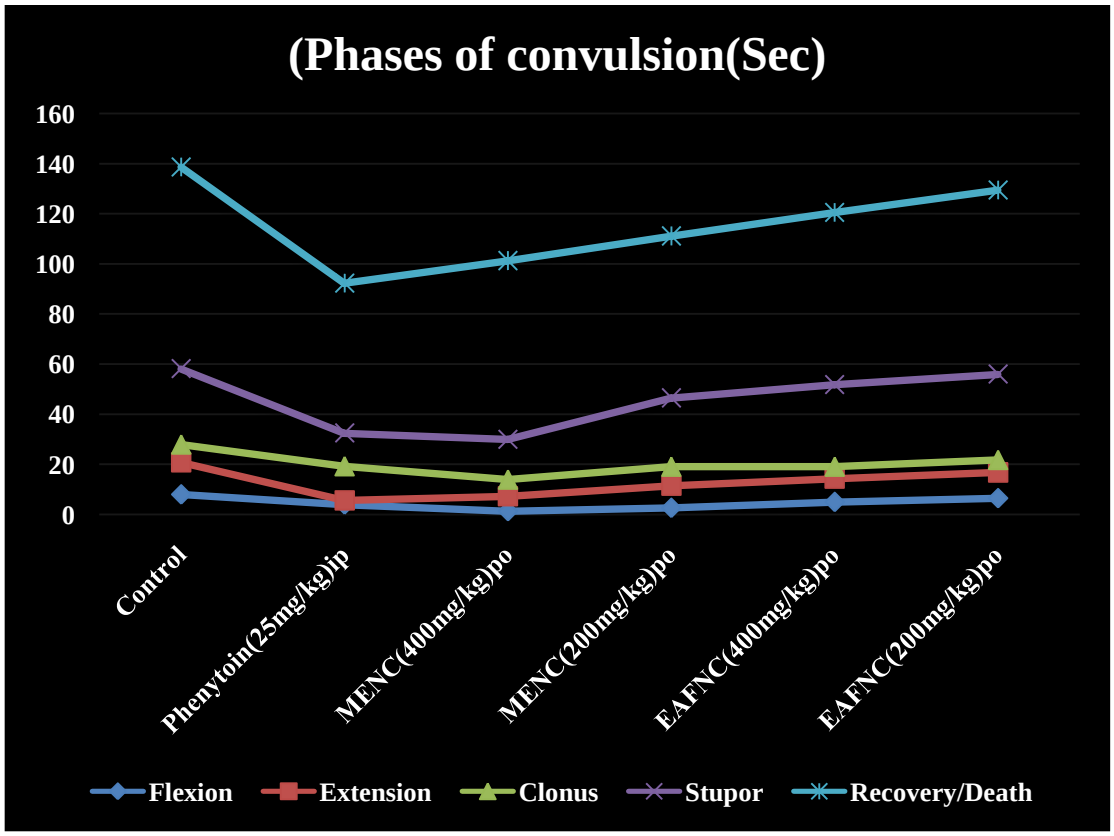

Fig. no: 4.5.2.b MES induced seizure on MENC and EAFNC

ANTIDEPRESSANT ACTIVITY

4.5.4.a Forced swimming test

Table no: 4.5.4.a Effect of MENC and EAFNC on immobility in FST

SL. NO:	TREATMENT GROUP	DURATION OF IMMOBILITY (Sec)
1	Control	202±1.65
2	Fluoxetine(10mg/kg)(po)	106.6±2.40[b]
3	MENC(400mg/kg)(po)	257.83±3.86[b]
4	MENC(200mg/kg)(po)	241.16±2.75[b]
5	EAFNC(400mg/kg)(po)	228.33±1.11[b]
6	EAFNC(200mg/kg)(po)	218.5±1.17[b]

The findings was represented as M±SEM; (n=6). The one-way ANOVA was used to evaluate the findings with the Dunnett's Multiple Comparison test.

When compared to the positive control, b - P<0.01(**).

Table 4.5.4.a shows the length of immobility in the forced swim test following oral administration of two doses of MENC and EAFNC. Fluoxetine (10 mg/kg) (p.o.) administered animals displayed shorter periods of immobility, demonstrating a significant (p< 0.01) difference from the control group.

