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BETULA UTILIS D. DON: STUDY OF ANTICONVULSANT AND ANXIOLYTIC AGENT

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ABSTRACT
There is chemical examination and pharmacological activity of *Betula utilis*barkwas studied. The bark of *Betula utilis* bark was collected from suburban hills of Uttrakhand and subjected to extraction in hydroalcoholic solvent. Extraction of bark of *Betula utilis* with hydroalcoholic solution yielded a dark brown, semi-solid residue (HABE) (9.0 %). The hydroalcoholic extract of *Betula utilis* was subjected to phytochemical investigation for further study of pharmacological activity. Acute oral toxicity study was perform according to OECD 425 Guidelines and revels that at dose of 2000 mg/kg, 63% of the animals died. So that 1/20th and 1/10th (i.e. 100mg/kg and 200 mg/kg orally) was selected for convulsant and anxiolytic activity. The extract showed a decrease in the duration of the extensor phase and an increase in percentage protection at doses of 100 and 200 mg/kg. Phenytoin completely inhibited the duration of the tonic extensor phase and protected 100% of animals.

KEYWORDS: *Betula utilis*, Anxiolytic activity.

INTRODUCTION
Plant review
Betulautilis D. don commonly called as bhojpatra (Hindi) and Himalayan birch (English) belong to the family betulaceae, burjhkul (in ayurveda).

Figure 1: Betula Utilis D. Don.

Taxonomical classification
Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Fagales
Family: Betulaceae
Genus: Betula
Species: Utilis

Vernicular names – Language	Plant names
English	Himalayan silver birch , jacquemon tree
Hindi	Bhojpatra
Kannada	Burjjamara
Malyalam	Bhujamaram

Convulsion

Convulsions are specific types of seizures where the attack is primarily manifested by involuntary muscular contractions. Seizures are discrete, time – limited alteration in brain function – including changes In motor activity, autonomic functions, consciousness, or sensation that result from an abnormal and excessive electrical discharge of a group of neurons within the brain.

Epelepsy

Epilepsy is a group of neurological disorders characterized by epileptic seizures. Epileptic seizures are episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking. These episodes can result in physical injuries including occasionally broken bones. In epilepsy, seizures tend to recur and as a rule, have no immediate underlying cause. Isolated seizures that are provoked by a specific cause such as poisoning are not deemed to represent epilepsy. People with epilepsy in some areas of the world experience stigma due to the condition.

Seizure types

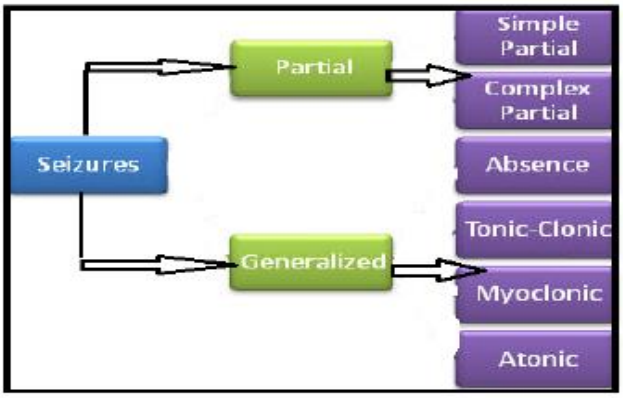

Figure 2: Types of seizure.

Experimental

Extraction

Barks was washed thoroughly 2-3 times with running tap water and once with sterile water, shade dried, powdered and used for extraction. Extraction of bark of *Betulautili*s with hydroalcoholic solution yielded a dark brown, semi-solid residue (HABE) (9.0%), the solvent was removed under pressure to obtain a total extracts.

Pharmacological studies

Acute oral toxicitytest

Different doses of HABE (175, 550 and 2000 mg/kg) were examined for their oral toxicity and LD50 was found to be 1098 mg/kg. When HABE was administered orally to mice up to the dose level of 550 mg/kg, after single dose of administration no mortality was recorded during 48 h study period. However, at 2000 mg/kg, 67% of the animals died. So that $1/20^{th}$ and $1/10^{th}$ (i.e. 100mg/kg and 200 mg/kg orally) was selected for convulsant and anxiolytic activity. For convulsant activity of hydroalcoholic extract of bark of *Betulaulitis*was prepared in distilled water for oral rout of administration.

