Effect of Extractive Phytoconstituents of *Limonia acidissma Linn.* and their probable mechanism against Phenothiazine Induced Extra Pyramidal Side Effects

Rajnish Srivastava*, Chandel H.S., Nagar Hemant, Sexena Rajiv, Deepa

Department of pharmocology, Truba institute of pharmacy, Karond, Gandhi Nagar Bypass Road Bhopal, Madhya Pradesh, India

ABSTRACT

Aim: The present study investigated the preventive effect and probable mechanism of ethanolic extract of Limonia acidissima (EELA) stem bark as compared to standard (L-dopa) in phenothiazine induced extra pyramidal side effects (catatonia) in experimental rats. The acute as well as chronic dose of chlorpromazine (CPZ) was administered to induce catatonia. **Settings and Design:** In case of acute study all the animals receive CPZ (8 mg/kg) only on the 7th day followed by prior treatment of EELA whereas in chronic study all the animals receives CPZ (3 mg/kg) OD for 21 days followed by prior treatment with EELA for 21 days. Body temperature, Catatonic score, Muscle grip strength and locomotor responses were measured to evaluate the extrapyramidal side effects (EPS). **Methods and Material:** The animals were divided into four groups in Control(CPZ)as Group1, Standard treated (L-dopa + CPZ) as Group 2, Test (extract 100 mg/kg + CPZ) as Group 3 and 200 mg/kg body weight as Group 4 and the effect of extract was evaluated in acute as well as chronic induced EPS in experimental rats. **Results:** Pretreatment with EELA at 200 mg/kg significantly increased the muscle grip strength, decreased the catatonic severity and increased the locomotor effect as compared to control. Increased body temperature (Hyperthermia) indicates that the action of extract is similar as atropine. **Conclusion:** The statics clearly shows that the EELA stem bark was shown dose dependent anti-catatonic potential in CPZ induced acute and chronic catatonia.

Key words: Extra pyramidal side effects (EPS), *Limonia acidissima linn.,* Chlorpromazine(CPZ), Catatonic severity, Hyperthermia, EELA.

INTRODUCTION

Limonia acidissima linn, known as kabeet or kaitha (Hindi) is a small to medium size herb, thorny, deciduous tree that attains height up to 6-15 m with shallow furrowed and grey to brown bark. The spines are axillary, short, straight and the premature branches and foliage are covered with minute short hairy and glabrous. The leaves are pinnate, having 5-7 leaflets, each leaflet 20–30 mm long and 15–20 mm broad lamina with notched tip.[1] The bark is ridged, fissured, and scaly long on some of the zigzag twigs. The deciduous, alternate leaves are dark-green in color, leathery, minutely toothed, and blunt or notched at the apex, are spotted with oil glands and slightly lemon-scented when crushed. It is native in the Indo Malaya eco-zone to Bangladesh, India (Chota Nagpur, Madhya Pradesh and Maharashtra.), Pakistan, Sri Lanka, and in Indochinese eco-region east to Java and the Malaysia eco-region. It grows naturally in areas of Sri Lanka, India, Myanmar and Indochina, and then spread to Malaysia and Indonesia.[1] As per literature survey the plant have diverse range of active constituents like psoralene, xanthotoxin, 2, 6 dimethoxybenzoquinone and osthenol. The stem bark of plant yielded(-)-(2S)-5,3'-dihydroxy-4'-methoxy-6",6"-dimethylchromeno-(7,8,2",3")-flavanone along with several known compounds

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Correspondence Address
Prof: Rajnish Srivastava
Department of Pharmacology, Truba Institute of Pharmacy (Capitalize each word), Karond, Gandhi Nagar Bypass Road Bhopal Madhya Pradesh, India. India
Phone No. +91 9770073665
E-mail: phrajnish14091989@gmail.com

