# Acute Toxic Study And Pharmacogenetic Analysis Of The Methanolic Extract Of *Justicia Adhatoda*

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**ABSTRACT**
Acute oral toxicity studies aim to determine the therapeutic index of a substance. A pharmacogenetic study was conducted on the methanolic extract of Justicia adhatoda L, following the revised draft guidelines 423 of the Organization for Economic Co-operation and Development (OECD). The study involved methods such as color and odor, ash value, extractive value, and limit test for heavy metals. The results showed that the alcoholic extract or aqueous extract suspension was orally fed to overnight starved wistar albino rats at a dose of 2000mg/kg body weight. Behavioral changes were observed at intervals of 4 hours, 6 hours, 24 hours, and 48 hours during the next 14 days.
The study used healthy young albino rats, both male and female, weighing between 150-200 g and aged 8 to 12 weeks. The LD50 (lethal dose 50%) of an extract from a specific medicinal plant called Adhatoda Vasika was determined. The animals were initially monitored after receiving a dose, at least once during the first 30 minutes and then periodically throughout the first 24 hours. Mortality was recorded in all instances within the initial 24-hour period. Further attention was devoted to the examination of convulsions and tremors.

**Key words:** Toxicity, Albino rats, Therapeutic index, Mortality

## 1- INTRODUCTION

Plants are essential for life, providing 90% of human calories and 80% of protein. They have historically served as medicinal foundations for medicine. India, with 80% of its population living in isolated regions, has a variety of plants with medicinal properties. To harness this natural asset, nutraceuticals should be used without adverse effects. Traditional medicine has gained global recognition due to its effectiveness in healing diseases. Advanced microbiological and chemical processes can produce therapeutic compounds, but synthetic alternatives are reducing their use in modern medicine.[1,2,3]
Herbal medication development is a field that combines traditional knowledge with modern scientific methods to explore the therapeutic qualities of plants. Indigenous societies have historically used plants for medicinal purposes, and many modern drugs can be traced back to herbal remedies.[4,5] Researchers identify potential medicinal plants through ethnobotanical investigations, extract, fractionate, and purify materials, and use advanced analytical techniques to isolate and characterize compounds. After identifying compounds, pharmacological experiments are conducted to evaluate their medical effectiveness. The wide range of plant species and complex chemical compositions make herbal drugs appealing for therapeutic advancement. Historical usage can guide the development of innovative herbal medicines and simplify the drug discovery process.[6]

Extract preparation is a crucial step in the study of bioactive compounds derived from plants, marine organisms, and other biological materials. It involves the extraction and concentration of bioactive compounds from complex biological matrices, including alkaloids, flavonoids, terpenoids, and phenolic compounds. These compounds have potential therapeutic benefits and can be used in various disciplines like pharmaceuticals, nutraceuticals, and cosmetics. Extract preparation involves various methods, each customized to the properties of the target compounds and the characteristics of the source material.[7,8]

Maceration is a simple and oldest method, involving prolonged immersion of plant material in a solvent. Soxhlet extraction is a continuous extraction technique that uses a specialized apparatus to achieve higher extraction efficiency. Steam distillation is used to extract volatile compounds, particularly essential oils, from aromatic plants. Supercritical Fluid Extraction (SFE) uses supercritical fluids like carbon dioxide as solvents, achieving selectivity, efficiency, and the ability to produce extracts free of residual solvents. Ultrasound-Assisted Extraction (UAE) uses ultrasonic vibrations to improve extraction efficiency.[9,10]

Extractive fractionation is a critical process in natural product chemistry, separating complex assemblages of compounds

from natural sources into homogeneous fractions enriched in specific bioactive components. This process is essential for the isolation and purification of bioactive compounds from crude extracts, enabling researchers to partition mixtures into more manageable and enriched fractions. Pure substances are obtained through this process, which is crucial for their development into therapeutic agents or functional constituents in various applications, as well as for biological testing and structural elucidation.[11,12]

Adhatoda vasica, often known as Malabar Nut, is a perennial shrub belonging to the Acanthaceae family. This plant is held in great esteem in traditional healing systems, such as Ayurveda., Unani, and Siddha, for its diverse therapeutic properties, particularly in the treatment of respiratory ailments. Adhatoda vasica, which is indigenous to the Indian subcontinent, is cultivated and employed globally for its medicinal properties.[13]

