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Anticonvulsant and anxiolytic activity of ethanolic extract of *Betula utilis* bark

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Abstract

The hydroalcoholic extract of *Betula utilis* was subjected to phytochemical investigation, the results revealed the presence of alkaloids, tannins, flavonoids, carbohydrate in the hydroalcoholic extract of *Betula utilis*.
Acute oral toxicity study was performed according to OECD 425 Guidelines and revels that at dose of 2000 mg/kg, 67% 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. 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).

Keywords: *Betula utilis*, Anti-Convulsant Activity, Anxiolytic Activity, Elevated Plus –Maze Test, Ethnobotany, OECD Guidelines.

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1. Introduction

Ethnobotany is the study of the symbiotic relationship between humans and plants, more specifically on the ways that humans use plants in everyday life. Ethnobotanical species are used as sources of food and medicinal remedies [1-3]. Across the world, it is still common for plants to be used as a major component in natural medicines [4]. Medicinal plants have also been found to be the number one source of biologically active compounds, and many documented medicinal plants have been scientifically proven to have therapeutic applications [5-8]. Ethnobotany is an important branch of science because many cultures, including many Western cultures, are looking for better alternatives to the already existing synthetic medicines [9]. In addition to the drawback of having adverse side effects and frequent addiction with therapeutic usage, synthetic medicines also lose effectiveness over time as the biological system builds a tolerance to it, requiring different doses or even different drugs for the same effect [10]. This opens up the possibility of using natural resources, such as plants, to see if a better alternative may exist in the natural world. Out of the 250,000-500,000 plants that exist on this planet, only 1-10% have been studied to determine if any potential medicinal value exists [11]. This statistic supports the idea that plant species need to be studied and their medicinal values determined. Another benefit of ethnobotany

is that many of the compounds that have already been discovered are secondary metabolites, meaning that they are not directly involved with the plant's metabolic processes [12]. Therefore, harvesting these compounds for mass production will not destroy or alter the plant's normal processes, but will allow for a steady renewable resource to support man's needs for treatment [13].

As per the WHO, about 50 million people worldwide have epilepsy at any one time. Anxiety related disorder is cause of disabilities and 1/8th of the total population worldwide affected with anxiety and becomes a very important area of research interest in psychopharmacology. Anxiety is also as obvious component of many psychiatric and medical condition [14].

In recent years use of alternative medicine in particular derived from plant have been increased in a number of patients with condition that affect the mind [15].

Contrary to the synthetic drugs, anticonvulsant of plant origin is not associated with side effects and have an enormous therapeutic potential to treat many brain disorders [16].

The potential for developing anticonvulsant and anxiolytic activity from higher plants appears rewarding as it will lead to the development of a Phyto-medicine to act against brain disorder [17].

Plant based antiepileptic have enormous therapeutic potential as the can serve the purpose with lesser side effects that are often associated with synthetic antiepileptic. epilepsy is a disease of high prevalence, being well known since thousands of years as "morbussacer". In spite of intensive investigations, the pathophysiology of epilepsy is still poorly understood. Studies with various animal models have provided ample evidence for heterogeneity in the mechanism of epileptogenesis [18].

As of 2015 about 39 million people have epilepsy. Nearly 80% of cases occur in the developing world. In 2015 it resulted in 125,000 deaths up from 112,000 deaths in 1990. Epilepsy is more common in older people. In the developed world, onset of new cases occurs most frequently in babies and the elderly [18]. In the developing world onset is more common in older children and young adults, due to differences in the frequency of the underlying causes [19]. About 5–10% of people will have an unprovoked seizure by the age of 80, and the chance of experiencing a second seizure is between 40 and 50%.

Anxiety disorders are the most common of all the mental health disorders. Considered in the category of anxiety disorders are: Generalized Anxiety Disorder, Panic Disorder, Agoraphobia, Social Phobia, Obsessive Compulsive Disorder, Specific Phobia, Post-Traumatic Stress Disorder, and Acute Stress Disorder. Anxiety disorders as a whole cost the United States between 42-46 billion dollars a year in direct and indirect healthcare costs, which is a third of the yearly total mental health bill of 148 billion dollars. In the United States, social phobia is the most common anxiety disorder with approximately 5.3 million people per year suffering from it. All most 5.2 million peoples suffer from post-traumatic stress disorder every year. People suffer from panic disorder range between 3-6 million every year, an estimate suggest almost twice the number of women suffers more than man from anxiety disorder. Specific phobias affect more than 1 out of every 10 people with the prevalence for women being slightly higher than for men. Obsessive Compulsive disorder affects about every 2 to 3 people out of 100, with women and men being affected equally.

