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# Evaluation of Acute Toxicity of Some Medicinal Plants and their Combination in Albino Mice

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**ABSTRACT**

Medicinal plants find use across different cultures in the world. People have derived numerous benefits by using various plants for centuries. Herbal drugs are supposed to be safe, but there are chances these might cause toxicity and other complications. Thus toxicity studies are essential for a medicinal plant before being used in humans. The present research revolves around studying the acute toxicity of *Ocimum kilimandscharicum*, *Thymus serpyllum*, *Spilanthes acmella* and their combination in equal ratio (COMB). For preparing the combination of extracts, the ethanolic extracts of the three plants were combined in equal amounts and administered to the animals. The acute toxicity study was carried out according to OECD (The Organisation for Economic Co-operation and Development) guideline 423 for acute toxicity. The animals were divided into four groups each containing three animals each. These groups were respectively administered ethanolic extract of *O. kilimandscharicum*, *T. serpyllum*, *S. acmella* and COMB in a dose of 2000 mg/kg. The animals were observed for signs of toxicity and mortality at durations specified by OECD. The results demonstrated that extracts of the three medicinal plants used in the study and their combination were found to be safe up to 2000 mg/kg.

**Keywords:** Medicinal plants; Acute toxicity; Combination of extracts; Mice

## 1. INTRODUCTION

Medicinal plants have been a boon to mankind since time immemorial. Many plants have been used by humans for various purposes. Before the advancement of medical science, medicinal plants were used for the treatment of numerous people. In today's world also medicinal plants are playing important roles in curing diseases which are incurable in allopathic medicine. Proper experiments which prove the therapeutic efficacy of plants are very necessary. Preclinical and clinical trials are very necessary to determine the therapeutic potential of a medicinal plant. Acute toxicity studies in animals are a very crucial step in drug development process. Since only after determining the acute toxicity profile of a drug we can further establish its therapeutic potential in animals and humans. In the present study three medicinal plants have been used for determination of their acute toxicity individually as well as in combination. The medicinal plants *O. kilimandscharicum*, *T. serpyllum*, *S. acmella* and their combination in equal ratio have been used in the present study. *O. kilimandscharicum* is a native plant of Kenya and was introduced in India from Kenya. It is cultivated in West Bengal, Jammu and Kashmir, Dehradun and Lucknow for commercial collection of camphor. Camphor obtained from *O. kilimandscharicum* is used in medical preparations which are used in pain and sprains[1]. Camphor crystals are used in medicines and cosmetics[2-3]. Various phenolic compounds like caffeic acid, syringic acid, rosmarinic acid, vanillic acid, hydroxybenzoic acid etc. are found in the methanolic extract of *O. kilimandscharicum*. Quercetin-3-O-rutinoside, Quercetin and luteolin-5-O-glucoside (also called galuteolin) have also been found in its hydro-methanolic extract (80 %)[4]. Ethanolic extract of leaves of *O. kilimandscharicum* contains sterols, saponins, carbohydrates, flavonoids, alkaloids, carbohydrates, proteins, phenols, steroids etc.[2]. The propagation of *O. kilimandscharicum* occurs from seeds and it can be grown in various types of soils in irrigated as well as non-irrigated conditions[5].

*T. serpyllum* is found commonly in open dry slopes spreading all over Himachal Pradesh, at an altitude of 1800 to 2800 meters. It is also found from Kashmir to Kumaun in the temperate zones[1], Nepal and Western Ghats[3]. The plant species is a native plant of European countries. It is grown in England, France, Germany, Spain, Italy[1], northern Austria and northern Ukraine[6]. In a study ethanolic extract of *T. serpyllum* was found to contain tannins, flavonoids, saponin glycosides, fats and oils whereas the aqueous extract consisted of carbohydrates, saponin, glycosides and tannins[7]. Another study on the chemical constituent of *T. serpyllum* indicated the presence of procyanidins, tannins, flavonoids and hydroxycinnamic acids[8]. Its decoctions used with milk acts as a diaphoretic. It also acts as an antiseptic. Herbal tea can also be prepared by using *T. serpyllum*. It is used in the cure of radicultieischias neuralgia[6]. There are various synonyms for *T. serpyllum* like common thyme, garden thyme, mother of thyme, Serp(h)yllum and Serpolet. It is called Quendel in England; in Germany it

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is called Wilder Thymian and Feldkummel Herbe de serpolet in France[6]. Commonly *T. serpyllum* is called Bona jowan[9] in Hindi.