Adhatoda vasica is a large, dark green plant native to the Indian subcontinent, including India, Pakistan, Sri Lanka, and Nepal. Its flowers are tubular, white or purple, and bloom from February to April. The fruit is a small capsule with silky seeds. The plant's roots are fibrous and help absorb water and nutrients from the soil. Adhatoda vasica is cultivated in gardens, farms, and occasionally in the wild, with seeds or stem cuttings being the most common methods of propagation. It has been introduced to tropical and subtropical regions worldwide due to its medicinal properties.[14,15]

To evaluate the efficacy of Adhatoda vasica in the treatment of respiratory conditions, including asthma and bronchitis, clinical trials have been conducted. These trials have contributed to the development of standardized pharmaceutical preparations and have provided evidence that supports its traditional applications.

The development of a comprehensive 2000-word paragraph on Adhatoda vasica (Malabar Nut) necessitates an in-depth examination of the plant's botanical characteristics, habitat, medicinal applications, chemical composition, cultivation methods, historical significance, and current research. The following is a comprehensive summary that addresses these elements:[16,17]

## 2- MATERIAL AND METHODS

**2.1 Plant materials:** The plant species included for this investigation were selected based on their established traditional usage in treating diabetes, pain, fever, infections, and oxidative stress. The current research used the leaves of Adhatoda Vasika.

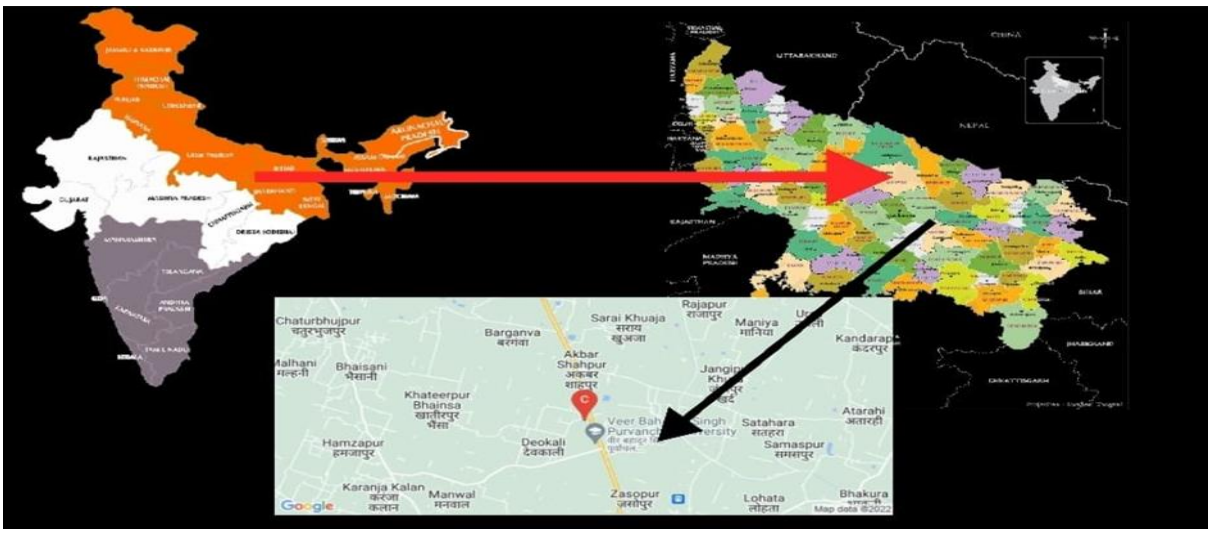



**Figure 2.1: Geographically location of plant collection**

**2.2 Collection, identification and authentification of plant parts:**

The plant material was collected from the local area of Veer Bahadur Singh Purvanchal University, located in Jaunpur, India, with the postal code 222003. Scientist E. Arti Grag from the Central Regional Centre of the Botanical Survey of India in Praygraj, Uttar Pradesh, conducted the process of identifying and verifying the authenticity. The samples are stored in the institutional herbarium for future reference, under the accession number Justicia adhatoda L. 104530.