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including an alkaloid, coumarins, a flavanone, a lignan, sterols and triterpene.[2-3] It has been reported as active constituents responsible for activities like anti microbial, antifungal, hepatoprotective activity. Apart from these activities it also contains neolignan, (+)-yangambin, (+)-syringaresinol, hederatriol, basic acid methyl ester, 3β-hydroxyolean-12-en-11-one, cascarillic acid, (+)-α-dimorphecolic acid, 8(*R*) hydroxylinoleic acid and (6*Z*,9*Z*,12*Z*)-pentadecatrienoic acid which inhibit NO production in LPS activated BV-2 cells, a microglial cell line.[4]

Parkinson's Disease (PD) is the most common neurodegenerative movement disorder, estimated to affect 1% of the population over 65 years of age. The pathological identifications of PD are the depletion of striatal dopamine caused by degeneration of dopaminergic neurons in the Substantia Nigra (SN) region of the midbrain, appearance of cytoplasmic inclusions, known as Lewy bodies in surviving neurons of the SN, and activation of glial cells.[5] The mitochondrial function is also impaired due to alteration in its DNA which ultimately influences the efficiency of its function and causes oxidative stress and deficits in ATP synthesis.[6-7] Environmental factors like pesticide use (rotenone), contact with certain industrial chemicals (trichloroethylene, manganese, carbon disulphide, carbon monoxide, cyanide, and methanol are positively correlated with the risk of developing PD.[8] After idiopathic PD, Drug-Induced Parkinsonism (DIP) is the second most common cause of Parkinsonism in the elderly. The blockade of dopamine receptors within the striatum results in relative dopamine deficiency. The efficacy and tolerability of antipsychotic drugs has been linked to their binding to dopamine D2 receptors. Elderly people are prone to antipsychotic induced Parkinsonism.[9]

MATERIAL AND METHODS

Plant material

The stem bark of the plant was collected in the month of February from area of Lalghati, Bhopal (M.P.) and was authenticated by Dr. Zia Ul Hasan (Professor), Safia Science College, Bhopal and the specimen voucher number assigned 424/Bot/Safia/13. The stem bark was dried under shade for 15-18 days. It was pulverized to coarse powder with the help of pestle mortar. The coarse powder was passed through sieve No.18 to maintain uniformity and packed into airtight container and stored in cool and dry place.

Extraction of plant material

Powdered stem bark was subjected to extraction with ethanol for 72 hrs at 80-85^{0}C. The extract was transferred in food grade plastic container and kept for drying at room temperature. Reddish brown extract was collected and store in air tight container.

Preparation of extracted formulation

Formulation of ethanol extract was prepared in 0.5% CMC (carboxyl methyl cellulose) as suspending agent. Concentration of 15 mg/ml was prepared as per as suitability of volume of administration. 300 mg of dried powdered extract was premixed in 10 ml of distilled water followed by addition of 50 mg of CMC; the mixture was agitated with the help of glass rod and was finally sonicated with help of ultrasonicator.

Chemicals

Chlorpromazine injection (Lorpromazine, N.I. Pharmaceutical Pvt. Ltd) was purchased from Raj medicos (station road), Bhopal. Levodopa was purchased from Himedia. All other chemicals used for study were of analytical grade.

Selection of Experimental animals

Animal Care and Handling

Healthy Wistar albino rats of either sex of 180-200 gm were used for experiments from the authorized animal house of Truba Institute of pharmacy, Bhopal. The animals were kept in air conditioning environment and temperature was maintained at 22°C (±3°C). The bedding of animals were changed every 3rd day and fed with standard pellet diet and water *ad libitum*. The experiment was approved by the IAEC and as per as CPCSEA guidelines (approval number 1196/a/08/CPCSEA)

Acute Oral Toxicity Study

Oral Acute toxicity study of EELA was evaluated as per OECD-425 on Wistar albino rats. Three animals were selected for maximum tolerable dose of (2000 mg/kg p.o.). Animals were individually observed for 24 hr and no mortality was found.