In mice given MENC dosages of two hundred and four hundred mg/kg, there was a substantial (Probability<0.01) (257.83±3.86 and 241.16±2.75) dose-dependent reduction in the length of immobility. It was shown that mice treated with 400mg/kg of EAFNC (228.33±1.11) demonstrated a significantly greater effect on the length of immobility caused by the CNS depressive activity than mice treated with the lower dose (200mg/kg) of ethylacetate fractions of NC (p<0.01) 218.5±1.17.

The control group in forced swimming test under anti-depressant activity showed the value for duration of immobility in seconds as 202±1.65. The duration of immobility in seconds for the standard drug that is Fluoxetine when given orally in the dose of 10mg/kg was found to be 106.6±2.40. The forced swimming test is used to determine the anti-depressant activity of both the standard and the test drug. The herbal extract proved to be much efficient than the standard drug. Thus the side effects caused due to synthetic drugs can be controlled by using such herbal approved anti-depressant drugs. The methanolic extract of *Naringi crenulata* (Roxb.) Nicolson leaves was the most effective one when compared with the other groups of drugs including the standard. The ethylacetate fractions were also effective but its action might be lower than that of the MENC.

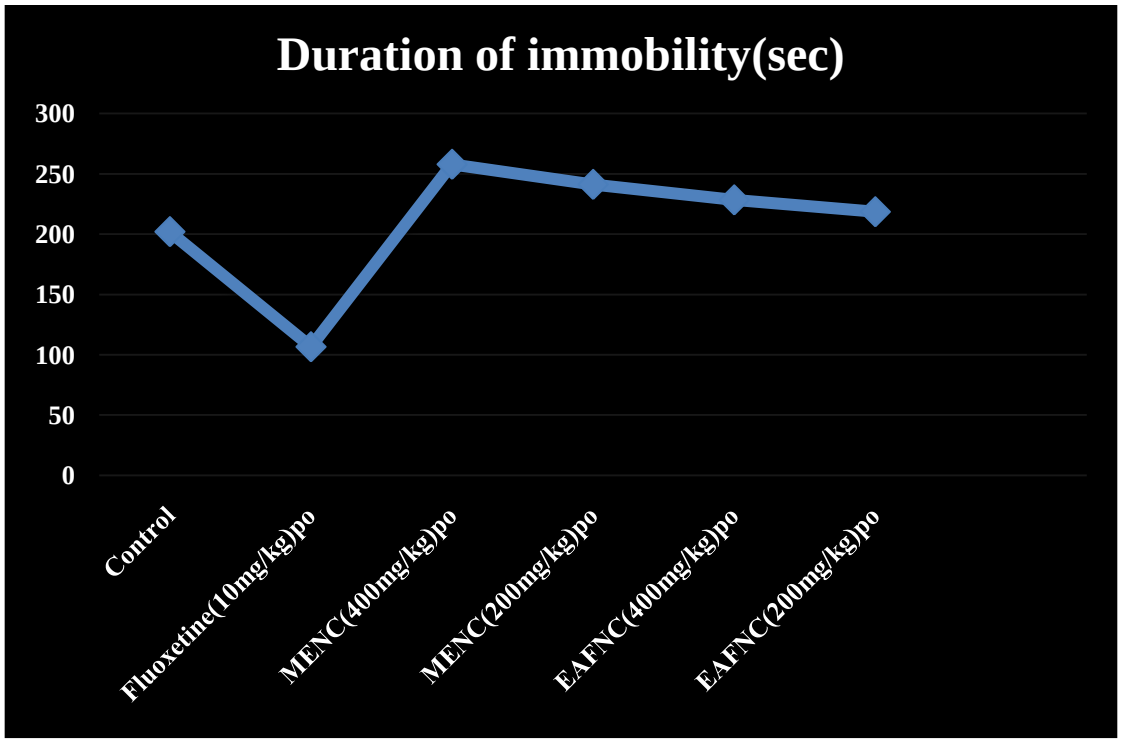

Fig. no: 4.5.4.a Duration of immobility in FST on MENC and EAFNC

4.5.4.b L-dopa produced restlessness and combative actions in mice

Table no: 4.5.4.bActivity of MENC and EAFNC onL-dopa produced restlessness and combative actions in mice

SL. NO:	THERAPY GROUP	BEHAVIORAL DOSAGE
1	Control	0.66±0.21
2	Lorazepam 2mg/kg (i.p)	1.77±0.57[b]
3	L-dopa(100mg/kg)(i.p)+ Lorazepam 2mg/kg (i.p)	2.56±0.33[b]
4	L-dopa(100mg/kg)(i.p)+MENC(400mg/kg)(po)	2.42±0.40[b]
5	L-dopa(100mg/kg)(i.p)+MENC(200mg/kg)(po)	2.33±0.49[b]
6	L-dopa(100mg/kg)(i.p)+EAFNC(400mg/kg)(po)	1.9±0.73[b]
7.	L-dopa(100mg/kg)(i.p)+EAFNC(200mg/kg)(po)	1.53±0.21[b]

The findings was represented as M±SEM; (n=6). The one-way ANOVA was used to evaluate the findings with the Dunnett's Multiple Comparison test.