**2.3 Chemicals and reagents**

The chemicals utilized in this study were obtained from HiMedia Laboratories Pvt. Ltd. (Mumbai, India), Sigma-Aldrich Chemical Co. (Milwaukee, WI, USA), SD Fine-Chem Chem. Ltd. (Mumbai, India), and SRL Pvt. Ltd. (Mumbai, India). All the chemicals utilized in this experiment were of analytical grade.

**2.4 Procedure for preparing extracts via successive solvent extraction:**

**2.4.1 Extraction process:**

Extraction is the process of isolating biologically active substances from plant or animal tissues by employing particular solvents according to established extraction methods. Crude medicines are subjected to conventional extraction processes in order to get the therapeutically necessary component and eliminate inactive substances through the use of particular

solvents. The solvents used in the extraction process are known as Menstrum.The extracts obtained from the extraction process can be used as medicinal agents in the form of tinctures or fluid extracts.This can be further incorporated into other dosage forms, such as tablets and capsules.Therefore, it is crucial to establish a standardized extraction procedure to precisely evaluate the overall quality of herbal remedies.[18]

**2.4.2 Preparation for extraction:**

The extraction efficiency of plant species extracts is significantly affected by the polarity of the solvent, which in turn affects the qualitative and quantitative content of the extracted compounds. Petroleum ether and water are commonly employed as solvents for extraction because of their little toxicity and exceptional extraction efficacy. An advantage of using these solvents is the capacity to modify the polarity of the solvent by applying different ratios of solvent mixtures.[19] The plant leaves were dried to control temperature, humidity, and safeguard the active components from damage (WHO, 2003).

**Figure 2.2:** Soxhlet extraction of Adhatoda Vasica

**2.5- Percentage yield**

The percentage yield of extract is a measure of the efficiency of the extraction process used to isolate specific compounds from a plant or other source material. It is calculated by comparing the weight of the obtained extract to the initial weight of the raw material, expressed as a percentage. This metric is important in fields such as pharmacognosy, herbal medicine, and natural product chemistry, where it helps determine the effectiveness of different extraction methods. A high percentage yield indicates that a significant portion of the desired compounds has been successfully extracted, which is desirable for both research and commercial applications. Conversely, a low percentage yield may suggest the need for optimization of the extraction process to improve recovery rates and ensure the efficient use of raw materials**.**

**2.6- Pharmacognostic Studies**

Pharmacognostic studies, which involve the identification, quality control, and analysis of crude drugs from natural sources, utilize a variety of materials and methods. These include macroscopic and microscopic examination of plant parts, physicochemical analysis (ash values, extractive values, etc.), and preliminary phytochemical screening. Additionally, techniques like thin-layer chromatography (TLC) and fluorescence analysis are employed to further characterize and analyze the plant extract

