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Assessment of Acute Oral Toxicity of *Sonchus wightianus* DC. Methanolic Extract Using OECD 423 Guidelines

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The pharmacological characteristics of *Sonchus wightianus* DC, a perennial herb belonging to the Asteraceae family, have been reported in many publications. This plant offers many benefits (antimicrobial, antioxidant), but data on its toxic potential are limited. It is necessary to confirm the safety of plants and pharmaceuticals prior to their use as medicines. Thus, this study's objective was to assess the acute oral toxicity of a methanolic extract obtained from *Sonchus wightianus* in a rat model using fixed dosage tests, with an upper limit administration of two thousand milligrams per kilogram body weight of the test animal, in accordance with OECD recommendations 423. The

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Albino Wistar rats were given one oral administration of 5, 50, 300, or 2000 mg per kilogram body weight. Following fourteen days of dosing the extract at intervals of 1, 2,4, and 24 hours, the results showed no evidence of toxic effects or death. The test animals exhibited writhing reflex and grooming behaviour, as well as unusual respiration whereas all the other responses noted remained normal and showed no changes in behavior or death at the maximum tested dosing (2000 mg per kilogram body weight). These findings indicate the safety of oral administration for the tested *Sonchus wightianus* methanolic extract.

Keywords: Sonchus wightianus DC.; acute oral toxicity; OECD Guidelines 423; Lethality (LD50).

1. INTRODUCTION

Humans have been utilizing natural resources, mostly plants, to produce food, clothing, tastes, scents, and medications since long ago. One notable trend in recent years has been a resurgence of interest in getting biologically active chemicals from natural sources [1]. Natural product-based preparations are getting recognition globally because to their low level of toxicity, 100% biodegradability, accessibility via renewable resources, and, in majority circumstances, cheaper than artificial ingredients [2].

Nowadays, people prefer using a variety of herbal remedies as an alternative to pharmaceutical prescription therapy. Certain chemical substances that are used to treat numerous illnesses can be synthesized by medicinal plants [3]. According to statistics from the World Health Organization (WHO), 80 percent of people globally utilize medicinal herbs, and fifty percent of all pharmaceuticals are derived from sources found in nature [4]. The principal source of conventional medications is the plant kingdom, which is abundant in secondary metabolites. Several researchers have investigated the safety and therapeutic applications of medicinal plants. Nevertheless, no matter if they are used for a prolonged period of time, the active components in medicinal plants may have negative, potentially harmful impacts on vital organs. Multiple studies on medicinal plants have revealed their toxicity and unfavorable effects, which include symptoms and signs in the neurological, digestive tract, and cardiovascular systems [5].

It is also necessary to follow the guidelines when looking for medicinal plants that could be turned into medications. Product safety testing requires an understanding of the drug toxicity processes in order to establish a foundation for drug risk evaluation [5].

The perennial plant *Sonchus wightianus* DC is a member of the Asteraceae family. At an elevation of 600–2,500 meters, it is dispersed over Nepal, India, Afghanistan, Pakistan, and Sri Lanka. It's perennial plant with milky, unpleasant juice and stems that are hollow. The prickly edges and pointy lobes of the alternating leaves vary in size. The vivid yellow blossoms bloom from June to September. It goes by the indigenous name Ban raayo or Dudhe, but it is popularly known as Sow Thistle [6].

There have been many reports of pharmacological activities related to the genus Sonchus. Indian village tribes make earaches from the leaves of *S. wightianus* DC [7]. This diuretic herb is beneficial for persistent fevers. There have been reports of antibacterial and antimotility effects from its leaves. To treat diarrhoea, a teaspoon of the root decoction two times a day is used. Pulverized leaves can be applied immediately to small incisions to stop bleeding. Boils and abscesses are treated with leaves. Scientists have discovered that the plants belonging to the Sonchus family possess anti-aging, antioxidant, anti-tumor, and antidiabetic properties. Different Sonchus species parts are employed in yellowing of the skin, hearing loss, gout, cough, bronchitis, vision problems, throat infection and appendicitis, according to ethnobotanical knowledge [8].

Despite the fact this specific plant has numerous advantages, its reliability is unknown as any safety parameter of this plant are not studied before [5]. Before botanicals or medications are utilized as medicines, their safety must be established. Conducting tests for toxicity in suitable models of animals is a crucial step in assuring the safety of pharmaceuticals; acute toxicity investigations are merely one of several toxicity studies that are employed. Our research's main objective was to assess the extract for adverse consequences prior to using them for uses that the general public would find significant [9].

To find out if this plant satisfies the criteria for a medicine in terms of efficacy and safety, we tested its harmful effects [5]. We assessed toxicity through behavioural measures by applying a fixed dosage method i.e. five, fifty, three hundred, and two thousand milligram per kilogram body weight of an animal as per the criteria provided by the OECD (Organization for Economic Co-operation and Development) over a span of fourteen days. Since female Wistar rats are more highly sensitive, they were chosen for assessing acute oral toxicity [5,9].

