Neuropharmacological activities of *Taxus wallichiana* bark in Swiss albino mice

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**ABSTRACT**

**Aims:** The bark of *Taxus wallichiana* is widely used for preparing a decoction and consumed as a tea by several tribal communities of the Indian subcontinent. The sedative, motor coordination, anxiolytic, and antidepressant effects of the hydroalcoholic extract of *T. wallichiana* bark and its ethylacetate fraction were evaluated in mice models of behavior analysis.

**Materials and Methods:** The effects were evaluated on diazepam-induced sleeping time, elevated plus maze and light and dark box, and on the forced swimming test. General locomotor activity and motor coordination effects were evaluated in the actophotometer and rota-rod tests respectively.

**Statistical Analysis:** Results are expressed as mean ± standard error of the mean. Statistical analysis was performed using ANOVA, followed by post-hoc Dunnett’s test.

*P* < 0.05, **P** < 0.01, ***P** < 0.001 were considered as significant.

**Results:** Both the hydroalcoholic extract and ethylacetate fraction showed a marked decrease in latency of sleep onset, prolonged the diazepam-induced sleeping time, decreased spontaneous locomotor activity; whereas ethylacetate fraction produced anxiolytic and antidepressant activity.

**Conclusions:** Both hydroalcoholic extract and its ethylacetate fraction of the bark of *T. wallichiana* have bioactive principles, which induce neuropharmacological changes.

**KEYWORDS:** Bark, behavioral study, hydroalcoholic extract, Swiss albino mice, Taxaceae, *Taxus wallichiana*

**Introduction**

*Taxus wallichiana* is a precious gymnosperm of Himalayan region. It has enjoyed the wide patronage of use among some tribal communities of Indian subcontinent because of its potential therapeutic properties. *T. wallichiana* is reported to have analgesic,[1] antipyretic,[1] anticonvulsant,[1] anticancer,[2] immunomodulator,[3] antibacterial,[4] antifungal,[5] and anti-inflammatory[5] properties. In Indian subcontinent, traditionally tincture is prepared from the aerial parts Himalayan Yew and used in several central nervous system (CNS) disorders such as epilepsy, hysteria, grittiness, biliousness and nervousness.[6] In addition, it is a component of folk medicine “zarnab,” which have sedative and aphrodisiac properties.[9] Because of its medicinal importance there has been a practice of collection of bark for preparing and consuming tea (decoction) throughout the year.[7]

Based on above, it was observed that although the plant is traditionally used for several CNS problems but there are only a few experimental studies conducted till date regarding its neurological potential, which has prompted us to screen hydroalcoholic extract of *T. wallichiana* (HATW) bark and its ethylacetate fraction for its sedative, motor coordination, anxiolytic and antidepressant effects on experimental animals.

**Materials and Methods**

**Collection and Identification Herb**

Barks of *T. wallichiana* tree were collected from district Shimla of Himachal Pradesh, which is Northern State of India (latitude 31° and 7 min and longitude of 77° 21 min) in the month of September, 2012. Plant materials were authenticated at Y. S. Parmar University of Horticulture and Forestry, Nauni, Solan, Himachal Pradesh. The herbarium sheet of the said
Extract Preparation

The collected barks were prepared by removing an outermost layer, inner layer and a middle reddish brown portion (as used traditionally) was selected, cut into small pieces which were then dried in shade for 4 weeks. Dried materials were milled using a manual grinder to get coarse powder. The 420 mg of milled material was extracted by continuous hot percolation with 3L ethanol and water (1:1) at a temperature of 60°C. The extraction was carried out for 48 h after which the drug was completely exhausted, and reddish-brown colored components were extracted completely. The obtained extract was concentrated using rotary evaporator under reduced pressure and then lyophilized to get a yield of 108 g (25.71% w/w). For the preparation of flavonoid-rich ethylacetate fraction, 30 g HATW was suspended in water and heated over water bath at 50°C for 15 min with intermittent shaking. The volume was then made 500 ml with Na₂CO₃ water solution (pH 9.22) and fractionated with petroleum ether using a liquid-liquid extraction technique. The ether layer was separated, and aqueous part was partitioned with ethyl acetate (100 ml, 4 times, 5 min shaking). In each time, the organic fraction was collected. Further, remaining aqueous fraction was then neutralized with HCl 2.0 N (pH 6.8), and partitioned with fresh ethyl acetate (100 ml, 2 times). All the organic shakings were then pooled together and concentrated under reduced pressure to get yield of 1.783 g (5.94% w/w).