**2.7Toxicity Studies:**

**2.7.1 Acute oral toxicity – Acute toxic class method**: (OECD Guidelines, 2001)

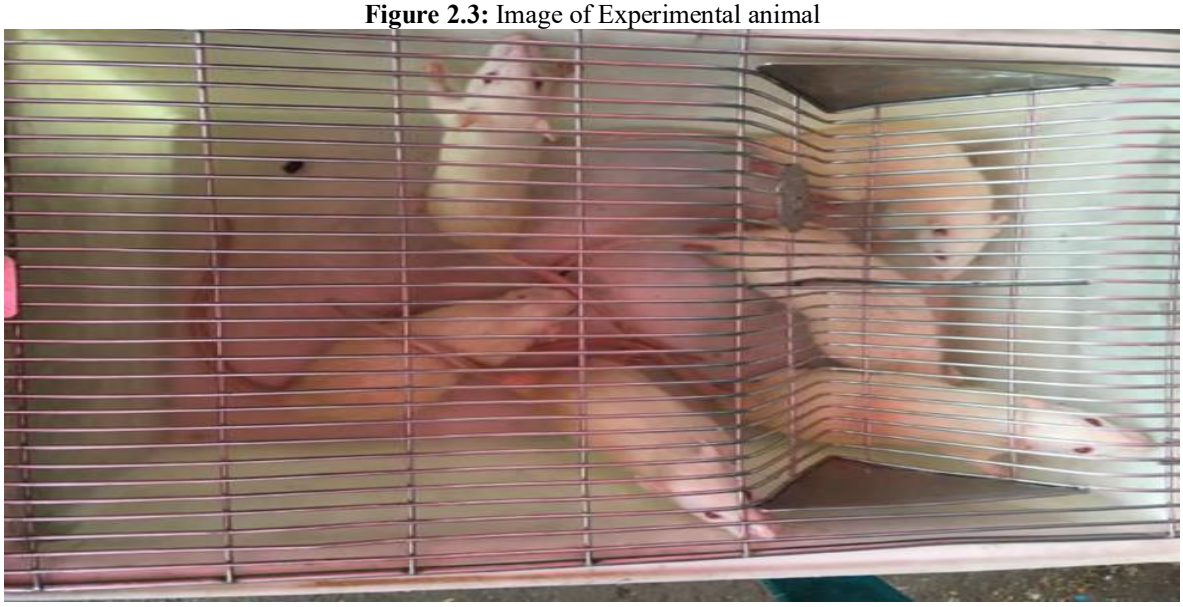
The main goal of acute oral toxicity study is to determine the therapeutic index. The acute oral toxicity study was conducted following the revised draft guidelines 423 of the Organization for Economic Co-operation and Development (OECD). These guidelines were obtained from the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), which is under the Ministry of Social Justice and Empowerment, Government of India. [20,21]

The regulation is based on a step-by-step process that requires using a minimum number of animals at each stage to collect enough data on the test substance's acute toxicity in order to determine its categorization. Three animals from each species are subjected to testing at every stage of the testing process. The alcoholic extract or aqueous extract suspension was orally fed to overnight starved wistar albino rats (n=6) at a dose of 2000mg/kg body weight by observing the presence or absence of the suspension. The animals' behavioral changes were observed at intervals of 4 hours, 6 hours, 24 hours, and 48 hours during the next 14 days. Behavioral criteria

include heightened breathing, grooming, lack of righting response, drowsiness, increased activity, and convulsions.

**2.7.2. Selection of animal species:** In this acute toxicity study, we used healthy young albino rats, both male and female, weighing between 150-200 g and aged 8 to 12 weeks. The purpose of the study was to determine the LD50 (lethal dose 50%) of an extract from a specific medicinal plant called Adhatoda Vasika.
**2.7..3 Housing and feeding conditions:** The temperature in the experimental chamber was kept at a consistent room temperature of around 25 degrees Celsius. The lights was programmed to follow a diurnal cycle consisting of 12 hours of darkness and 12 hours of light. A sufficient amount of drinkable water was supplied to the standard laboratory diet.
**2.7.4 Animal Preparation:** The animals used for the experiment were randomly picked, labeled for easy identification, and kept in polypropylene cages for one week before being given the dose. This allowed them to adjust to the laboratory environment.
**2.7.5 Animal Count and Dose Levels**: For each phase, a total of three animals were used in each cohort. The trial began with an initial dose of 2000 milligrams per kilogram of body weight. The procedure for dosage selection and determination of LD50 cut-off values is as follows: The following table lists the LD50 values for several extracts: Restrict the quantity of milligrams per kilogram of body weight in the vehicle. The term "LD50" denotes the dosage at which 50% of the subjects exposed to a substance will die. The term refers to the minimal number of dosages required to eradicate 50% of the test samples. This is the traditional approach for evaluating the drug's toxicity. To assess the anti-diabetic and hepatoprotective effects, a therapeutic dosage that was one-tenth of the fatal dose was given.
**2.7.6 Observations:** The animals were initially monitored after receiving a dose, at least once during the first 30 minutes, and then periodically throughout the first 24 hours. Mortality was recorded in all instances within the initial 24-hour period. Furthermore, alterations in the skin, fur, eyes, mucous membranes, respiratory system, circulatory system, autonomic nervous system, central nervous system, and somato motor activity and behavior patterns can be detected. Further attention was devoted to the examination of convulsions and tremors.[22,23]