In a study on *S. acmella*, the aqueous and ethanolic extract of leaves and roots of *S. acmella* were analysed for various phytoconstituents. The aqueous extract of the roots contained tannins, alkaloids and carbohydrate. The ethanolic extract of the roots contained amino acids, alkaloids, tannins, carbohydrates and sesquiterpenes[10]. Flower heads of *S. acmella* are chewed and are useful in toothache. The plant is administered to women after childbirth in Assam[11]. *S. acmella* is a constituent of 'Diadev', which is an important Ayurvedic preparation that possesses antidiabetic activity. The essential oil obtained from *S. acmella* is used for manufacturing toothpastes[12]. Flower heads are also used for affections of throat and gums and in paralysis of the tongue[13].

Different acute toxicity studies have been carried out on various plants in the past. An acute toxicity study was carried out in mice and the plant taken was *Pericampylus glaucus* (Lam.) Merr. Various behavioral and other important parameters were observed for evaluation of acute toxicity. It was shown in the study that the ethanolic leave extract of the plant was found to be safe at 4000 mg/kg[14]. Another study was carried out to study the acute toxicity of *Canscora heteroclita* (L) Gilg. Aqueous extract of the plant was used in the study. The animals used in the study were albino mice. The results of the study demonstrated that the extract did not show mortality or signs of toxicity till 2000 mg/kg[15]. Methanolic extract of *Aloe rabaiensis* Rendle was used in a study for evaluation of its acute toxicity profile. The animals used in the study were BALB/c mice and OECD guideline 423 was used. The extract was found to be safe up to 3000 mg/kg in the present study[16]. A study was undertaken to determine the acute toxicity of hydro-ethanolic extract of leaves of *Withania frutescens* in Swiss albino mice. The extract of the plant was found safe up to 2000 mg/kg[17].

The importance of the acute toxicity studies lies in the fact that if acute toxicity studies are properly conducted they can provide important information regarding the biological activities of a test substance[18]. Acute toxicity studies provide valuable information regarding the dangers associated with the use of new chemical substances in humans. Toxicity studies play a very important role in drug discovery and development since it is only after performing toxicity studies in animals that a test substance can be considered to be safe for human use. Toxicity studies not only give an idea about the safety profile of a particular substance but also help in characterizing the toxic effects which a test substance produces[19]. From a long time, scientists have looked up to medicinal plants to find a cure for several diseases. Plants contain several bioactive components that are used as raw materials for the development of new drugs. Plants possess several therapeutic activities and numerous health benefits for humans, still they can be dangerous to use and produce various toxic effects. Thus the assessment of toxicity associated with plants by proper scientific research is very necessary before these plants can be used further in humans. Many plants have been used in traditional medicine whose toxic potentials have not been fully explored[17]. The aim of the present study is to evaluate the acute toxicity profile of *O. kilimandscharicum*, *T. serpyllum*, *S. acmella* and COMB. OECD guideline 423 was referred to evaluate the acute toxicity of these plants and their combination. The above-mentioned plants were used in this study since all these plants have shown good antioxidant activity in past studies and can be future candidates for the treatment of various diseases[4,8,20].

## 2. MATERIALS AND METHODS

### 2.1 Chemicals and Instruments Used

Absolute ethanol (99.9 %) (Changshu Yangyuan Chemical, China); Tween 80 (5 % v/v) (Loba Chemie PVT. LTD, Mumbai). All other reagents and chemicals used were of good quality. The instruments used in the study were: Rotatory vacuum flash evaporator and cages to house the animals. All other types of equipments used were of good quality.

### 2.2 Preparation of the Extract

The collection of aerial parts of medicinal plants like *O. kilimandscharicum*, *T. serpyllum* and *S. acmella* were done from Defense Institute of Bioenergy Research, Pithoragarh, Uttarakhand. The plant samples were authenticated by Botanical Survey of India, Northern Regional Centre, Dehradun, Uttarakhand. After carefully collecting the plants they were dried. After drying of the aerial parts, the aerial parts were powdered and extracted with absolute ethanol (99.9 %). Soxhlet's assembly was used for the extraction. The extract so obtained was then dried using rotator vacuum flash evaporator[21]. The individual extracts and their combination were dissolved in tween 80 (5 %) and administered to the animals at a single dose of 2000 mg/kg (milligrams/kilograms).

### 2.3 Animals

Female Swiss albino mice, weighing 20-30 gm were procured from the animal house of Department of Pharmaceutical Sciences, Bhimtal (Kumaun University, Nainital). The animals were kept in cages and placed in well ventilated housed conditions with food and water ad libitum. They were maintained on a natural 12 hour light and dark cycle. The present research was approved in the meeting of the Institutional Animals Ethics Committee (IAEC) conducted in the Department of Pharmaceutical Sciences, Bhimtal. The approval number is KUDOPS/44.

### 2.4 Acute Toxicity Study

#### *2.4.1 Preparation of Animals*

The animals used in the study were selected randomly for the study. They were acclimatised to laboratory conditions before the study. The animals were marked to enable their proper identification during dosing[22].