Table 1: Acute oral toxicity test.

s. no	Number of Mice	Dose of Extract g/kg	Number of mice dead	Percentage (%) of mice dead
1.	06	175	00	00
2.	06	550	00	00
3.	06	2000	03	63

Anticonvulsant activity

Convulsions are specific type of seizurs where the attach is primarily manifested by involuntary muscular contractions **.**Seizures are discrete time – limited alterations In brain function – including changes in motor activity ,autonomic function, consciousness or

sensation – that result from an abnormal and excessive electricaldischarge of a group of neurons within the brain.

Material
- Name - Albino Swiss Mice
- Body wt. – 22-25g
- Sex - Either Sex

Drug and Chemical
- Phenytoin
- Bark extract of betula utilis

Equipment
- Electro-convulsometer
- Coneal electrode
- Stop watch

METHOD
- Maximum electo shock convulsion model
- Pentyenetetrazole (Metrazol) induced convulsion
- Isoniazid induced convulsion model
- Picrotoxin induced convulsion model

Maximum electro shock convulsion model
In MES convulsions electro shock Is applied through the cornial electrodes. through optic stimulation cortical excitation is produced. the MES convulsion divided in to five phase such as
a. Tonic flexion
b. Tonic extensor
c. Clonic convulsions
d. Stuper
e. Recovery of death

A substance is known to possess anticonvulsant property if it reduced or abolishes the extensor phase of MES convulsions.

Group of 6-10 male albino mice (18-30g) are used. The test is started 30 minutes after i.p. injection or 60minutes after oral treatment with the test compound or the vehicle. An apparatus with corneal or earelectrodes is used to deliver the stimuli. The intensity of stimulus is dependent on the apparatus. e.g. 12mA, 50 Hz for 0.2 s have been used under these conditions all vehicle treated mice show the characteristics extensor tonus.

The following parameters will be recorded during test –
Tonic flexion
- Tonic extensor
- Clonus convulsions
- Percen protection

Anxiolytic activity
It is an emotional state, unpleasant in nature, associated with uneasiness, discomfort andconcern or fear about some defined or undefined future threat .some degree of anxiety is a part of normallife.

Mechanism of action
Diazepam enhance the response to GABA by facilitating the opening of GABA – activated chloride channels. They bind specifically to a regulatory site of the receptor. Distinct from the GABA binding site, and act allosterically to increase the affinity of GABA for the receptor.

MATERIAL
Animal –
- Name - Albino Swiss Mice
- Body wt. – 22-25g
- Sex - Either sex

Drug and Chemical
- Diazepam
- Gum acacia or carboximethylcellulose
- Bark extract of betula utilis

Equipment
- **Elevated plus –** Maze
- **Stop watch**

METHOD
- Elevated Plus –Maze Test
- Staircase Test
- Hole – Board Apparatus
- Open Field Behavioral Model

Elevated plus –Maze test
The plus –maze consists of two open arms 50,10,40 cm, and two enclosed arms 50,10,40 cm with an open roof, arranged so that two open arms are opposite to each other. The maze is elevated to a height of 50 cm. the mice (22-25 g body wt.) are housed in pairs for 10 day prior to testing In the apparatus. During this time mice are handled by the investigator on alternate days to reduce stress. group consist of6 mice for each dose. thirty min after i.p. administration of the test drug or the standard, the mice isplaced in the Centre of the maze, facing one of the encl during a 5 min test period the followingmeasures are taken; the number of entries into and time in the open and enclosed arms; the total numberof arm entries. The procedure is conducted preferably in a sound attenuated room.

Statistical analysis
All values will be expressed as mean + - SEM from 6 animal. statistical difference in mean will beanalyzed using one –way ANOVA (analysis of variance) followed by post hoc test (Dunnet't test). $P<0.05$ will be considered as statistically significant.

Evaluation of anticonvulsantactivity
(i) Maximum Electroshock (MES) Induced Convulsion
100 and 200 mg/kg doses of HABE exhibited an anticonvulsant effect. The extract showed a decrease in the duration of the extensor phase and an increase in

percentage protection at doses of 100 and 200 mg/kg (Table 3.12 and Figure 3.23). Phenytoin completely inhibited the duration of the tonic extensor phase and protected 100% of animals. Control animals exhibited hind limb tonic extension (HLTE) after the delivery of anelectroshock.

Table 2: Maximum Electroshock (MES) Induced Convulsion.