**Figure 2.3:** Image of Experimental animal



**2.8 Pharmacological Evaluation using Animal Models:**
**2.8.1 Animal selection:**
The entities The Swiss albino mice were kept in spacious and clean polypropylene cages, following normal protocols. The mice were maintained at a temperature of $22 \pm 2$ ◦C and subjected to a 12/12-hour light and dark cycle. The mice were obtained from PBRI's in-house animal facility. Water was provided freely throughout the duration of the study, and all animals were given a commercially available rat normal pellet diet (NPD) obtained from Keval Sales Corporation, Vadodara.
The animals were mandated to refrain from eating for at least 12 hours before each activity began. The experimental methods were carried out in accordance with the rules set by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). [24]

**3-RESULT**
Phytochemical screening is a process used to identify and study the various chemical compounds present in plants. These compounds, known as phytochemicals, include a wide range of biologically active substances such as alkaloids, flavonoids, tannins, saponins, and terpenoids. The screening involves a series of qualitative and quantitative tests that help in determining the presence and concentration of these compounds. This is crucial for understanding the medicinal properties of plants, as phytochemicals are often responsible for the therapeutic effects seen in traditional and modern medicine. Through phytochemical screening, researchers can isolate and analyze these compounds, paving the way for the development of new drugs and treatments derived from plant sources.

### 3.1 Percentage yield

The percentage yield of extract is a measure of the efficiency of extracting specific compounds from a source material. It is crucial in fields like pharmacognosy, herbal medicine, and natural product chemistry. High yields indicate successful extraction, while low yields suggest process optimization for efficient use of raw materials.

**Table 3.1** Percentage yield of extract of *Adhatoda Vasica*

| Solvent used | Extract Color | Theoretical weight (gm) | Yield in gms | % Yield |
|---|---|---|---|---|
| Petroleum Ether | Yellow | 252.82 | 0.19 | 0.075 |
| Ethyl Acetate | Green | 250.24 | 0.52 | 0.207 |
| Methanol | Green | 245.28 | 9.20 | 3.75 |

### 3.2 Pharmacognostic study:

A pharmacogenetic study was conducted on the methanolic extract of the entire plant of Justicia adhatoda L. The study involved the use of methods such as Color and Odor, Ash value, extractive value, and Limit test for heavy metals. The results of the pharmacognostic analysis of the methanolic extract of Justicia adhatoda L are presented in Table 5.2 below.

**Table 3.2** Pharmacogenetic analysis of the methanolic extract of Justicia adhatoda L

| **Tests** | **Results** |
|---|---|
| Description | It is Green colour powder |
| Color | Green colour |
| Odour | Characteristic |
| Flavor | Characteristic Flavor |
| **Physical and chemical characteristics** | |
| Ash content | 05.87% |
| Acid-insoluble ash value | 01.68% |
| Water-soluble ash, | 03.81% |
| water-soluble extractive value | 16.91% |
| Extractable substances that can be dissolved in ethanol. | 13.59% |
| Limits for heavy metals | |
| The maximum allowable concentration of arsenic is 5 parts per million (ppm). | Conforms |
| The maximum allowable concentration is 10 parts per million (ppm) of lead. | Conforms |
| Analysis of microbial burden | |
| **Total microbial count 1000 colony-forming units per gram.** | 117 cfu/g |
| Yeast and molds | Nil |
| Presence of E.coli (should be eliminated) | Absent |
| Salmonella presence (should be non-existent) | Absent |
| Presence of Streptococcus (should be negative) | Absent |
| Presence of Pseudomonas should be eliminated. | Absent |

NMT: Not more than Result (n=3) are reported as Mean ± Standard deviation

### 3.3 Solubility determination

A solubility test of an extract is a fundamental analytical procedure used to determine the solvent compatibility of the extracted compounds. This test involves dissolving a small amount of the extract in various solvents, such as water, ethanol, methanol, chloroform, and hexane, under controlled conditions. The solubility behavior of the extract in different solvents provides valuable insights into its chemical nature and potential applications. For instance, water-soluble extracts are often indicative of polar compounds, such as alkaloids, flavonoids, and glycosides, which might have different therapeutic properties compared to non-polar, lipid-soluble compounds. Understanding the solubility profile is essential for formulating extracts in pharmaceuticals, nutraceuticals, and cosmetic products, ensuring the right solvent is used to maximize efficacy and stability. Moreover, solubility tests can guide further purification and separation processes, enhancing the overall quality and usability of the extract.

