JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

PHARMACOLOGICAL SCREENING OF *TERMINALIA CHEBULA* FRUIT EXTRACTS AGAINST NEURO DEGENERATIVE DISORDERS IN RODENTS

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Abstract

Terminalia chebula Retz (T. chebula) which is a member of the Combretaceae family is frequently used medicinal herb in Ayurvedic, Unani, and Siddha & Homeopathy system of medicine. *Terminalia chebula* is called the 'King of Medicine' in Tibet and is always listed at the top of the list in Ayurvedic Materia Medica due to its extraordinary power of healing.

To evaluate the *Terminalia chebula* fruit extracts against neurodegenerative disorders in rodents. To screen the *Terminalia chebula* fruit extracts against haloperidol induced catatonia model in SD rats (Anti-parkinsonism/ catatonia activity), ethanol- induced cognitive impairment & diazepam induced amnesia (learning and memory activity in Alzheimer's disease).For anti-parkinsonism activity scoring of Catalepsy by using block method and motor activity by using actophotometer whereas learning and memory activity was performed to evaluate the effect of *Terminalia chebula* on Alzheimer's disease by using the 8-arm radial maze (8-RAM), Morris water maze (MWM)& histopathological studies by comparing with the control group.

KEYWORDS:

Terminalia chebula Retz, neurodegenerative disorders, anti-parkinsonism activity, learning and memory activity in Alzheimer's disease & histopathological studies.

INTRODUCTION

- **Neurodegenerative Diseases (NDs)**

NDs are characterized by the progressive and irreversible loss of neurons in selective regions of the brain. In afflicted individuals, symptoms typically manifest as memory loss, anxiety, and depression, which evolve to severe motor dysfunction, profound cognitive deterioration, and loss of independent function. The risk of

developing a ND rises sharply with age; the number of people with a neurodegenerative disease is low at younger ages, but the prevalence of people suffering from neurodegeneration doubles every 5 years after age 65.3 AD, the most common form of NDs, currently affects about 10 percent of the population over age 65 and 47 percent of adults aged over 85 years.3 NDs typically involve a slow decline in human function that results in an eventual need for constant care and assistance with the most basic activities of daily life, consequently generating a substantial social and financial burden.[1]

- **Parkinson's Disease (PD)**

Parkinson's disease (PD) is a slowly progressive neurodegenerative disease caused when a small group of brain cells that control body movements die. This disease was first described by **James Parkinson** in **1817**. It is characterized clinically by bradykinesia, resulting tremor, rigidity and postural instability. Pathological features of PD include loss of dopamine neurons in substantia nigra and presence of intracytoplasmic inclusions known as Lewy bodies in surviving dopamine neuron. It is not clear why Lewy body formation causes neuronal cell death. Among the available antiparkinsonian drugs, levodopa remains the most efficacious and still the mainstay of therapy. However, long term use of levodopa leads to wearing off phenomenon, on- off phenomenon, motor fluctuations and dyskinesia, which limit its further usage. Even though antiparkinsonian drugs are highly effective in alleviating the symptoms of Parkinsonism, but they do not give complete cure. Moreover, these drugs are often associated with frequent side effects like nausea, vomiting, depression, hallucinations, dizziness, dry

mouth, sore throat, postural hypotension, diarrhea, mydraiasis, anxiety etc. The significance of many indigenous medicinal plants and their phytoconstitutents in the management of Parkinsonism with minimal side effect profile arise in this context. There has been an enormous demand for further scientific development of animal models that can mimic the progressive motor impairment as in PD. One such model is Haloperidol induced catalepsy i.e., a state of akinesia with muscular rigidity in animals. It is an established model for screening the drugs for antiparkinson effect. [2]

Schematic representation of the normal nigrostriatal pathway: -It is composed of dopaminergic neurons whose cell bodies are located in the substantia nigra pars compacta (SNpc; see arrows). These neurons project (thick solid red lines) to the basal ganglia and synapse in the striatum (i.e., putamen and caudate nucleus). The photograph demonstrates the normal pigmentation of the SNpc, produced by neuromelanin within the dopaminergic neurons. [3]