Acute Catatonia induced by Chlorpromazine

A catalepsy test was modified.[10] All the groups except control receives prior treatment of EELA for 7 days and on the 7th day in all the groups the acute catatonia was induced by chlorpromazine (single dose of 8 mg/kg i.p.) one hour after EELA administration. The acute catatonia was induced by chlorpromazine (single dose of 8 mg/kg i.p.) in rats. The catatonic severity was evaluated after chlorpromazine administration at 0, 30, 60, 90 and 120 minutes. The animals were considered to be catatonic if they remained immobile for a period of five second or more after their paws were placed on 3 cm and 9 cm boxes. Other parameters like muscle grip

strength by Rota-rod apparatus, locomotor activity by actophotometer and body temperature by telethermometer was evaluated on the 7th day after catatonic inducing.

Experimental designs

Animals were divided into four groups and each group comprises 6 animals.

Group-I Control, receives CPZ (8 mg/kg i.p) only on 7th day for final evaluation

Group-II Treated by L-dopa (100 mg/kg i.p.) once daily for 7 days and CPZ (8 mg/kg i.p.) was injected on 7th day.

Group-III Treated by EELA (100 mg/kg p.o.) once daily for 7 days and CPZ (8 mg/kg i.p.) was injected on 7th day.

Group-IV Treated EELA (200 mg/kg p.o.) once daily for 7 days and CPZ (8 mg/kg i.p.) was injected on 7th day.

Chronic Catatonia induced by Chlorpromazine

This catalepsy test also modified as mentioned.[10]The chronic catatonia was induced by chlorpromazine at dose of 3 mg/kg i.p. once daily for 21 days 1hr after EELA treatment in rats. The catatonic severity and other parameters as stated above were evaluated on day 7, day 14 and day 21.

Experimental designs

Animals were divided into four groups and each group comprises 6 animals.

Group-I Control, receives CPZ (3 mg/kg i.p.) once daily for 21 days

Group-II Treated by L-dopa (100 mg/kg i.p.)+CPZ (3 mg/kg) once daily for 21 days

Group-III Treated by EELA (100 mg/kg p.o.)+CPZ (3 mg/kg) once daily for 21 days.

Group-IV Treated by EELA (200 mg/kg p.o.)+CPZ (3 mg/kg) once daily for 21 days.

Evaluation parameters

Catatonic severity

Catatonic severity was evaluated on following basis of catatonic response[10]

Stage 1: If rats moves normally when placed on the table, score 0 (as shown in Fig.1A).

Stage II: when rats moves only when touche or pushed, score 0.5 (as shown in Fig.1B)

Stage III: When rat placed on the table with front paws set alternatively on 3 cm high block fails to correct the posture in 10 seconds, score 0.5 for each paw with a total of 1 for this stage (as shown in Fig.1C).

Stage IV: When rat fail to remove when the front paws are placed alternatively on a 9 cm block, score 1 for each paw with a total score of for this stage (as shown in Fig.1D)

Muscle grip strength

Muscle grip strength was evaluated by placing individual animal on rotating road (speed 25 rpm) of Rota-rod and not down the "fall off time".

Locomotors activity

The locomotor activity was evaluated by placing individual animal in actophotometer for 10 min and not down the "cut off score".

Body temperature

The body temperature was evaluated individually by telethermometer in degree Celsius.

RESULTS

Muscle grip strength

The study related to the muscle relaxant activity was also used to evaluate the muscle gripping strength. The losses of the muscle-grip indicate the symptomatic effect of the diseases. The percentage changes in the

Table 1: Effect of *Limonia acidissima linn.* Stem bark extract on percentage decrease in the fall off time during single dose study on albino rats.

Groups	Fall off Time (sec)			Percentage change (%)
	0 hr	60 min	120 min	
Group-I	49.5±0.56	17.5±0.42	7.66±0.33	82.57
Group-II	53.33±0.49 a***	46.83±0.47 a***	36.33±0.33 a***	32.72
Group-III	51.5±0.50	36.16±0.40 a***, b***	26.33±0.33 a***, b***	46.97
Group-IV	50±0.51 b***	40±0.44 a***, b***	27.5±0.22 a***, b***	45.09

All the values are mean ± SEM, n=6, ***p<0.001; a-Significant difference as compared to control (group-I); b-Significant difference as compared to standard (group-II).

Table 2: Effect of *Limonia acidissima linn* stem bark extract on percentage decrease in the fall off time during multiple dose study on albino rats.