Treatment	Duration of tonic flexion (sec)	Duration of tonic extension (sec)	% Protection against mortality
Control (3% Tween80)	4.98 ± 0.21	14.17 ± 0.87	16.40
Phenytoin (25 mg/kg)	5.83 ± 0.98	Not observed	100
HABE (100 mg/kg)	5.86 ± 0.55	7.83 ± 0.63*	83.03
HABE (200 mg/kg)	3.79 ± 0.71	3.34 ± 0.20*	100

Values are expressed as mean ± SEM from 6 mice. Significant at *P < 0.05 as compared to control group using one way ANOVA followed by Tukey – Kramer's post hoc test.

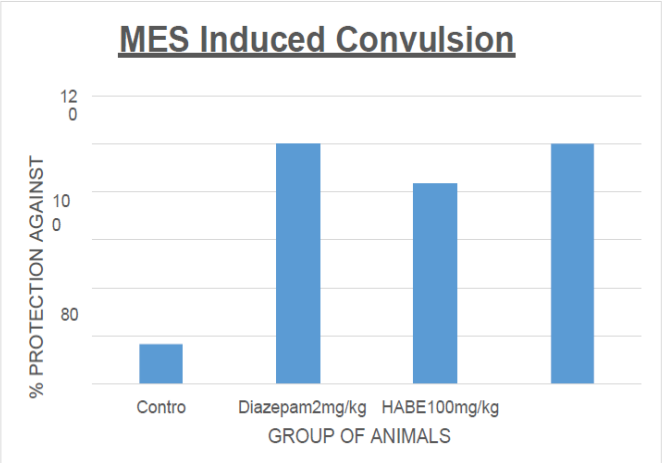

Figure 3: Maximum Electroshock (MES) Induced Convulsion.

HLTE is the universal feature of the MES test in mice, rats, rabbits, cats, monkeys and humans (Swinyard 1972). The electroshock assay in mice is used primarily as an indication for compounds which are effective in grandmal epilepsy. Protection against HLTE in the MES test predicts the ability of a drug to prevent the spread of seizure discharge from the epileptic foci in the brain. In addition, its efficacy in the MES test correlates with the efficacy of drugs that suppress generalised tonic– clonic and partial seizures by causing dose dependent blockade of voltage sensitive sodium channels and by enhancing GABAergic mediated neurotransmission.

All currently available antiepileptic drugs that are clinically effective in the treatment of generalised tonic–clonic seizures (phenytoin, carbamazepine, phenobarbital, lamotrigine and oxcarbazepine) are effective in the MES model (Macdonald and Kelly 1995). An anticonvulsant effect in the MES test model further indicates the ability of the drugs to inhibit or prevent seizure discharge within the brainstem. This indicates the effectiveness of a drug in generalised tonic clonic and partial seizures (White 1995).

SUMMARY AND CONCLUSION

Chemical examination and pharmacological activity of *Betula utilis*bark|was studied. The bark of *Betula utilis* bark was collected from suburban hills of Uttrakhand and subjected to extraction in hydroalcoholic solvent.

Extraction of bark of *Betula utilis* with hydroalcoholic solution yielded a dark brown, semi-solid residue (HABE) (9.0%). The hydroalcoholic extract of *Betula utilis* was subjected to phytochemical investigation for further study of pharmacological activity.

Acute oral toxicity study was perform according to OECD 425 Guidelines and revels that at dose of 2000 mg/kg, 63% of the animals died. So that $1/20^{th}$ and $1/10^{th}$ (i.e. 100mg/kg and 200 mg/kg orally) was selected for convulsant and anxiolytic activity.

The extract showed a decrease in the duration of the extensor phase and an increase in percentage protection at doses of 100 and 200 mg/kg. Phenytoin completely inhibited the duration of the tonic extensor phase and protected 100% of animals. Control animals exhibited hind limb tonic extension (HLTE) after the delivery of an electroshock in maximum electroshock (mes) induced convulsion model.

HABE produced a dose dependent increase in time spent in open arm along with an increase in number of open arm entries. HABE at a dose of 100 and 200 mg/kg

significantly increased number of entries into the open arms and the time spent there. The magnitude of the anxiolytic effects of 100 mg/kg and 200 mg/kg of HABE was comparable to that of diazepam 2 mg/kg p.o. The increased number of entries into the open arms and the time spent there, indicates the stress alleviating effect of HABE (100 and 200 mg/kg).

The result shows that the hydroalcoholic extract of bark of *Betula utili*s was found to be effective against the anti-convulsant as well as anxiolytic activity. The hydroalcoholic extract of this plant is attractive material for the development of a potent phytomedicine for the CNS disorder

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