Schematic representation of the diseased nigrostriatal pathway: - In Parkinson's disease, the nigrostriatal pathway degenerates. There is a marked loss of dopaminergic neurons that project to the putamen (dashed line) and a much more modest loss of those that project to the caudate (thin red solid line). The photograph demonstrates depigmentation (i.e., loss of dark-brown pigment neuromelanin; arrows) of the SNpc due to the marked loss of dopaminergic neurons. [3]

Symptoms: [4]

Parkinson's entails symptoms of many types – motor and non – motor. However, not every symptom affects every PwP, & the intensity of symptoms varies across individuals. In addition to these four cardinal motor

symptoms there are many others which are also considered in the diagnostic process. Often the non-motor symptoms are more challenging for the person living with Parkinson's. Non-motor symptoms such as pain, depression and problems with memory and sleep can also occur and have an impact on the day to day life of the person with Parkinson's. The Four main symptoms of Parkinson's disease affect physical movement:

Tremor: The most common symptom of Parkinson's disease is the unilateral, typically resting tremor in body parts, most commonly in the upper extremities. However, this finding can spread to the other parts of the body like lips, chin, jaw and tongue during the course of the disease. It is an early symptom and is seen in about 70% of people presenting with Parkinson's. The tremor of PD is a rest tremor-the shaking occurs when the patient is not trying to use the limb, and diminishes when the limb is in use. Tremor is related to an imbalance of neurotransmitters, dopamine and acetylcholine, for this reason, tremor may be the least responsive symptom to dopamine replacement therapy. This usually begins in the hand or arm and is more likely to occur when the limb is at rest.

Slowness of movement (bradykinesia): Bradykinesia can be the most disabling symptom of the condition and refers to slowness, decreased movement amplitude, and dysrhythmia. Physical movements are much slower than normal, which can make everyday tasks difficult and can result in a distinctive slow, shuffling walk with very small steps.

Muscles stiffness (rigidity): Parkinson's disease can create greater tension in the tendon, leading to structural adjustment and an increase in tendon stiffness. Muscle rigidity may not be apparent to the person with Parkinson's but is felt by the medical practitioner in limb muscles when they are passively moved. Stiffness and tension in the muscles, which can make it difficult to move around and make facial expressions and can result in painful muscle cramps (dystonia).

Early Parkinson's: During the initial stages of Parkinson's, the symptoms may be mild and interfere with fine motor activities like buttoning a shirt, tying shoe laces, a change in handwriting and slowed movement. Tremor if present may appear on one side of the body, starting either with the finger/hand or toe/foot.

Advanced Parkinson's: As Parkinson's progresses, the symptoms that appeared earlier tend to become more pronounced and problems with balance and change in posture become evident. After years of Parkinson's, a PwP tends to walk with a stooped posture with short steps.

LITERATURE REVIEW

- Ayurvedic and Modern aspect of *Terminalia chebula* Retz. *Haritaki* An Overview

Due to globalization the Ayurvedic science has been reached to every corner of the world. This science of life is well accepted today by many of countries and positive response to Ayurvedic is increasing day to day. The use of herbal drugs for prevention and treatment of various health ailments has been practice since time immemorial *Terminalia chebula* Retz. (Family-Combretaceae) is traditionally recommended by the Indian Ayurvedic medicine for treatment of several disorders. According to Ayurveda, due to its Rasayana (rejuvenating), and Vayasthapana (age-sustaining) actions it provides long healthy life and fights against variety of diseases. It is endowed with diverse pharmacological activities like antidiabetic, anti-arthritic,

Hepatoprotective, antioxidant, anti-plasmodia activity etc. It contains many important Phytochemicals such as chebulic acid, Gallic acid, ellagic acid, tannic acid, amino acids, flavonoids like luteolin, rutins and quercetin etc. It also consists of nutrients such as vitamin C, protein, amino acids and minerals. The present review is an effort to highlight the various traditional uses as well as Phytochemical and pharmacological activities reported so far from *Haritaki* which will surely help researchers to explore it at molecular level and pharmaceutical industries to develop a new product.