**Table 3.3** Solubility test of extract of *Adhatoda Vasica*

| Solvent | Pet. Ether | Ethyl Acetate | Methanol |
|---|---|---|---|
| Aquatic i.e Water | Not soluble | Not soluble | Completely Soluble |
| Methanol | Not soluble | Completely Soluble | Completely Soluble |
| Ethyl Acetate | Partially soluble | Completely Soluble | Partially soluble |
| DMSO | Soluble | Completely Soluble | Completely Soluble |
| P.Ether | Completely Soluble | Partially soluble | Not soluble |

**3.4: Toxicity Studies:**
**3.4.1 Acute oral toxicity**

**Table 3.4:** Toxicity parameters after dosing of 5, 50, 300 and 2000 mg/kg

| Sr. No. | Toxicological parameters | Observations of administrated liposomes | | | |
|---|---|---|---|---|---|
| | | (5 mg/kg) | (50 mg/kg) | (300 mg/kg) | (2000 mg/kg) |
| 1 | Eyes | Usual | Usual | Usual | Usual |
| 2 | Mucous membranes | Usual | Usual | Usual | Usual |
| 3 | Salivation | Usual | Usual | Usual | Usual |
| 4 | Stool | Usual | Usual | Usual | Usual |
| 5 | Diarrhoea | No | No | No | No |
| 6 | Sleeping pattern | Usual | Usual | Usual | Usual |
| 7 | Mortality (14 days) | No | No | No | No |

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During this experiment, the rats were administered the extract and their condition was monitored for 7 days to identify the highest point of systemic toxic effects. Additionally, the animals were studied for 14 days, as per the recommendation outlined in the OECD guideline. The experiment on acute toxicity investigation assessed behavioral alterations, body weight, and death. The weight variation is determined by subtracting the beginning weight of the animals from their final weight. At the 7-day and 14-day mark, it was determined that the rats that received the extract remained safe when given a dosage of 2000 mg/kg bw. No indications of toxicity or alterations in behavior were detected.

**3.5: In Vivo study**
An in vivo study refers to research conducted within a living organism, typically involving animals or humans. These studies are crucial for understanding the complex interactions within biological systems in a natural environment, which cannot be fully replicated in vitro (in a lab dish) or in silico (via computer simulations). In vivo studies are essential for evaluating the efficacy and safety of new drugs, understanding disease mechanisms, and developing medical treatments. They provide insights into the physiological and pathological processes in a living system, enabling researchers to observe the effects of interventions in a holistic context. While in vivo studies offer invaluable data, they also raise ethical considerations, particularly regarding the use of animals, necessitating strict adherence to ethical guidelines and regulations to ensure humane treatment and scientific integrity

## 4- SUMMARY AND CONCLUSION
Phytochemical screening is a process used to identify and study the chemical compounds present in plants, such as alkaloids, flavonoids, tannins, saponins, and terpenoids. This process involves qualitative and quantitative tests to determine the presence and concentration of these compounds, which are crucial for understanding the medicinal properties of plants. High yields indicate successful extraction, while low yields suggest process optimization for efficient use of raw materials.
A pharmacognostic study was conducted on the methanolic extract of Justicia adhatoda L, using methods such as color, odor, ash value, extractive value, and limit test for heavy metals. The results showed that the extract was green color powder with a microbial burden of 117 cfu/g.
Solubility determination was also performed to determine the solvent compatibility of the extracted compounds. This test helps determine the chemical nature and potential applications of the extract. Understanding the solubility profile is essential for formulating extracts in pharmaceuticals, nutraceuticals, and cosmetic products, ensuring the right solvent is used to maximize efficacy and stability.
Toxicity studies were conducted on rats administered the extract, and their condition was monitored for 7 days to identify the highest point of systemic toxic effects. At the 7-day and 14-day mark, it was determined that the rats receiving the extract remained safe when given a dosage of 2000 mg/kg bw.
In vivo studies are crucial for understanding the complex interactions within biological systems in a natural environment, providing insights into physiological and pathological processes in a living system. However, they also raise ethical considerations, particularly regarding the use of animals, necessitating strict adherence to guidelines and regulations to ensure humane treatment and scientific integrity.

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