Groups	Fall off Time (sec)				Percentage change (%)
	0day	7th day	14th day	21st day	
Group-I	54±2.30	10.66±1.14	10±0.94	6.83±0.65	87.35
Group-II	48.50±0.84	45±1.46 a***	40.83±2.57 a***	37±0.96 a***	23.71
Group-III	49.83±2.85	42.66±2.27 a***	37.5±2.48 a***	31±2.6 a***	37.78
Group-IV	53±1.24	48±1.93 a***	38.16±0.70 a***	34.5±1.72 a***	34.90

All the values are mean ± SEM, n=6, ***p<0.001 a-Significant difference as compared to control (group-I); b-Significant difference as compared to standard (group-II).

fall of time for both acute and chronic study were given in Table 1 and 2 respectively. It was clearly observed that the severity of muscle grip loss in multiple dose study was more than single dose study. At the end of study the percentage change in muscle grip strength in case of multiple dose study at 200 mg/kg of ethanolic extract and single dose study was found to be 45.09 and 34.90% respectively which proving the ability of extract to combat the loss of muscle grip strength.

Catatonic score

Table 3 and 4 are the observations during single and multiple dose effects of extract of *Limonia acidissima* against CPZ induced acute and chronic catatonia. The extract shows dose dependent effect both in case of single and multiple dose study. At the end of study the catatonic score of limonia extract at 200 mg/kg was found to be significant ($p<0.05$) and sustain in acute catatonia induced by CPZ as compared to control. In

Table 3: Effect of extract of *Limonia acidissima linn* for catatonic response during single dose study on rats.

Group	Mean ±S.E.M degree of Catatonic response(min)				
Initial	30	60	90	120	
Group I	0.083±0.1083	1.75±0.11	2.08±0.15	2.25±0.11	2.41±0.27
Group II	0±0.00	0±0.00 a***	0.58±0.23 a***	0.83±0.16 a***	1.08±0.20 a***
Group III	0 ±0.00	1.41±0.20 b***	1.66±0.10 b***	1.83±0.24 b***	2.08±0.20 b*
Group IV	0±0.00	1.08±0.23 a*, b***	1.25±0.21 a*	1.5±0.18 a*	1.60±0.11 a*

All the values are mean ± SEM, n=6, ***p<0.001, *p< 0.05 a-Significant difference as compared to control (group-I); b-Significant difference as compared to standard (group-II).

Table 4: Effect of extract of *Limonia acidissima linn* for catatonic response during multiple dose study on albino rats.

Groups	Catatonic score			
	0day	7th day	14th day	21st day
Group-I	0.5±0.25	2.6 ±0.24	2.91±0.23	3.25±0.11
Group-II	0.08±0.08	1.33±0.21 a**	1.25±0.11 a***	1.08±0.2 a***
Group-III	0.66±0.21	2.08±0.27	2.08±0.23 a*, b*	1.91±0.15 a***, b*
Group-IV	0.58±0.23	2.25±0.21	1.91±0.15 a**	1.75±0.21 a***

All the values are mean ± SEM, n=6, ***p<0.001, **p<0.01,*p< 0.05 a-Significant difference as compared to control (group-I); b-Significant difference as compared to standard (group-II).

Table 5: Effect of Limonia acidissima linn stem bark extract on percentage change in the locomotor activity during single dose study in albino rats.

Groups	Cut off score			Percentage change (%)
	0hr	60 min	120 min	
Group-I	357.5±0.88	64.66±2.02	48.33±1.17	86.48
Group-II	342±3.73 a**	284.66±3.25 a***	256±1.17 a***	25.14
Group-III	336.66±4.08 a***	223.83±1.97 a***, b***	187.5±3.11 a***, b***	44.30
Group-IV	351±1.73	237.66±3.70 a***, b***	190.5±1.45 a***, b***	45.72

All the values are mean ± SEM, n=6, ***p<0.001, **p<0.01 a-Significant difference as compared to control (group-I); b-Significant difference as compared to standard (group-II).

Table 6: Effect of *Limonia acidissima linn* stem bark extract on percentage change in the locomotor activity during multiple dose study in albino rats.