- Phytopharmacological overview of *Terminalia chebula* Retz

Phytotherapy is the traditional method used to cure many diseases. Various medicinal plants found in many parts of India are well known for their various medicinal values. The *Terminalia chebula* Retz a native plant of Asia is found to have various properties like anti-oxidant and free radical scavenging activity, anti-carcinogenic activity, ant-imutagenic activity, anti-bacterial activity, anti-fungal activity, anti-viral activity, anti-diabetic, renoprotective activity, cardio-protective activity, anti-inflammatory and anti-arthritic activity. These properties of *T. chebula* discussed in this review are mainly due to the presence of various types of phytoconstituents.

- Biological and pharmacological properties of *terminalia chebula* retz. (haritaki)- an overview

Medicinal plants have been considered valuable and cheap source of unique phytoconstituents which are used extensively in the development of drugs against various diseases. A large proportion of the world population, especially in the developing countries relies mainly on the traditional system of medicine. The use of plants and plant products in medicines is getting popularized because the herbal medicines are cheap and have natural origin with higher safety margins and lesser or no side effects. *Terminalia chebula* Retz. (*T. chebula*) belongs to the family Combretaceae and is one of the most important medicinal plants used in medicines of ayurveda, siddha, unani and homeopathy. It is called the "King of Medicines" in Tibet and is listed first in the Ayurvedic material medica because of its extraordinary power of wound healing and a wide spectrum of medicinal properties. *T. chebula* possesses antibacterial, antifungal, antiviral, antidiabetic, antimutagenic, antioxidant, antiulcer and wound healing properties. It also prevents cardiac damage and is used for the treatment of kidney disease. It is a mild, safe and effective laxative in traditional medicine. *T. chebula* and its phytoconstituents have therapeutic effect with no toxicity. *T. chebula* is an active ingredient of the well known herbal preparation, Triphala, which is used for the treatment of enlarged liver, stomach disorders and pain in eyes. This review gives a bird's eye view on the biological and pharmacological properties of various extracts and isolated phytoconstituents of *T. chebula* to enrich our knowledge about this plant.

- Terminalia Chebula A Traditional Herbal Drug – A Short Review

The usage of medicinal plants used from ancient times to treat various diseases due to its potential medicinal applications. Terminalia chebula is one of the common herbal drugs used

in traditional systems in worldwide. The review tries to focus the traditional use of Terminalia chebula as herbal drug and the importance and its impact in the medicinal applications.

MATERIALS AND METHODS

Collection & Authentication of Plant Material:

The fruits of *T. chebula* was authenticated by Dr.P.Satyanarayana Raju (Plant taxonomist) of department of botany and microbiology in Acharya Nagarjuna University, Guntur.

Preparation of Extract:

The *terminalia chebula* fruits are powdered in a mechanical grinder.The collected powder was successively, extracted with water & ethanol by using Soxhlet apparatus.The extraction was carried out for 72 hrs at a temperature not exceeding the boiling point of the solvent.Excess solvent was removed by the solvent evaporation to obtained the dry weight of the plant extracts.

Preliminary Phytochemical Screening:

The preliminary phytochemical investigation was carried out with both aqueous & ethanolic extracts of *terminalia chebula* for identification of phytochemical constituents. Phytochemical tests were carried out by standard methods.

Experimental Animals:

SD rats of either sex (200-300g) were maintained for 7 days in the animal house of Chalapathi Institute of Pharmaceutical Sciences, Guntur under standard conditions temperature (24 ± 10 C), relative humidity (45-55%) and 12:12 light: dark cycle. The animals were fed with standard rat pellet and water ad libitum. The animals were allowed to acclimatize to laboratory conditions 48 h before the start of the experiment. 5 rats/group were used in all sets of experiments.