Drugs and Chemicals

Diazepam tablets ([Ranbaxy, India], diazepam injections [Ranbaxy, India], fluoxetine [Cadilla, India]), were used as standard drugs. Diazepam was employed as a standard drug for the anxiolytic and motor coordination evaluation. Fluoxetine was used as standard drug for the antidepressant evaluation in the forced swimming test (FST). Other chemicals and reagents used were of laboratory grade.

Animals and Treatment

Swiss albino mice of either sex weighing between (20 and 25 g) were procured from the Animal House at Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar. A week after animal procurement, different groups were made arbitrarily; with each group having six animals. The animals were given standard laboratory feed and water ad libitum. All animals (6 in each cage) were maintained under controlled conditions of temperature at 22°C ± 2°C, humidity 60–65%, having 12 h light-dark cycle, with free access to food and water. All groups were subjected to experimentation between 9:00 am and 5:00 pm. The experimental protocol (Pharma Sc./485) was approved by the Institutional Animal Ethical Committee (Reg. no. 134/99/CPCSEA).

Selection of Test Doses and Toxicity Study

The acute toxicity study of herbal extract was done according to OECD guidelines, 407 (OECD, 1995). A single dose of 2000 mg/kg was given to a group of six female mice orally and were observed for 7 days. Mice were observed for their gross behavior; neurologic, autonomic and toxic effects at 15, 30, 60 min and then once in 7 days. Results with no mortality were regarded as confirmation of nontoxicity of dose. The different test doses of HATW bark given were 50, 100, 200 mg/kg body weight and its ethylacetate fraction of hydroalcoholic extract of T. wallichiana (EATW) were 50, 100 mg/kg, Diazepam (2 mg/kg, p. o.) dissolved in a vehicle (0.9% saline, 10 ml/kg) was used as a positive control. Negative control was given (0.9% saline, 10 ml/kg) only. All doses were given in the volume ranging between 0.20 ml and 0.24 ml orally.

Locomotor Activity

The locomotor activity of experimental groups was determined using actophotomotor (Digital photometer, Rolex), which is based on the principle that when there is a breaking of infrared beams, the instrument registers locomotion of experimental animals automatically.[8] Before introduction to locomotion test, each mouse was given oral dose and after 60 min was placed in a cage having infrared beams. The locomotor activity was measured at 5 min interval for 15 min.

Diazepam Induced Sleep

Evaluation of HATW and EATW for their sedative effects, diazepam-induced sleep models was used.[9] Briefly, Swiss albino mice of either sex were randomly divided into six groups with each group having six mice. The mice were treated with HATW at the dose of 50, 100, 200 mg/kg and EATW (50, 100 mg/kg) body weight or normal saline (10 ml/kg). Thirty minutes posttreated, the mice administered diazepam at 20 mg/kg, i.p. The onset and duration of sleep were determined for each animal. Loss of righting reflex was considered as the criterion for sleep while the interval between the loss and the recovery of righting was regarded as the duration of sleep.

Elevated Plus Maze

This test is widely validated to measure anxiety in rodents.[10] The apparatus used has some modification. It was made of wooden plywood brownish in color. It consists two open arms (15 cm × 5 cm) and two closed arms (16 cm × 5 cm) with 14.5 cm walls. The two open arms have rims of 1 cm covering the three sides of two open arms, to prevent mice from falling. The arms extended from the central platform (5 cm × 5 cm). The maze was elevated 25.3 cm from the room floor. Each animal was placed in central platform facing one of the open arms. Number of entries and the time spent in the open and enclosed arms were recorded for 5 min test. For each animal, the percent of time spent in the open arms (100 × open/open + closed) and the percent of open arm entries (100 × open/open + closed) were computed.

Light-Dark Test

The apparatus consists of a wooden box with two compartments of (20 cm × 20 cm each), one of which was subjected to light while the other remained dark. Each animal was placed at the illuminated compartment near the wall separating light and dark compartment. The time spent in respected illuminated and dark places of the compartments was recorded for 5 min.[11] For each animal, the time spent in the open lighted area was computed.

Rotarod Test

Motor coordination test was carried in rotarod test (Digital Rota rod with six compartments, Rolex). The mice were treated with HATW (50, 100, 200 mg/kg), EATW (50, 100 mg/kg body weight), DZP 2 mg/kg and saline water 10 ml/kg. Treated mice, after 60 min, were then placed with their forepaws on a 2.5 cm
diameter bar, 25 cm above the floor, which was turning at 12 rpm. For each animal, the number of falls (up to three falls) and the time of permanence on the bar for 1 min were recorded.