When compared to the positive control, b - P<0.01(**).

Table 4.5.4.b illustrates the effects of L-dopa produced restlessness and combative actions in rodents following oral administration of, the two doses of the preparations MENC and EAFNC. It was discovered that the behavioural score for the standard drug was around 1.77±0.57.

When MENC (400mg/kg) and EAFNC (200mg/kg) were compared with control, the behavioural score for MENC was found to be around 2.42±0.40 and for EAFNC it was found around 1.53±0.21 (P< 0.01).

The L-dopa induced hyperactive aggressive behaviour in mice for the control group was observed as 0.66±0.21. The behavioural dose for intraperitoneally administered L-dopa 100mg/kg and Lorazepam given intraperitoneally in the dose of 2 mg/kg was noted as 2.56±0.33.The behavioural response of lower dose of methanolic extract of *Naringi crenulata* (Roxb.) Nicolson leaves along with Levodopa 100mg/kg given intraperitoneally was found to be 2.33±0.49. The higher dose of ethylacetate fraction of NC with L-dopa administered intraperitoneally in the dose of 100mg/kg, the behavioural dose was estimated to be 1.9±0.73. Thereby, the herbal extracts was marked to be effective.

Fig.no: 4.5.4.b L-dopa produced restlessness and combative actions in mice on MENC and EAFNC

GC MS OF MENC

With the inclusion of 26 distinct major

recognisable chemicals in the methanolic preparation of *Naringi crenulata*, the GC-MS investigation has shown impressive results (Roxb.)

The existence of 26 functional phytoconstituents in the methanolic extract of *Naringi crenulata* is shown in Table no: ,along with the bioactive components' molecular formulas, molecular weights and structural details.The listed activities in some of the bioactive compounds are also tabulated in Table no:.Among the identified compoundspsi. psi.-Carotene,1,1',2,2' – tetrahydro-1,1'-dimethoxy (R match: 611, F match:598 , Probability: 2.39), lycopene(R match : 595, F match: 585, Probability : 1.40), lycoxanthin (R match :585, F match:577, Probability: 1.04), astaxanthin (R match: 565, F match:569, Probability:0.76), tocopherol (R match:996, F match: 824 , Probability:2.70) vitamin E(R match: 891, F match:867, Probability: 17.29) and vitamin D(R match:664, F match: 515, Probability: 0.17) have got the antioxidant property.