Ethical Approval:

All the protocols were approved by Institutional Animal Ethical Committee (IAEC) and conducted according to Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA) registered no: 1523/PO/Re/S/11/CPCSEA at Department of Pharmacology. Sims college of pharmacy Guntur

Drugs and Chemicals:

For anti-parkinsonism activity:

Inducing agent- Haloperidol (4mg/kg, p.o),

Standard drug – Syndopa (Levodopa + Carbidopa) (10mg/kg, p.o).

For learning and memory activity in Alzheimer's disease:

Inducing agents -Ethanol - 60% (Ethanol was prepared as a 60% solution in distilled water and administered i.p at a dose of 2.5 mg/ kg),

-Diazepam- was diluted in normal saline and administered i.p at a dose of (1 mg/kg).

-Ethanol- 20% (Ethanol was prepared as a 20% solution in sterile normal saline and administered subcutaneously at a dose of 4.5 gm/ kg),

Standard drug- Donepezil hydrochloride (2.5 mg/kg, p.o)

Haloperidol Induced Catatonia Model in SD Rats:

Haloperidol {4-(4-chlorophenyl)-1-(4-(4-flurophenyl)-4-oxobutyl)-4-piperidinol} is the widely used antipsychotic drug and it shares some structural similarity with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP is identified as the toxic agent present in heroin and responsible for neurodegenerative condition similar to Parkinson's disease. MPTP is commonly used to induce Parkinsonism in experimental animals. Haloperidol is metabolized in liver, it undergoes oxidation to the pyridinium metabolite, 4-(4-chlorophenyl)-1-(4-(4-fluorophenyl)-4-oxobutyl)-pyridinium (HPP+) which shares some structural similarity and toxic actions with pyridinium metabolite of MPTP 1-methyl-4-phenylpyridine (MPP+). This suggests that HPP+ might produce neurological effects similar to MPTP. Therefore, in the present study haloperidol is used to induce Parkinsonism in rats. [(26)] Haloperidol is known to produce extrapyramidal side effects in man. These effects, such as akinesia, rigidity and tremors, are called Parkinson's-like because in Parkinson's disease the major clinical symptoms include difficulty to move and change posture (akinesia and rigidity) and tremors. These effects of antipsychotic drugs are due to excessive blockade of dopamine receptors in the extrapyramidal motor system. Therefore, butyrophenones [haloperidol (or) trifluperidol] are commonly used to produce Parkinson's-like extrapyramidal symptoms in laboratory animals and to study anti-parkinsonian drugs**.** [(27)]

- **Selection of Dose and Treatment Period:**

The anti-parkinsonism activity of the aqueous and ethanolic fruit extracts of *Terminalia chebula* was investigated using the haloperidol induced catatonia method [Haloperidol is widely used to induce Parkinsonism like condition in the dose 0.5 to 4 mg/kg daily for a week in rats]. [(26)] The test animals were randomly chosen and divided into four groups having five rats in each as follows:

Group I: Inducing group - Haloperidol (4mg/kg, p.o once/day x 1 week).

Group II: Standard group - Syndopa plus [(28)] [(Levodopa+ carbidopa) (10mg/kg, p.o, once/day x 1 week)] +Haloperidol.

Group III: Test-I - Aqueous fruit extract of *Terminalia chebula* [TCAE- 100mg/kg P.O x1 week] +Haloperidol.

Group IV: Test –II - Ethanolic fruit extract of *Terminalia chebula* [TCEE- 100mg /kg P.O x1 week] +Haloperidol.

All the treatment group animals received respective control, standard and test treatment 30 minutes prior to the haloperidol administration for 7 days of experimental period.