2. EXPERIMENTAL

2.1 Collection and Authentication of Plant

The fresh leaves of *Sonchus wightianus* DC. were gathered from the Eastern Himalayan region i.e. Kalimpong, West Bengal, India. The verification was done by Central Ayurveda Research Institute, Govt. of India, Ministry of AYUSH, Central Council for Research in Ayurvedic Science, Bengaluru. (Dr. V. Rama Rao), Research Officer, Botany, and (Dr. S.H. Doddamani), Assistant Director in charge, identified and confirmed the plant material of authentication number: SMPU/CARI/BNG/2023-24/2035.

2.2 *Sonchus wightianus* DC. Extraction

The cleaned, crumbled leaves were carefully mixed and prepared into a powder. The powder that has been prepared were kept in a sealed container and extracted via the Soxhlet technique in methanol [10]. The extract of methanol includes components that can be examined for their anti-inflammatory and antipyretic properties, such as β-sitosterol glycoside and hexadecanoic methyl ester. By storing, the extracts in a water bath below 70°C, they were dried [6]. A rotatory evaporator was used for eliminating the solvent following the extraction procedure [11].

2.3 Experimental Animals

From the Krupanidhi College of Pharmacy, Bangalore, India, Albino Wistar rats weighing 150–200g [12] were collected. They were housed and acclimated utilizing animal housing with adequate ventilation. Facilities in the laboratory were kept for seven days before conducting the study, as recommended via the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA). This includes maintaining a regulated humidity of 50-60% and a temperature range of 25 ± 2°C. Furthermore, food and water were given to the animals [13].

2.4 Grouping of Animals

The Wistar rats were randomly separated into 4 distinct sets of 3 in each set. Using a yellow stain, the markers allowed for their identification. To facilitate investigation, Group 1 was left unmarked, Group 2 had their head marked, Group 3 had their head and body marked, and Group 4 had their head, body, and tail marked. All the groups received different doses of plant extract (as indicated in Table 1).

Table 1. Grouping of animals as indicated

S.No.	Group	Marking	Dose mg/kg
1	Group 1	unmarked	5
2	Group 2	head	50
3	Group 3	head and body	300
4	Group 4	head, body and tail	2000

2.5 Method of Dosing

Utilizing an oral needle made specifically for rats, only one dose of a test drug was gavaged. Three hours before the dose, the animals were fasted (just food, but not water, was deprived for three hours) [14].

2.6 Dosing of Animals

Wistar rats were checked for weight after the time of fasting, and oral doses of the test drug (5, 50, 300, and 2000 mg/kg) were given. The rats were denied food for two hours following the delivery of the test drug [15].

2.7 Amount of Test Drug Delivery

1mL per kilogram of the rat's body weight was the dosage quantity. The amount of the test drug was determined by calculating the rat's body weight during the day of administration [16].

2.8 Time of Examination

Throughout the initial twenty-four hours and every day after that, for the entire period of fourteen days, each animal was monitored

separately at least once during the one, two, and four hours following the dosing. At a minimum of two times per day, all the animals were monitored in order to note any unusual behaviors or signs of illness [15,16].

2.9 Responses Noted during the Acute Toxicity Studies

The following are conditions for direct assessment: tremors, convulsions, salivation, diarrhoea, lethargy, sleeplessness, and coma. Additional criteria that were noted were somatomotor activity, behavior pattern, respiratory, circulatory, autonomic, and central nervous systems, eyes, mucous membranes, skin, and fur. If there was an incident of mortality, it was noted. Food was not allowed for an additional one to two hours once the test compound was administered. After an entire day, the total count of surviving animals was recorded, and they were kept under surveillance continuously for an additional fourteen days [15].

3. RESULTS

The existing investigation, which followed OECD recommendations 423, found that even though the maximum dose was kept at 2000mg per kilogram of body weight, the aforementioned herbal extract failed to result in any deaths all over the course of fourteen-day test period. Since the oral LD50 was more than 2000 mg/kg of body weight, it remained unknown. Therefore, it might not be required to investigate the extract at greater doses, as they were essentially non-toxic. The responses seen both prior to and following the test material was administered with the *Sonchus wightianus* DC extract are shown in Table 2. Animals given 2000 mg per kilogram of the extract exhibited the writhing reflex and grooming behavior, and also the extract showed unusual respiration; however, the rest of the responses remained usual, regardless of the maximum dosage of two thousand milligrams per kilogram of the test animal. This demonstrated unequivocally that *Sonchus wightianus* DC methanolic extract administration does not result in oral toxicity. Since the extracts' medium lethal dose (LD50) is greater compared to two thousand milligrams per kilogram of body weight, the extract did not cause any side effects when administered as one dosage.