Plants have been one of the rich and important sources of medicine since the down of human civilization [21].

Plants are the gift of nature to the mankind for treating different types of disease. Almost from prehistoric period, herbal medicine used for relieving from suffering caused by different disease in human are well documented in India and other countries. Even today they are in great use in these countries [22]. There are several beliefs / claims regarding the therapeutic utility of herbal and herbal formulation they are –

I. The herbal medicine exhibits fewer side effect and are safe.
II. Herbs and herbal formulations are cheaper and easily available.
III. For certain diseases like hepatitis, the herbal drugs are the only remedies.
IV. Certain chemical constituents from the herbs are serving as prototypic molecules for the discovery of more effective drugs than existing ones.

Considering the important of plants as sources of medicine even today. people are adopting different herbal drugs for the treatment of epilepsy in present study.

We have selected a plant *Betula utilis* (betulaceae) which has been traditionally used for the treatments of wounds and injuries, schizophrenia, epilepsy, paralysis, blood impurity.

According to the exhaustive literature survey the anticonvulsant and anxiolytic activity of this plant has not been reported therefore it has been decided to investigate this plant for its anticonvulsant and anxiolytic activity.

2. Material and methods

2.1 Pharmacognostical Studies

2.1.1 Collection of Plant Material -

Betula utilis were obtained locally from sub-urban hills of Bhopal, M.P.

2.1.2 Identification and Authentication of Plant-

They were authenticated by botanist, **Dr. Pushpendra Kumar Khare, (Ref. No. 021/Bot/2025)** and the voucher specimen was deposited in Department of Botany, Govt. PG College, Bhopal (M. P.)

2.1.3 Washing, drying the size reduction of plant material-

Bark of *Betula utilis* D. Don will be washed thoroughly 2-3 times with running tap water and once with sterile water, shade, dried, crushed to coarse powdered and used for extraction.

2.1.4 Preparation of Extract –

Dried bark powder of *Betula utilis* will be continuously extracted using hydroalcoholic mixture (ethanol + water in the ratio of 70:30 respectively) till exhaustion. The so obtained extract will be concentrated by distilling off the solvent and then evaporating to dryness on the water bath. The dried extract will be then stored in an air tight container and reconstituted in water for injection just before use. The extract will be subjected to anticonvulsant and anxiolytic activity.

2.1.5 Preliminary phytochemical screening –

The preliminary phytochemical investigations will be carried out with the bark extract of *Betula utilis* D. Don. (hydroalcoholic) for qualitative identification of phytoconstituents by following standard procedure.

2.2 Pharmacological Studies

2.2.1 Acute Toxicity Studies

Acute toxicity study will be evaluated. The toxicity of bark extract will be determined by using female albino mice (20-25 g), maintained under standard husbandry conditions. The animals will be fasted for 3 hrs prior to the experiment. Animals will be administered with single dose of bark extract of *Betula utili*s observed for its mortality up to 48 hrs study period (short term toxicity). Based on the short-term toxicity profile, the next dose will be determined as per OECD guidelines No 425. From the LD_{50} dose appropriate fractions of doses are to be selected and considered as low and high doses respectively.

2.2.2 Anticonvulsant Activity

Convulsions are specific type of seizures where they 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 electrical discharge of a group of neurons within the brain.

2.2.3 Maximum Electro Shock Convulsion Model

Albino mice of either sex weighting between 22-25g each group consisting of six animals will be divided into four groups.