Measurement of Catalepsy by Block Method: [(29)]

Two wooden blocks, one is being 3cm high and other 9cm high. Catalepsy of an individual rat was measured by a scoring method given below. Severity of catatonic response was recorded as follows:

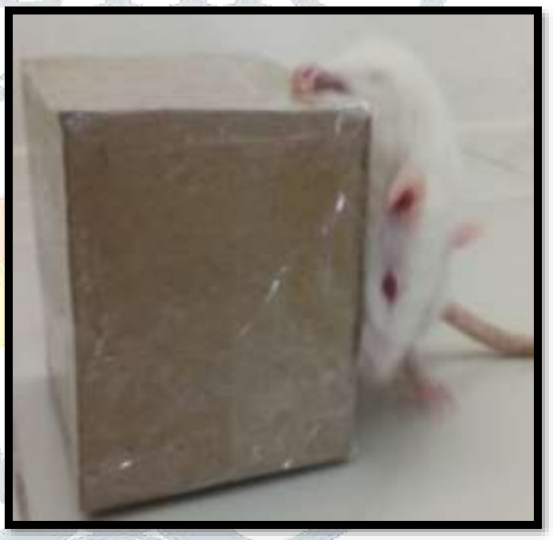
TABLE

Stages	Description/Behaviour	Score
Stage- I	Rat moves normally when placed on the table	0
Stage- II	Rat moves only when touched or pushed	0.5.
Stage -III	Rat placed on the table with front paws set alternatively on 3cm high block fails to correct the posture in 10 sec, score=0.5 for each paw with a total of 1 for this stage.	1
Stage -IV	Rat fails to remove when the front paws are placed alternatively on 9cm block, score= 1 for each paw a total score of 2 for this stage.	2

Thus, for a single rat, the maximum possible score would be 3.5 revealing total catatonia. Severity of catatonia was observed at 30, 60, 90,120 & 240 min after haloperidol administration. Plot a graph, time along on X-axis and catatonic scores along the Y-axis. [29]

FIGURE-6: Catatonia-stage-III

FIGURE-7: Catatonia-stage-IV



- **Evaluation Parameters:**

Scoring for catatonia.

Locomotor Activity Using Actophotometer: [29]

The locomotor activity (horizontal activity) can be easily measured using an actophotometer which operates on photo electric cells which are converted in circuit with a counter. When a beam of light falling on the photocell is cut off by the animal, a count is recorded. An actophotometer could be either circular or square area in which the animal moves.

Calculate the % decrease in motor activity (or) % activity change (Before - After 30 minutes / before × 100).

FIGURE-9: Actophotometer

- **Evaluation parameters:**

i. No. of counts / 5 min i.e. after 30 min.

ii. % decrease in motor activity (or) % activity change (Before - After 30 minutes / before × 100).

iii. **Morris Water Maze (MWM):**

To assess hipocampal dependent spatial learning and memory, all rats were trained in a standard Morris water maze task (Morris et al., 1982; Stackman et al., 2002).[30] Maze consisted of large circular pool (75cm &30cm) filled with water at a depth of 20cm. The pool was divided into four quadrants. A circular platform was placed at the centre of one quadrant. The rats performed four trials per day for four consecutive days. In the swimming trials, each individual rat was released gently into the water at a randomly chosen quadrant. The rats swim and learned how to find the hidden platform within 60 s. After reaching the platform rat was allowed to stay on the platform for 15 s and was then taken back into the cage. The rats were placed on the platform by hand for 15 s, if they could not escape to the platform within 60 s by themselves, and their escape latency was accepted as 60 s. During the inter-trial intervals, animals were kept in a dry home cage for 60 s. The time to reach the platform (latency) was recorded. 24h after the last day of training, subjects were tested on a probe trial, during which the escape platform was removed and the time spent in the correct quadrant was measured for a 60 s trial. [31]

Evaluation parameters:

Transfer latency in sec

Ethanol- Induced Cognitive Impairment: [32]

Ethanol is neurotoxin that able to alter behavioural and cognitive performance in experimental animals in addition to humans. It mainly impairs hippocampus-dependent learning and memory functions. The mechanism of ethanol-induced neurotoxicity is not well understood. Several studies show that free-radical mediated oxidative stress play an imperative role. The brain is extremely susceptible to oxidative stress due to high level of polyunsaturated fatty acids (PUFAs) and catecholamines, large amounts of oxygen (O_2) in

relatively small mass and in conjunction with low antioxidant activities. Furthermore, certain regions of the central nervous system (CNS), especially

Diazepam Induced Amnesia:

Diazepam 1mg/kg, i.p was administered to rats and TL was noted after 45 min of injection on 8th day and after 24hrs. Extracts and standard Donepezil hydrochloride were administered for successive 8 days. After 60 min of administration of the last dose on 8th day, Diazepam 1mg/kg i.p was administered. TL was noted after 45 min administration of diazepam and after 24 hrs. [33]

Evaluation parameters:

i. No. of entries in baited arms and non-baited arms.

ii. Time taken to reach the paired arm.

iii. Weights of different organs of rat.

iv. Histopathological studies.