**Forced Swimming Test**

The FST is an *in vivo* model for assessing antidepressant activity, which is based on the cessation of persistent-escape direct behaviors measured by immobility shown when the mice are placed in an escapable cylinder filled with water[12] The mice were forced to swim individually in a glass cylinder (diameter, 12 cm; height, 30 cm) containing 20 cm of water at 25°C ± 1°C temperature. The test doses in experimental groups were administered three times: Immediately after the 15-min pretest, 18 h and 1 h prior to the swimming test. The duration of immobility was recorded for duration 5 min. During the test session a trained observer registered the immobility time, which was considered when mouse made no further attempts to escape, apart from the movements necessary to keep the head above the water.

**Phytochemical Screening**

Phytochemical screening of HATW and EATW were carried out as per the procedure mentioned in the standard books.

**Statistical Analysis**

Results are expressed as mean ± standard error of the mean. Statistical analysis was performed using ANOVA followed by post-hoc Dunnett’s test. *P* < 0.05, **P* < 0.01, ***P < 0.001 were considered as significant.

**Results**

**Behavioral Studies**

**Locomotor activity and motor coordination**

The diazepam DZP (2 mg/kg) treatment to standard group decreased the locomotor activity significantly (***P < 0.001). The treatment of HATW (200 mg/kg) showed a decrease in locomotor activity, which was less significant (**P < 0.01) compared with the standard group as shown in Table 1. The other groups failed to show any significant decrease in the locomotor activity. In the motor coordination study it was found that hydroalcoholic extract (HATW, 50–200 mg/kg, p.o.) and EATW (50–100 mg/kg p.o.) showed no significant impairment in motor performance of animals in comparison to standard group, which showed significant increase (*P < 0.05) for number of falls in 1-min in rota-rod test comparative to control group as evident from Table 1.

**Diazepam induced sleep**

The observation of mean sleep latency time and duration of diazepam induced sleep in control and test groups of mice on mentioned in Table 2. HATW (200 mg/kg) has shown a most significant result in mean sleep latency and duration of sleep.

**Elevated plus maze**

In the elevated plus maze (EPM), the behavior of the standard group, control group and test groups in percent open arm entries and percent time spent in open arms is shown in Table 3. DZP (2 mg/kg) confirmed the anxiolytic activity, by showing significant (***P < 0.001) increase in percent open arm entries and percent time spent (**P < 0.01) in open arms. The groups of mice treated with HATW (100 mg/kg) and EATW at the dose of 100 mg/kg of body weight have shown anxiolytic activity, however, less significant (*P < 0.05) to

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Table 1: Motor coordination (locomotion and skeleton muscle relaxant) effect of *Taxus wallichiana* in experimental mice

| Groups          | Locomotor activity scores (mean±SEM) | Number of falls in one minute expressed in rota-rod apparatus (mean±SEM) |
|-----------------|-------------------------------------|---------------------------------------------------------------|
| Control (10 ml/kg, 0.9% saline) | 898.0±29.57                        | 3.66±0.21                                                    |
| Standard (2 mg/kg) | 718.5±35.40***                     | 4.83±0.30*                                                   |
| HATW (50 mg/kg) | 840.7±41.80                        | 4.33±0.33                                                   |
| HATW (100 mg/kg) | 819.8±12.22                        | 4.50±0.34                                                   |
| HATW (200 mg/kg) | 744.5±17.74**                      | 4.66±0.21                                                   |
| EATW (50 mg/kg) | 834.0±14.11                        | 4.16±0.16                                                  |
| EATW (100 mg/kg) | 811.2±22.64                        | 4.26±0.30                                                  |

*P<0.05, **P<0.01, ***P<0.001 versus control. Locomotor activity count observed for 15 min at 5 min interval in actophotometer and muscle-relaxant activity studied for number of falls in rota-rod test apparatus for 1 min. n=6. Values are expressed as mean±SEM.

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Table 2: Sedative effect of *Taxus wallichiana* in experimental mice evaluated by their sleep latency and duration of sleep

| Treatment (mg/kg) | Mean sleep latency (min) | Mean duration of sleep (min) |
|-------------------|--------------------------|-----------------------------|
| Control (10)      | 9.38±0.72                | 113.3±3.32                  |
| HATW (50)         | 7.53±0.33                | 135.8±9.108*                |
| HATW (100)        | 6.23±0.71**              | 145.8±2.405***              |
| EATW (50)         | 6.87±0.22*               | 131.7±4.924                 |
| EATW (100)        | 6.57±0.61**              | 135.3±4.638b                |

*P<0.05, **P<0.01, ***P<0.001 are significant. Values are expressed as mean±SEM. ANOVA followed by Dunnett’s multiple comparison test shows significant treatment group. SEM=Standard error of mean, HATW=Hydroalcoholic extract of *Taxus wallichiana*, EATW=Ethyl acetate fraction of bark of *Taxus wallichiana*.