Group A -Normal control (vehicle only)
Group B - Standard (Phenytoin 25mg/kg p.o)
Group C -Bark extract of *Betula utilis* (low dose p.o)
Group D -Bark extract of *Betula utilis* (high dose p.o)

2.2.4 Experimental procedure:

Albino mice of either sex with a body weight of 22-25g will be divided into four groups of 6 animals in each. Group A will serve as normal and will receive MES (50 mA for 0.2 Sec), Group B will be administered with phenytoin (25mg/kg p.o) and will serve as standard. Group C and D will be administered with two different doses (low and high) of bark extract of *Betula utilis* for seven consecutive days. On the eighth day one hour after oral administration of the extract/vehicle/standard drug, MES seizures will be induced by electro-convulsometer. A 50mA current will be delivered trans auricularly for 0.2sec in mice via small alligator clips attached to each pinna. This current intensity should elicit complete tonic extension of the hind limbs in control mice. For recording various parameters, mice will be placed in a clear rectangular plastic cage with an open top, permitting full view of the animal's motor responses to seizure. In the pilot study various phases of convulsions, viz., tonic flexion, extension, clonus, stupor and mortality due to convulsions will be selected as the parameters.

2.2.5 Anxiolytic Activity

It is an emotional state, unpleasant in nature, associated with uneasiness, discomfort and concern or fear about some defined or undefined future threat. Some degree of anxiety is a part of normal life.

2.2.6 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 days prior to testing in the apparatus. During this time mice are handled by the investigator on alternate days to reduce stress. Four Group consist of 6 mice for each dose. Group A will serve as normal and will receive saline, Group B will be administered with diazepam (2mg/kg i.p.) and will serve as standard. Group C and D will be administered with two different doses (low and high) of bark extract of *Betula utilis*. thirty min after i.p. administration of the test drug or the standard, the mice is placed in the Centre of the maze, facing one of the enclosed during a 5 min test period the following measures are taken ; the number of entries into and time spent in the open and enclosed arms; the total number of arm entries. The procedure is conducted preferably in a sound attenuated room.

2.3 Statistical Analysis

All the extract treated groups were compared with control in order to determine the significant anticonvulsant& anxiolytic activity**.** All the values that are generated out of this study execution will be expressed as mean ± SEM from 6 animals. Statistical difference in mean will be analyzed using one-way ANOVA (analysis of variance) followed by Dunnett's 't' test. 'p' values lower than 0.05 will be considered as statistically significant.

3. Results and discussion

3.1 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 *Betula utili*s with hydroalcoholic solution yielded a dark brown, semi-solid residue (HABE) (9.0 %), the solvent was removed under pressure to obtain a total extract.

3.2 Phytochemical Investigations

The hydroalcoholic extract of *Betula utilis* was subjected to phytochemical investigation, the results revealed the presence of alkaloids, tannins, flavonoids, carbohydrate in hydroalcoholic extract of *Betula utilis*. (Table 1).

Table 1. Phytochemical Investigation

Category	Name of the test	Result
Alkaloids	a) Mayer's test b) Wagner's test c) Dragendorff's test	**+ve** **+ve** **+ve**
Flavonoids	a) Lead acetate test b) Shinoda test	**+ve** **+ve**
Phenolics &Tannins	a) Ferric chloride test b) Bromine water test	**+ve** **-ve**
Carbohydrates	a) Molish's test b) Fehling's test c) Benedict's test	**+ve** **+ve** **+ve**
Proteins	a) Biuret test b) Millon's test	**-ve** **-ve**
Fixed oil and Fats	a) Stain test	**-ve**
Saponins	a) Froth test	**-ve**
Steroids	a) Salkowski test b) Liebermann Burchard test	**-ve** **-ve**

Present = +ve, Absent = -ve

3.3 Acute oral toxicity test

Different doses of HABE (175, 550 and 2000 mg/kg) were examined for their oral toxicity and LD_{50} 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 *Betula ulitis* was prepared in distilled water for oral rout of administration.

Table 2. Acute Oral Toxicity Test

S. No	Number of Mice	Dose of Extract g/kg	Number of mice dead	Percentage (%) of mice dead
01.	06	175	00	00
02.	06	550	00	00
03.	06	2000	04	67

3.4 Evaluation of anticonvulsant activity

(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 and Figure 1). 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.

Table 3. Maximum Electroshock (MES) Induced Convulsion

Treatment	Duration of tonic flexion (sec)	Duration of tonic extension (sec)	% Protection against mortality
Control (3% Tween 80)	4.98 ± 0.21	14.17 ± 0.87	16.66
Phenytoin (25 mg/kg)	5.83 ± 0.98	Not observed	100
HABE (100 mg/kg)	5.86 ± 0.55	7.83 ± 0.63*	83.33
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.