Statistical Analysis:

The values are expressed as mean± SEM. The statistical analysis was performed using one way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. Comparisons were made between haloperidol group and test/standard groups. P-values <0.05 was considered statistically significant. The statistical analysis was done by using Graph pad prism version no:

RESULTS AND DISCUSSION

In this study, we found that aqueous & ethanolic fruits extract of *Terminalia chebula* Retz Possess the following chemical constituents (Table).

TABLE : Phytochemical screening of TCAE & TCEE

Phytochemical constituents	**TCAE**	**TCEE**
Alkaloids	++	++
Carbohydrates	+	+
Flavonoids	_	_
Phenols	+	+
Saponins	+++	+++
Terpenoids	+	+
Sterols	+	+
Tannins	+	+
Proteins	+++	+++
Amino acids	+++	+++
Glycosides	++	++

Fixed oils and fatty acids	-	-

+ indicate the compulsory present, ++ indicate the slightly present, +++ moderately present and – indicate the absent.

Effect of Fruit Extracts of *Terminalia chebula* Retz on Cataleptic Activity:

Haloperidol induced a time dependent increase in cataleptic state in rats, as compared to vehicle treated groups. Maximum catalepsy score was noted at a time interval of 120-180 min. All the groups i.e. standard (L-dopa + carbidopa), TCAE and TCEE showed significant ($P<0.05$) reduction in scores at all time periods. The average scores for the standard and the test drugs were reduced to that of the haloperidol group (Group I).

TABLE Effect of fruit extracts of *Terminalia chebula* Retz on degree of catatonic response after min

S.No	**Group**	**Treatment**	**Degree of catatonic response after min**				
			30	**60**	**90**	**120**	**240**
1.	I	**Haloperidol**	0.59±0.06	1.73±0.09	2.72±0.08	2.99±0.03	3.53±0.06
2.	II	**Standard + haloperidol**	0.31±0.02	0.49±0.02	0.32±0.02	0.31±0.01	0.22±0.02
3.	III	**TCAE + haloperidol**	0.33±0.02	0.51±0.02	0.53±0.02	0.32±0.01	0.24±0.02
4.	IV	**TCEE + haloperidol**	0.32±0.02	0.50±0.02	0.32±0.02	0.31±0.02	0.23±0.02

Effect of Fruit Extracts of *Terminalia chebula* Retz on Behavioural Parameters

(Locomotor Activity):

Actophotometer: Animals treated with haloperidol (4 mg/kg, P.O) alone for 7 days showed a decrease of locomotor activity [no. of counts / 5 min i.e. after 30 min] on 1st day,4th day &7th day and also reduction in the %change activity when compared to other groups.

Effect of fruit extracts of Terminalia chebula Retz on transfer latency (diazepam induced amnesia)

S.No.	Group	Treatment	Transfer latency (In seconds)	
			8TH DAY	After 24 hours (i.e.9TH DAY)
1.	I	**Diazepam**	26.2±3.89	24.8±4.43
2.	II	**Standard+ diazepam**	4.4±0.81	2±0.32
3.	III	**TCAE+ diazepam**	9.6±2.40	6.6±1.12
4.	IV	**TCEE+ diazepam**	5.6±0.40	2.2±0.80

Effect of fruit extracts of Terminalia chebula Retz on diazepam induced amnesia. Values are expressed as mean ± SE, $p < 0.05$ vs. control (n = 5 animals).