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Table 3: Anxiolytic activity of *Taxus wallichiana* in experimental mice in elevated plus maze model

| Groups              | Percentage open arm entries | Percentage time spent in open arms |
|---------------------|-----------------------------|-----------------------------------|
| Control (10 ml/kg)  | 9.00±2.033                  | 8.07±2.231                       |
| Diazepam (2mg/kg)   | 33.60±1.608***              | 18.77±2.267**                    |
| HATW (50 mg/kg)     | 23.6±1.599*                 | 10.09±2.316                      |
| HATW (100 mg/kg)    | 24.8±4.174*                 | 17.39±1.951*                     |
| HATW (200 mg/kg)    | 19.17±4.199                 | 12.52±1.293                      |
| EATW (50 mg/kg)     | 21.67±4.773                 | 12.67±1.229                      |
| EATW (100 mg/kg)    | 26.67±4.216**               | 17.67±2.486*                     |

*P<0.05, **P<0.01, ***P<0.001 significant versus control, n=6. Values are expressed as mean±SEM. Anova followed by Dunnett’s multiple comparison test showed a significant treatment effect. HATW=Hydroalcoholic extract of *Taxus wallichiana*, EATW=Ethylacetate fraction of hydroalcoholic extract, SEM=Standard error of mean.
show percentage open arm entries as well as percentage time spent (*P < 0.05) in the open arms in comparison to standard group.

### Light and dark box

Light and dark model is one of the established models for evaluation of the anxiolytic activity of drugs in rodents. The DZP group showed a significant (**P < 0.01) time spent (s) in the light compartment of the light and dark box (LDB). The HATW and EATW both were less significant (*P < 0.05) when evaluated for the time spent in the light area of the LDB in comparison to the standard group as shown in Table 4.

### Forced Swimming Test

The antidepressant-like effect of fluoxetine or vehicle and different doses of the HATW (50–200 mg/kg) and EATW (50–100 mg/kg) treated groups, on active behaviors in FST is shown in Table 5. Fluoxetine treated group showed a significant decrease (**P < 0.001) in immobility compared with control group. On observation of different test groups in FST, HATW (200 mg/kg) and EATW (50, 100 mg/kg) treated groups have shown antidepressant-like effect, but was less significant (*P < 0.05) compared to standard group.

### Phytochemical Screening

The results of phytochemical screening of the hydroalcoholic extract of bark Taxus wallichiana is shown in Table 6.

### Discussion

In the present study, HATW and EATW effects on locomotor activity were dose-dependent decrease in the number of counts as registered on obstruction of the infrared beam in actophotometer. HATW at the dose of 200 mg/kg showed a significant decrease in the motor counts, however, less pronounced compared to the standard group. The sedative activity of HATW and EATW is evident from the decrease in latency and increase in sleeping time of induced sleep by diazepam given by intraperitoneal route. For evaluation of anti-anxiety activity EPM was used since it provides spontaneous or natural aversive stimuli such as height, unprotected opening and novelty which generate fear and made naïve mice to spend more time in closed arms; therefore any agent that increase open arm exploration are considered anxiolytic.[13] The present study has found diazepam as an effective anxiolytic. On comparing, groups treated with HATW and EATW have shown dose-dependent sensitivity, which was less significant in comparison to the standard group. However, it is worthwhile to add that HATW (200 mg/kg) failed to show any significant result in percent open arm entries and percent time spent in open arms, which could be due to sedative effect at this dose. The other model used for anxiolytic evaluation was LDB which is based on the inborn aversion of rodents to brightly illuminated areas and aversion from the spontaneous exploratory behavior in response to novel surroundings and in this model measurement of time spent in the light area is the most consistent and useful parameter for assessing an anxiolytic action.[14] In the present experiments mice treated with HATW and EATW at different doses have shown anxiolytic-like activity, which was mild in comparison to diazepam treated group when evaluated in similar paradigm, as evident from comparative evaluation of the time spent by different test groups of mice in light compartment of LDB. The skeleton muscle relaxant of HATW and EATW were evaluated by using rotarod test, which detect motor impairment due to pharmacological agents such as skeletal muscle relaxants or CNS depressants[15] and is based on the assumption that an animal with normal motor efficiency are able to maintain its equilibrium on a rotating rod and any alterations in maintaining