Groups	Cut off score				Percentage change (%)
	0 day	7th day	14th day	21st day	
Group-I	285.83±1.77	210.83±2.45	62.66±0.61	38.83±0.87	86.41
Group-II	309±1.51 a***	254.85±1.68 a***	273±1.63 a***	256.51±1.04 a***	16.98
Group-III	310.33±2.72 a***	301.16±2.75 a***, b***	290.33±2.33 a***, b***	230±2.20 a***, b***	25.88
Group-IV	331.66±1.96 a*** b***	291.33±1.38 a***, b***	320.5±1.76 a***, b***	260.66±2.24 a***	21.40

All the values are mean ± SEM, n=6, ***p<0.001, **p<0.01,*p< 0.05 a-Significant difference as compared to control (group-I); b-Significant difference as compared to standard (group-II).

case of chronic catatonia the catatonic score was found to more significant (p<0.001) as compared to control.

Locomotor Activity

Table 5 and 6 depicting the locomotor response against phenothiazine induced EPS and shows dose dependent effects in both single and multiple dose study and shows 45.72 and 21.40 percentage change respectively at 200 mg/kg as compared to control denotes the drug is capable to combating the muscle tone loss due to phenothiazine.

Body temperature

Body temperature was measured on 21st day of study for multiple dose study and was found to increase in treated group as compared to control (as shown in Table 7). The elevated body temperature in the extracted treated group (p<0.05 and p<0.001) suggested that the action as extract might be as anticholinergic.

Statistical analysis used

All the data was statistically by one way ANNOVA, multiple comparision (Tukey Kramer) method and all the values are mean ± SEM, n=6, ***p<0.001, **p<0.01,*p< 0.05 as compared to control group and standard group.

DISCUSSION

On the basis of all the possible findings we are now in a position to conclude the work about the probable mechanism behind the anti-Parkinson's effects of (EELA) and tested its efficacies in antipsychotic induced rat models of PD. The results presented here show that the LA extract suppresses the extra pyramidal side effects, and attenuates the motor activity. The exact etiology of Parkinsonism is unknown in most of the cases but in case of DIP (drug induced Parkinsonism) it has pointed out that all effective antipsychotic drugs have the potential for producing a parkinsonian-like reaction in man.[11] The study was divided in two parts; acute Catatonia induced by Chlorpromazine and chronic catatonia induced by Chlorpromazine, the results of the first study on the basis of evaluation parameter quite favors the treatment.

Chlorpromazine is a classical neuroleptic drug which produces therapeutic effects as well as unwanted side effects in human such as sedation, autonomic, endo-

Table 7: Effect of Limonia acidissima linn stem bark extract on percentage change in temperature during multiple dose study in albino rats.

Group	Body temperature
Group-I	36.3±0.17
Group-II	37.41±0.16 a**
Group-III	38.41±0.17 a*** b*
Group- IV	39.4±0.73 a***, b***

All the values are mean ± SEM, n=6, ***p<0.001, **p<0.01,*p< 0.05 a-Significant difference as compared to control (group-I); b-Significant difference as compared to standard (group-II).

crine and neurological effects.[11] Daily administration of chlorpromazine (1, 3 and 10 mg/kg, i.p) to rats for 21 days induced catalepsy, tolerance to catalepsy and locomotor sensitization.[12-13] To assured the effect of *Limonia acidissima*, the chronic catatonic activity was performed via catatonic scoring, muscle grip strength and locomotor performance. It is thought that blockade of dopamine D-2 receptors caused by chlorpromazine induces these untoward side effects. Pre-clinical studies on catalepsy have been proposed as an animal model for neuroleptic induced extrapyramidal side effects.[14]

Apart from DIP, increasing evidence like environmental toxins like rotenone, trichloroethylene, pesticides etc. indicates that neuroinflammation and mitochondrial impairment may synergistically trigger a vicious cycle ultimately leading to neuronal death.[14-15]The presence of a wide variety of inflammatory cytokines in brains and CSF of PD patients corroborates with the increased activation of binding to their receptors on neurons and subsequent second messenger pathways, but they can also induce microglial iNOS, NAPDH oxidase and myeloperoxidase, all of which have been found in PD and mediated oxidative stress in PD animal models.[16-17]

Rise in body temperature occurs at higher doses of atropine. Children are highly susceptible to atropine fever. It is due to both inhibition of sweating as well as stimulation of temperature regulating center in the hypothalamus.[10] So for getting an ideology behind the probable mechanism of the extract, temperature measurement was selected as evaluation parameter and it was found to be increase in treated (EELA) groups.