Effect of Fruit Extracts of Terminalia chebula Retz on Behavioural Parameters i.e. 8-RAM:

Animals treated with ethanol [4.5 mg/kg] alone for 21 days showed an increase in time taken to reach paired arm & number of entries in baited arms and non-baited arms in 1st,7th , 15th & 21 st days.

TABLE : Effect of fruit extracts of Terminalia chebula retz on time taken to reach paired arm (ethanol-induced cognitive impairment)

S.No.	Group	Treatment	Time Taken to reach Paired arm (Sec)			
			1st day	7th day	14th day	21st day
1	I	**Ethanol**	147.4±0.75	138.4±0.93	120.4±2.73	100.4±1.72
2	II	**Standard+ethanol**	76.2±0.97	66.6±1.89	57.8±0.86	46.4±2.6
3	III	**TCAE+ ethanol**	127.8±0.86	121.6±0.93	102.2±0.86	76±1.76
4	IV	**TCEE+ ethanol**	103±0.84	96±0.71	89.2±1.43	75.2±1.46

Effect of fruit extracts of Terminalia chebula Retz on time taken to reach Paired arm. Values are expressed as mean ± SE, $p < 0.0001$ vs. control (n = 5 animals).

TABLE: Effect of fruit extracts of Terminalia chebula Retz on number of entries in baited arms and non-baited arms (ethanol- induced cognitive impairment)

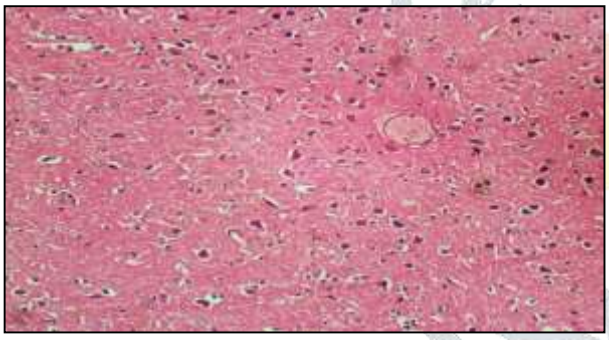
Group	Treatment	Number of entries in baited arms and non-baited arms							
		1st day		7th day		14th day		21st day	
		B.A	N.B.A	B.A	N.B.A	B.A	N.B.A	B.A	N.B.A
I	**Ethanol**	1.4±0.3	1.2±0.2	1.2±0.2	1.6±0.3	1.2±0.2	1.6±0.3	0.8±0.2	0.8±0.2
II	**Standard+ethanol**	3.6±0.3	3.4±0.3	3.2±0.4	2.2±0.6	5.8±0.4	8.8±0.4	9.4±0.5	12.8±1.6
III	**TCAE+ ethanol**	2.2±0.4	2.4±0.4	2.6±0.2	4.4±0.5	5.4±0.5	6.8±0.8	5.8±1.0	7.2±1.6
IV	**TCEE+ ethanol**	6.4±0.5	7±1.3	7±1.3	11±0.9	10.4±0.9	9±1.0	8.8±1.0	10.2±1.2

Effect of fruit extracts of Terminalia chebula Retz on number of entries in baited arms and non-baited arms. Values are expressed as mean ± SE, $p < 0.0001$ vs. control (n = 5 animals).

TABLE NO.10: Effect of *Terminalia chebula* fruit extracts on the weights of different organs (ethanol-induced cognitive impairment)

Organs	**Weight in gms**			
	Inducing group	**Standard group**	**Test-I (TCAE)**	**Test-II (TCEE)**
Brain	2.22±0.28	2.02±0.01	2.13±0.01	2.02±0.01
Heart	1.42±0.16	0.75±0.01	1.13±0.01	0.7±0.03
Lungs	2.01±0.02	1.62±0.01	1.55±0.01	1.54±0.02
Liver	8.18±0.02	5.43±0.01	6.28±0.03	5.37±0.02
Kidneys	2.37±0.21	1.38±0.03	1.35±0.02	1.05±0.01
Pancreas	1.18±0.03	0.51±0.02	0.65±0.02	0.51±0.01