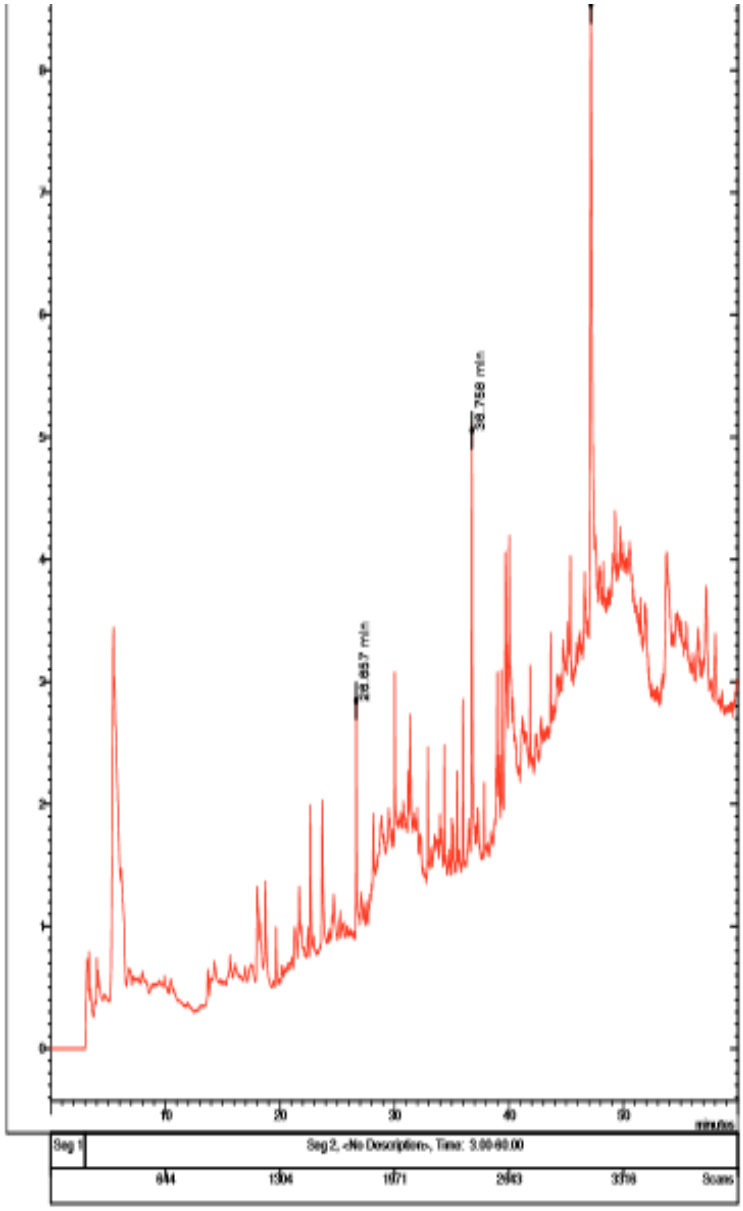

Fig.no: 3 GC MS Chromatogram of leaves of MENC

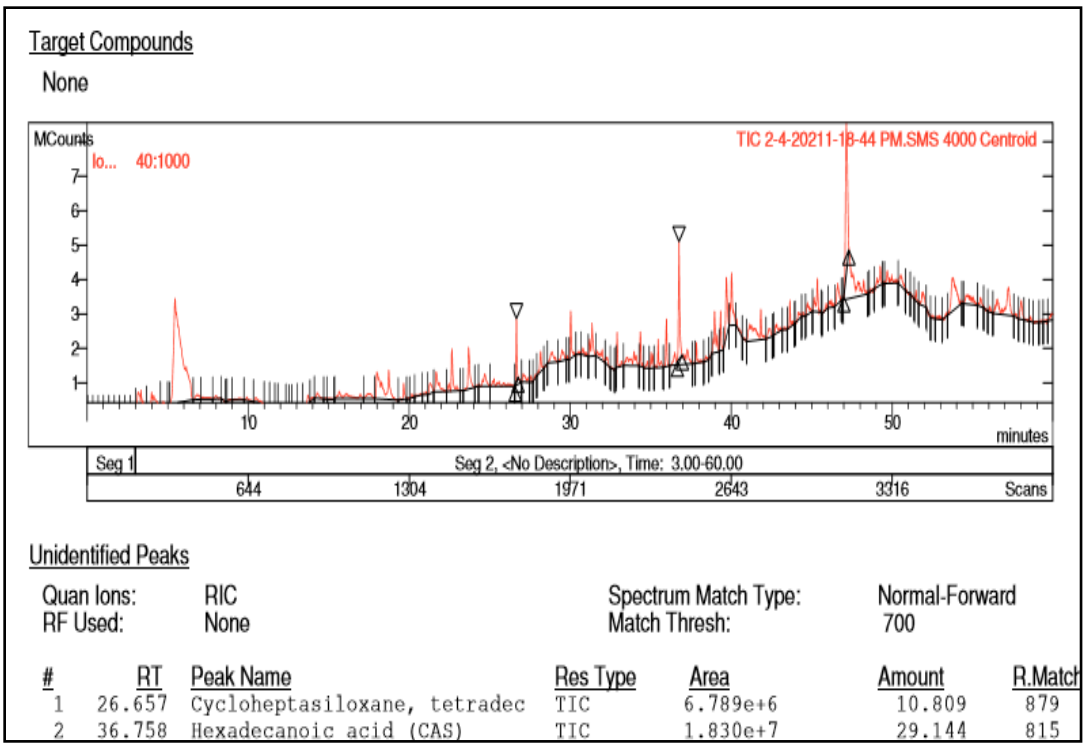

Fig.no: 4 Target compounds of leaves of MENC.

Conclusion: The findings showed that *Naringi crenulata* (Roxb.) extracts can be employed as an antioxidant and in the treatment of some neurological illnesses.

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