#### *2.4.2 Dose Preparation*

According to OECD guidelines, the volume of the test solution administered to rodents should not exceed more than 1ml/100g of body weight. Keeping this in mind the animals were weighed and the dose of the extracts of *O. kilimandscharicum*, *T. serpyllum*, *S. acmella* was administered to mice according to the bodyweight of the animals. For the combination extract

**Table 1. Physical observations in mice after administration of extract of *O. kilimandscharicum*, *T. serpyllum*, *S. acmella* and COMB in a single dose of 2000 mg/kg. n=number of animals.**

| Dose (2000 mg/kg) | *O. kilimandscharicum* n=3 | *T. serpyllum* n=3 | *S. acmella* n=3 | COMB n=3 |
|---|---|---|---|---|
| Skin color | Normal | Normal | Normal | Normal |
| Body weight | Normal | Normal | Normal | Normal |
| Fur color | Normal | Normal | Normal | Normal |
| Eye color | Normal | Normal | Normal | Normal |
| Respiration | Normal | Normal | Normal | Normal |
| Urine color | Normal | Normal | Normal | Normal |
| Edema | Absent | Absent | Absent | Absent |

**Table 2. Reflexes and sensory responses in mice after administration of extract of O. *kilimandscharicum*, *T. serpyllum*, *S. acmella* and COMB in a single dose of 2000 mg/kg.**

| Dose (2000 mg/kg) | *O. kilimandscharicum* n=3 | *T. serpyllum* n=3 | *S. acmella* n=3 | COMB n=3 |
|---|---|---|---|---|
| Corneal reflex | Normal | Normal | Normal | Normal |
| Touch response | Normal | Normal | Normal | Normal |
| Pain response | Normal | Normal | Normal | Normal |
| Sound response | Normal | Normal | Normal | Normal |

also the dose to be administered to the animals was according to the bodyweight of the animals. Preparation of the stock solution and dose calculation was done according to the relevant literature[22-23].

*2.4.3 Dosage Administration*

The animals were divided into four groups each containing three animals and administered the dose using oral feeding cannula. The first group received an extract of *O. kilimandscharicum*, the second group received an extract of *T. serpyllum*, the third groups received an extract of *S. acmella* and the fourth group received COMB[22].

*2.4.4 Procedure*

Acute toxicity study was conducted in compliance with The Organisation for Economic Co-operation and Development (OECD) guideline 423. According to this guideline, the number of animals required per step is three and four-fixed dose levels (5, 50, 300 and 2000 mg/kg body weight) are used. This guideline also states that if the substance to be administered is safe according to available information than a limit test should be performed with the highest dose level (2000 mg/kg). Since medicinal plants are generally considered safe, a limit test according to OECD guideline 423 was performed. The animals were fasted (3-4 hours) by withholding food but not water. According to their respective group mentioned before the animals were given a single dose of individual extract in a dose of 2000 mg/kg. Also, the animals in the COMB group received the combination of the individual extracts in a dose of 2000 mg/kg (the dose consisted of equal amounts of individual extracts). Immediately after dosing during a period of thirty minutes the animals were observed at least once individually. Thereafter they were observed periodically during the first twenty four hours, with special attention during the first four hours. After 24 h the animals were thereafter observed daily for a period of fourteen days. The animals were observed for signs of toxicity which are as follows: alterations in eyes, skin, fur, respiratory system, central nervous system, autonomic nervous system, behavior pattern etc. Convulsions, tremors, coma, diarrhea etc. in animals were observed with alertness. Also, the animals were observed for mortality[22-25,17].

## 3. RESULT

### 3.1 Acute Toxicity Study

Table 1, 2, 3, 4 and 5 summarise the acute toxicity assessments (OECD guideline 423) in mice given a single dose of 2000 mg/kg of the extract of *O. kilimandscharicum*, *T. serpyllum*, *S. acmella* and COMB according to their respective groups.

## 4. DISCUSSION

Toxicology is an important branch of pharmacology that revolves around the determination of adverse effects and lethal effects of bioactive substances. There are various types of studies that can be performed on animals like acute toxicity studies, sub-acute toxicity studies and chronic toxicity studies. Toxicity study in animals can give an idea about possible adverse effects and lethal effects of drugs and medicinal plants. Toxic substances can lead to physical, mental and behavioral complications[26]. In the present study ethanolic extracts of *O. kilimandscharicum*, *T.serpyllum*, *S.acmella* and COMB were administered to albino mice. Administration of extracts of *O. kilimandscharicum*, *T. serpyllum*, *S. acmella* and COMB did not produce mortality or a moribund status in animals (Table 5) till 2000 mg/kg. No alterations in physical characteristics (Table 1) were observed in these mice. Also, there were no abnormal effects produced in mice regarding sensory responses and reflexes (Table 2). The observations relating to behavioral (Table 3), central (Table 3) and autonomic nervous system (Table 4) parameters were also found to be normal. According to literature any compound or drug with the oral $LD_{50}$ higher than 1000 mg/kg could be considered safe and low in toxicity[27]. According to OECD guideline 423 for acute toxicity study, a limit test can be performed by giving the animals the highest dose of 2000 mg/kg, if there is information