The results of anti-catatonic effect of EELA stem bark are presented from Table 1 to 6. To study the anti-catatonic effect, scoring of catatonic response, muscle grip strength and locomotor responses were evaluated and analyze for how much the test drug combats the extra pyramidal side effects with respect to control and standard treatment**.** As per as acute and chronic catatonia induced by CPZ, there was significant difference ($p<0.001$) in muscle grip strength at 200 mg/kg body

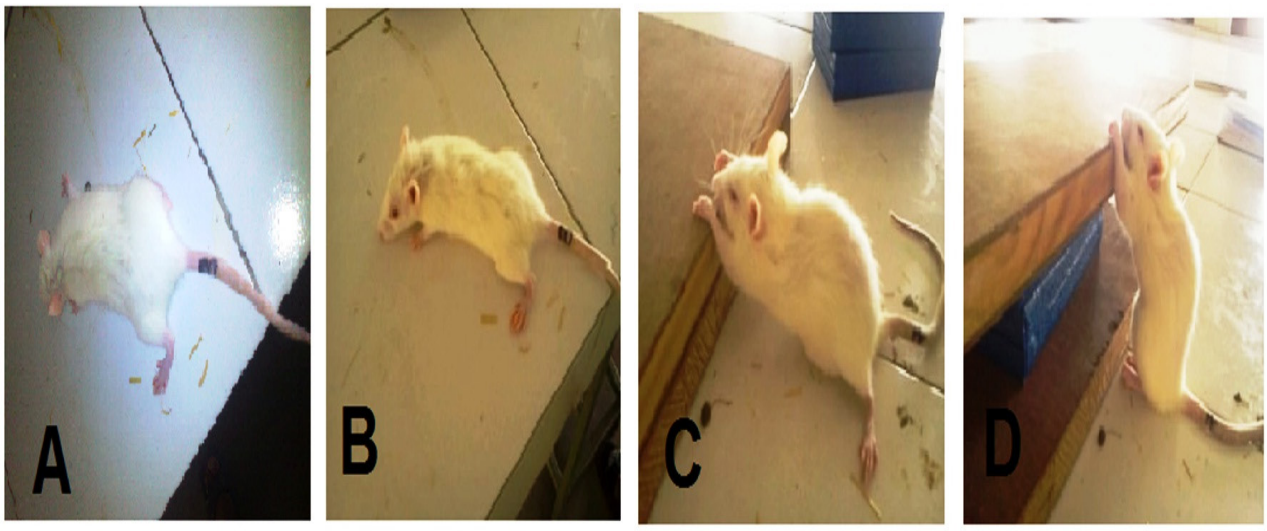

Figure 1: Different catatonic scores, A- catatonic score 0, B- catatonic score 0.5, C- catatonic score 1, D- catatonic score 2

weight as compared to control. There was also a significant locomotor response in both the cases at 200 mg/kg body weight ($p<0.001$) as compared to control. The catatonic severity in case of acute catatonia was found to be sustained and significant ($p<0.05$) at 200 mg/kg of body weight as compared to control. In comparison to acute study and the catatonic severity in case of chronic catatonia was found to be more sustained the significant ($p<0.001$) at 200 mg/kg as compared to control.

CONCLUSION

On the basis of results the present study reveals that the EELA stem bark was effective in both acute and chronic catatonia induced by CPZ. EELA was found effective in dose dependent manner in acute as well as chronic conditions. Extract treated group was found elevated body temperature which indicate that extract act on cholinergic system of body which might be indicative to work as cholinergic agonist. These findings may have important translational implications for treating PD patients.

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