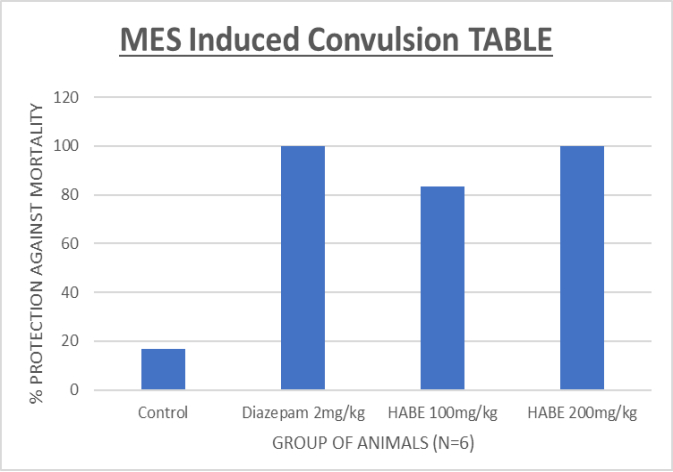

Figure 1. Maximum Electroshock (MES) Induced Convulsion

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. 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.

3.5 Evaluation of anxiolytic activity

Elevated Plus Maze (EPM) Model Test:

In the EPM, control (3 % Tween 80 used as vehicle) treated mice tended to prefer to stay in the closed arm for a longer period of time than in the open arm. Treatment with diazepam (2 mg/kg) increased the number of open arm entries, and time spent in the open arm suggests that diazepam produces anxiolytic activity, which is in accordance with the earlier findings.

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. (Table 4 and Figure 2).

Table 4. Elevated Plus Maze (EPM) Model Test

Treatment	Number of entries in open arm (counts/5min)	Time spent in open arm (sec/5min)
Control (3%Tween 80)	6.00 ± 0.93	53.67 ± 7.49
Diazepam (2 mg/kg)	10.67 ± 0.88 ***	105.66 ± 24.43 ***
HABE (100 mg/kg)	12.67 ± 1.22 ***	107.33 ± 2.98 ***
HABE (200 mg/kg)	12.17 ± 1.35 ***	114.00 ± 20.34 **

Values are expressed as mean ± SEM from 6 mice. Significant at **P < 0.01 and ***P < 0.001 as compared to control group using one way ANOVA followed by Tukey – Kramer's post hoc test.

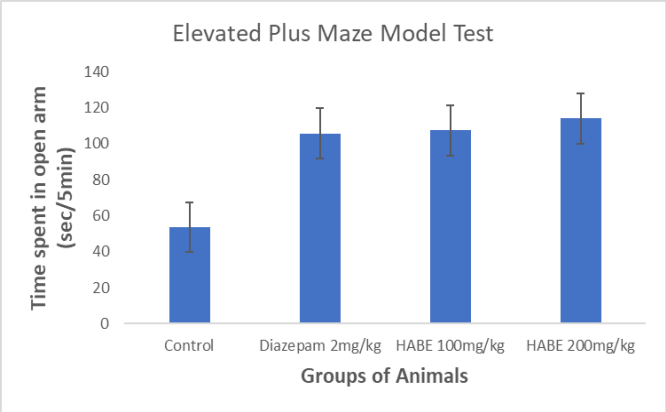

Figure 2. Elevated Plus Maze (EPM) Model Test

The EPM test has a strong predictive validity for screening anxiolytic drugs and used to evaluate psychomotor performance and emotional aspects of rodents. Open arms are more fear provoking than closed arms. Anxiolytic drugs specifically decrease and anxiogenic drugs specifically increase the aversion to the open arm. 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).

4. Conclusion

The bark of *Betula utilis* bark was collected 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, the results revealed the presence of alkaloids, tannins, flavonoids, carbohydrate in hydroalcoholic extract of *Betula utilis*.

Acute oral toxicity study was performed according to OECD 425 Guidelines and revels that at dose of 2000 mg/kg, 67% 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. 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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