**Table 3. Observations relating to behavioral parameters and central nervous system in mice after administration of extract of *O. kilimandscharicum*, *T. serpyllum*, *S. acmella* and COMB in a single dose of 2000 mg/kg.**

| Dose (2000 mg/kg) | *O. kilimandscharicum* n=3 | *T. serpyllum* n=3 | *S. acmella* n=3 | Combination n=3 |
|---|---|---|---|---|
| Alertness | Normal | Normal | Normal | Normal |
| Restlessness | No abnormal restlessness | No abnormal restlessness | No abnormal restlessness | No abnormal restlessness |
| Irritability | Absent | Absent | Absent | Absent |
| Reactivity | Normal reactions to stimulus | Normal reactions to stimulus | Normal reactions to stimulus | Normal reactions to stimulus |
| Drowsiness | Absent | Absent | Absent | Absent |
| Convulsions | Not present | Not present | Not present | Not present |
| Coma | Absent | Absent | Absent | Absent |
| Sleep | Normal sleeping behavior | Normal sleeping behavior | Normal sleeping behavior | Normal sleeping behavior |
| Food intake | Normal | Normal | Normal | Normal |
| Ataxia | Not present | Not present | Not present | Not present |
| Tremors | Absent | Absent | Absent | Absent |
| Twitches | Absent | Absent | Absent | Absent |
| Catatonia | Absent | Absent | Absent | Absent |

**Table 4. Observations related to the autonomic nervous system in mice after administration of extract of *O. kilimandscharicum*, *T. serpyllum*, *S. acmella*, COMB in a single dose of 2000 mg/kg.**

| Dose (2000 mg/kg) | *O. kilimandscharicum* n=3 | *T. serpyllum* n=3 | *S. acmella* n=3 | Combination n=3 |
|---|---|---|---|---|
| Salivation | Normal | Normal | Normal | Normal |
| Lacrimation | Normal | Normal | Normal | Normal |
| Defecation | Normal | Normal | Normal | Normal |
| Diarrhea | Absent | Absent | Absent | Absent |

**Table 5. Effect of administration of extract of *O. kilimandscharicum*, *T. serpyllum*, *S. acmella* and COMB on moribund status and mortality of mice in a single dose of 2000 mg/kg.**

| Dose (2000 mg/kg) | *O. kilimandscharicum* n=3 | *T. serpyllum* n=3 | *S. acmella* n=3 | Combination n=3 |
|---|---|---|---|---|
| Moribund status | Not present | Not present | Not present | Not present |
| Mortality | Not present | Not present | Not present | Not present |

available that the substance to be administered is safe and will not produce any mortality. A higher dose level of 5000 mg/kg is also sometimes used but only when it is justified by special regulatory needs. Since medicinal plants are considered safe, in many studies the acute toxicity of plants have been performed by giving animals a fixed dose of 2000 mg/kg and these plants are considered safe for use for further studies if no mortality and no toxic signs are observed at this dose level. By observing these studies a limit test at 2000 mg/kg dose for evaluating the acute toxicity of *O. kilimandscharicum*, *T. serpyllum* and *S. acmella* and COMB was performed in the present study. From the results obtained in the present study, it was found that all the extracts used in the study were found to be safe at 2000 mg/kg. The safety of the extracts in the present study up to a dose level of 2000 mg/kg can help in dose determination of these plants and their combination in other studies for evaluation of their pharmacological activities[22-25,17].

## 5. CONCLUSION

Plants are very important for humans since they provide various phytochemicals that can cure a variety of diseases. Toxicity studies form a crucial step in the development of raw medicinal plants to a useful formulation. Many medicinal plants are there that produce poisonous effects. Toxicity studies can give us an idea of whether to use a particular plant in humans or not. Human life is precious and thus without proper toxicological studies use of any plants in humans can be lethal. Many plants are generally safe and can be used safely in humans but, the determination of their correct dose is very essential. Proper toxicological studies can also instill a feeling of confidence in the patients that are using them that they are safe for use. The present study has showcased the safety profile of *O. kilimandscharicum*, *T. serpyllum*, *S. acmella* and COMB. This study gives a preliminary idea about the safety of these plants. All the plant extracts used in the study were found to be safe till 2000 mg/kg. There are numerous plants available in different countries but without proper toxicity studies, their potential cannot be fully explored. Toxicity study is thus vital before the investigation of any plant for its medicinal benefits. In the present acute toxicity study, the extracts taken in the study have proved their safety profile.

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