### Table 4: Anxiolytic activity of Taxus wallichiana in experimental mice evaluated in LDB

| Groups | Time spend in lighted area |
|--------|---------------------------|
| Control (10 ml/kg) | 37.00±5.309 |
| Diazepam (2 mg/kg) | 74.86±7.927** |
| HATW (50 mg/kg) | 62.71±5.743 |
| HATW (100 mg/kg) | 65.57±6.129* |
| HATW (200 mg/kg) | 63.57±11.82* |
| EATW (50 mg/kg) | 68.50±3.334* |
| EATW (100 mg/kg) | 67.33±2.860* |

### Table 5: Antidepressant activity of Taxus wallichiana in experimental mice during FST

| Group | Time of immobility (s) |
|-------|------------------------|
| Control (0.9% saline) | 72.33±2.883 |
| Fluxetine (10 mg/kg) | 29.50±4.703*** |
| HATW (50 mg/kg) | 52.83±10.68 |
| HATW (100 mg/kg) | 53.67±3.018 |
| HATW (200 mg/kg) | 47.33±4.660* |
| EATW (50 mg/kg) | 50.50±2.790* |
| EATW (100 mg/kg) | 47.33±4.137* |

### Table 6: Phytochemical analysis of HATW and EATW bark

| Chemical constituents | Inference |
|-----------------------|-----------|
| HATW                  | EATW      |
| Alkaloids             | +         | -         |
| Diterpenes            | +         | +         |
| Steroids              | +         | -         |
| Sterols               | +         | -         |
| Tannins               | +         | +         |
| Flavonoids            | +         | +         |
| Glycosides            | +         | +         |

Chemical nature of phytocompounds detected in hydroalcoholic extract of Taxus wallichiana and its ethylacetate fraction. (+) represent the presence; (−) represent the absence. HATW=Hydroalcoholic extract of Taxus wallichiana, EATW=Ethylacetate fraction of hydroalcoholic extract of Taxus wallichiana, SEM=Standard error of mean, LDB=Light and dark box.
equilibrium determine the dysfunction in the motor coordination ability of mice. The doses of HA and EA employed for the study did not reveal any significant motor impairment compared to the standard group which had shown motor impairment. Evaluation of antidepressant activity was done by FST and it was found that fluoxetine, the standard drug used, showed significant antidepressant effect. In comparison to standard, ethylacetate fraction was consistent to show an antidepressant-like effect at both test doses. The antidepressant behavior seems to be independent of any stimulatory effect of the herb since there was a decrease in locomotors activity as evident in actophotometer testing for locomotion.

The possible mechanism that could be proposed on the basis of obtained result is the probable action on gamma-aminobutyric acid (GABA)ergic neurons or enhancing the action of GABA on GABA receptors, since it is established that agents that enhances these action receptors are positive modulators and used for treatment of anxiety, cognitive disorders, epilepsy, insomnia, and schizophrenia.[17]

As far as chemical constituent’s presence in the bark that could be responsible biflavonoids can be regarded as important chemical constituents since they are chemotaxonomic markers of the majority of gymnosperms including family Taxaceae. Several biflavonoids have been reported, specifically the apigenin dimmers of C-8, C-3 from different species of genus Taxus. Biflavonoids obtained from T. wallichiana leaves are amentoflavone, scidopytisin, mono and O-dimethyl-amentoflavone. Beside, biflavonoids (apigenin-apigenin dimmers) conjugated flavonoids with glycosides have been isolated from genus Taxus. Significance of apigenin, biapigenin and flavonoid glycosides is evident from many studies, which have found their action on CNS, for example, apigenin have anxiolytic-like effect and similarly, experimental studies had linked amentoflavone (biapigenin) to anxiolytic and antidepressant activity. Since the preliminary phytochemical examination of hydroalcoholic extract and ethylacetate fraction, tested positive for the presence of flavonoids therefore, there is a possibility of above flavonoids in the bark. Other components contributing to CNS depression could be sterols, specifically the β-sitosterol, which have recently reported to have anxiolytic like effects and have been isolated from T. wallichiana bark. However, neuroactive action of defatted ethylacetate fraction, as found in present study, suggests that phenolic principle could also be responsible for the behavioral action. This preliminary study has investigated the behavioral properties of T. wallichiana bark in a different paradigm of behavioral analysis. Further studies are needed to determine the responsible chemical constituents and possible mechanisms of action.

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