The result displayed in Table 2: (Positive sign (+) represents presence and Negative sign (-) represents absence)

Table 2. The outcome of Sonchus wightianus upon acute oral toxicology testing in rats

		Dose (mg per kilogram)							
Sl.No.	**Parameters**	**5**		**50**		**300**		**2000**	
		Earlier	**Later**	**Earlier**	**Later**	**Earlier**	**Later**	**Earlier**	**Later**
1	**Writhing**	-	-	-	-	-	-	-	+
2	**Alertness**	Usual	Usual	Usual	Usual	Usual	Usual	Usual	Usual
3	**Grooming**	-	-	-	-	-	-	-	+
4	**Tremors**	-	-	-	-	-	-	-	-
5	**Touch response**	Usual	Usual	Usual	Usual	Usual	Usual	Usual	Usual
6	**Aggressiveness**	-	-	-	-	-	-	-	-
7	**Gripping strength**	Usual	Usual	Usual	Usual	Usual	Usual	Usual	Usual
8	**Urine output**	Usual	Usual	Usual	Usual	Usual	Usual	Usual	Usual
9	**Saliva production**	Usual	Usual	Usual	Usual	Usual	Usual	Usual	Usual
10	**Colour of skin**	Usual	Usual	Usual	Usual	Usual	Usual	Usual	Usual
11	**Respiration**	Usual	Usual	Usual	Usual	Usual	Usual	Usual	Unusual
12	**Convulsion**	-	-	-	-	-	-	-	-
13	**Lacrimation**	Usual	Usual	Usual	Usual	Usual	Usual	Usual	Usual
14	**Pupilary reflex**	Usual	Usual	Usual	Usual	Usual	Usual	Usual	Usual
15	**Pinna reflex**	Usual	Usual	Usual	Usual	Usual	Usual	Usual	Usual
16	**Diarrhoea**	-	-	-	-	-	-	-	-
17	**Hyperactivity**	-	-	-	-	-	-	-	-
18	**Motality**	-	-	-	-	-	-	-	-

4. DISCUSSION

Ancient medicinal herb items are becoming more and more common in basic medical care, especially in developing nations. Since these items come from natural sources, some might have been incorrectly believed to be harmless. Herbal medications continue to be used in villages today, however they are only employed for treating a range of ailments. On the other hand, using herbal medicines might sometimes result in unfavorable side effects. Toxicity tests are now necessary to verify the traditional usage of medicinal herbs due to their renewed popularity [16]. Acute toxicity is commonly understood to be the unfavorable alteration that happens either instantly or quickly after a brief or one-time treatment to a chemical or agents. Oral toxicological studies are done to figure out the dose that is more likely to cause undesirable reactions and to predict the lowest dose at which a drug or material will be life-threatening [17].

The study carried out following OECD Guidelines 423 clearly demonstrates the non-harmful characteristic of *Sonchus wightianus* methanolic extract, as evidenced by the test animals lack of death after oral administration with two thousand milligrams per kilogram of body weight [9,15]. No notable alterations were found in the behavioral tests at lesser and mid-doses, i.e., five fifty, and three hundred milligrams per kilogram of body weight; however, animals delivered two thousand milligrams per kilogram of the extract exhibited writhing reflex and grooming behavior, as well as unusual respiration whereas all the other responses noted remained normal, even at the maximum amount of two thousand milligrams per kilogram of the test animal (as indicated in Table 2). At such a high dose, the body may experience mild to moderate stress. The extract may interact with pain receptors or cause irritation in the gastrointestinal tract, leading to writhing as a natural reaction. Grooming, a sign of stress in animals, may indicate discomfort or coping with high dose effects. Unusual breathing may be due to a temporary effect on the respiratory system, possibly influencing the central nervous system or causing minor respiratory irritation. High doses are often used in acute toxicity studies to determine the safety margin of a substance. The absence of severe toxicity or mortality suggests it is within a tolerable range for animals. The dose of 2000 mg/kg may fall within the therapeutic index, which ranges between an effective and toxic dose. Observed behavioral changes may not indicate significant harm or toxicity, especially if they are transient and recover without lasting harm [15].

This demonstrated unequivocally that *Sonchus wightianus* DC extracts do not cause oral toxicity. Therefore, it could be suitable to utilize *Sonchus wightianus* DC methanolic extract for medical applications.

5. CONCLUSION

The acute oral toxicity study performed in accordance with OECD regulations 423 clearly demonstrates that the methanolic extract of *Sonchus wightianus* is not harmful. The testing animal's typical behavior over the course of two weeks points towards the extracts non-toxic nature. Therefore, *Sonchus wightianus* could be harmless in doses up to two thousand milligrams per kilogram of the animal's body weight. However, it is necessary to conduct additional research to identify long-term harmful effects.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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