Effectof fruit extracts of *Terminalia chebula retz* on the weights of different



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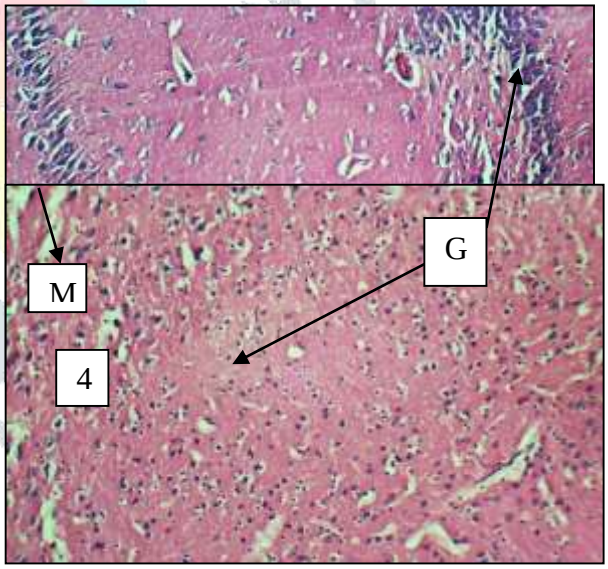

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Histological Findings:

The results showed that ethanol significantly increased neuronal death, while the co treatment of *Terminalia chebula* with ethanol significantly inhibited the neuronal death compared to ethanol treated group, which suggest that *Terminalia chebula* an antioxidant, may effectively protects against the deleterious effects of ethanol-induced abnormalities by decreasing neuronal death in rat brain, furthermore the cell counting under light microscope also showed the same increased neurodegeneration upon ethanol treated group and decreased significantly when treated with ethanolic extract *Terminalia chebula* of as compare to alone ethanol treated group.

SUMMARY AND CONCLUSION

- In the present investigation, *Terminalia chebula* possess the presence of alkaloids, carbohydrates, phenols, saponins, terpenoids, sterols, tannins, proteins, amino acids and glycosides.
- *Terminalia chebula* showed anti-cholinergic mechanism i.e., anti-parkinsonism effect, at an effective dose of 100 mg/kg against haloperidol induced parkinsonian symptoms.
- TCEE showed comparatively significant effect exerted to standard drug Syndopa in the finding of catalepsy score and locomotor activity. Catalepsy score and locomotor activites were recorded after administration of haloperidol at different time intervals and graphs were ploted according to the results obtained.
- *Terminalia chebula* showed cholinesterase inhibitor mechanism at an effective dose of 100 mg/kg against ethanol- induced cognitive impairment & diazepam induced amnesia in rats.
- TCEE showed comparatively significant effect exerted to standard drug donepezil hydrochloride in the finding of transfer latency in sec (i.e., learning and memory activity). Transfer latency was recorded after administration of ethanol & diazepam at different days and graphs were ploted according to the results obtained. This effect is attributed to its ability to improve the levels of the acetylcholine that are decreased in the Alzheimer's disease.
- *Terminalia chebula* showed cholinesterase inhibitor mechanism at an effective dose of 100 mg/kg against ethanol- induced cognitive impairment.
- TCEE showed comparatively significant effect exerted to standard drug donepezil hydrochloride in the finding of time taken to reach paired arm (sec) & number of entries in baited arms and non-baited arms (i.e., learning and memory activity). Time taken to reach paired arm (sec) & number of entries in baited arms and non-baited arms was recorded after administration of ethanol at different days and graphs were ploted according to the results obtained.
- The histopathological study showed that ethanol induced apoptosis neurodegeneration and the co treatment of ethanolic extract of *terminalia chebula* with ethanol decreased ethanol-induced apoptotic neurodegeneration in rat brain. This effect is attributed to its ability to improve the levels of the acetylcholine that are decreased in the Alzheimer's disease.
- Therefore, finally suggests ethanolic extract of *terminalia chebula* fruit show same effects exerted to the standard drugs.

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