Pharmacogn J. 2025; 17(5): 577-582
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Original Article

Acute Oral Toxicity Evaluation of Hydroalcoholic Extract of Salvia Officinalis Roots in Wistar Rats as per OECD 423 TG

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ABSTRACT

Background: In this study, we assessed the hydroalcoholic root extract of *Salvia officinalis* oral acute toxicity investigation using an animal model. **Methods:** The investigation of acute oral toxicity was conducted using OECD 423 guidelines. The Institutional Animal Ethics Committee approved the study (IAEC). A single oral dose of *Salvia officinalis* hydroalcoholic root extract (800, 1600, and 3200 mg/kg) was administered, and the subjects were monitored for 14 days. Animals were sacrificed on the fifteenth day, and body weight, haematological, and serum hepatic biochemical parameters were assessed and compared to the standard group. **Results:**Groups treated with *Salvia officinalis* showed no mortality or discernible alterations. The findings show that Wistar rats did not experience appreciable harmful effects from administering hydroalcoholic root extract from the *Salvia officinalis* plant. **Conclusions:** The extract can be utilized safely for therapeutic use in pharmaceutical formulations.

Keywords: Acute toxicity, Salvia officinalis, haematology, liver, kidney, heart.

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History

- Submission Date: 28-08-2025;
- Review completed: 22-09-2025;
- Accepted Date: 22-10-2025.

DOI : 10.5530/pj.2025.17.71

Article Available online

http://www.phcogj.com/v17/i5

INTRODUCTION

Acute toxicity studies are essential to preclinical trial safety assessments; they are commonly employed to ascertain the unfavourable consequences of a single dose or several doses given within24 hours[1]. Rats are popularas test subjects in this research because of their physiological parallels to humans and well-understood biology. These investigations evaluate the short- and immediate-term harmful effects of chemicals, medicines, and other substances on organisms. Rats are a good model for extrapolating toxicity data to humans because of their well-characterized genetic makeup, ease of handling, and relatively short lifespan, which makes them perfect for these investigations[2]. Furthermore, the information gathered from rat acute toxicity studies is useful in establishing safety standards, dosage recommendations, and preventative actions for novel substances and goods.The choice of whether to approve a new medication for clinical use or not is aided by toxicological studies. Drugs cannot be used clinically without undergoing a clinical trial and toxicity testing, according to OECD guidelines401,423, and 425[3].

*Salvia officinalis,*or Sage, is a perennial evergreen subshrub member of the mint family (Lamiaceae). Sage is a native of the Mediterranean region and has been grown for millennia for its culinary, medicinal, and decorative purposes[4]. The plant is well-known for its woody stems, violet-blue flowers, and grey-green leaves. It is also well-liked for its unique scent.Salvia officinalis is primarily grown in regions with temperate climates in India. The herb thrives in areas with well-drained soil and moderate temperatures, similar to its native Mediterranean conditions[5].The plant is cultivated in different regions of India, such as Himachal Pradesh, Uttarakhand, Jammu and Kashmir, Sikkim, Tamil Nadu (Nilgiris Hills), and Karnataka (Western Ghats).

Salvia officinalis is known for its rich content of essential oils, flavonoids, phenolic acids, and terpenes. It contains Essential oilslike Thujone, cineole, camphor, and borneol. Phenolic acids like Rosmarinic acid which has antioxidant and anti-inflammatory properties.Flavonoids like Apigenin, luteolin, and quercetin contribute to the plant's health benefits[6].

Sage has a long history of use in traditional medicine, particularly for its antiseptic, anti-inflammatory, and antioxidant properties[7]. Sage has been used to alleviate indigestion and bloating[6].Sage extracts are incorporated in mouthwashes and toothpaste due to their antibacterial and antimicrobial properties[8]. Growing evidence shows that sage may enhance memory and cognitive performance, potentially benefiting individuals with Alzheimer's disease[9]. Sage has been traditionally used to reduce hot flashes and excessive sweating during menopause[10].

The acute toxic effects of ahydroalcoholic root extract made from *Salvia officinalis* have been examined in Wistar rats as part of the current investigation's safety evaluation. The treatment's effects on the liver and kidney tissues' haematological, biochemical, and histological changes were also examined. Rat acute toxicity studies continue to be a valuable tool in toxicology. Still, efforts are being made to create and apply substitute techniques that minimize the use of animals and increase the predictability of human toxicity.

MATERIALS AND METHODS

Chemicals and reagents

Sigma Chemical Company, based in St. Louis, Missouri, USA, supplied the chemicals and reagents GSH, MDA, NBT, and SDS. H&E stain, TBA, and Folin's Ciocalteau reagent have been purchased from

Cite this article: Ranjini H S, Kadmad A H M A, Fayazul H S, Prashanthkumar G, Vinodakumar H R, Akash. Acute Oral Toxicity Evaluation of Hydroalcoholic Extract of Salvia Officinalis Roots in Wistar Rats as per OECD 423 TG. Pharmacogn J. 2025;17(5): 577-582.

Sisco Research Laboratories in Mumbai, India. The analytical grade (AR) acids, bases, solvents, and salts used in the investigation were purchased from SRL, Mumbai, India, whereas the diagnostic kits were obtained from Enzo Life Sciences.

Animals

The current investigations employed 150–200 g Wistar albino rats of both sexes. Clean polypropylene cages were used to house them, and they were kept in typical laboratory settings with a 12-hour light-dark cycle and a temperature of 22 ± 2°C. Without restriction, they were provided water and a regular pellet diet (Hindustan Lever, Kolkata, India)[11,12].The Institutional Animal Ethics Committee (IAEC), Saveetha Institute of Medical and Technical Sciences, Chennai, Tamilnadu, India approved the experimental protocol for the animal studies (BRULAC/SDCH/SIMATS/IAEC/12-2019/036).

Plant materials

Salvia officinalis roots were collected from a forest in Nilgiri Hills in Tamil Naduand Western Ghats of *Karnataka*, India, and botanist Dr Rama Bhat recognized and verified the sample. The material was ground using a mechanical grinder, dried in the shade, and sieved using a 30-mesh screen.

Extract preparation

Weighed accurately 500g of the sample in a glass stoppered flask. Added 2.0L of alcohol (approximately 95%) and 2.0L water (1:1). Shaken occasionally for 6 hours. Allowed to stand for 18 hours. It is filled rapidly,so it is careful not to lose solvent. Evaporated filtrate to dryness on a water bath. Kept it in an air oven at 105°C for 6 hours, cooled in a desiccator for 30 minutes and weighed. Calculated the percentage of extract for the sample of Salvia officinalis root powder.

Experimental design

The acute oral toxicity investigation followed OECD 423 criteria (OECD, 2001). The animals were fed a regular meal and provided regular access to water. The animals were divided into four groups, each with three animals. Group II, III, and IV rats received a single oral extract dose (800, 1600, and 3200 mg/kg, b.w.), while Group I rat was the control group. The rats were monitored for fourteen days for morphological and behavioural changes daily. On the fifteenth day, the animals were euthanized, and several histological and biochemical abnormalities were noted.

Mortality and Toxic Signs

During 14 days, visual observations were made once a day about mortality, various physical appearance changes, behaviour (sleepiness, salivation, lethargy), and any injuries or illnesses.

Relative Organ Weight

Ketamine was injected intraperitoneally to anaesthetizethe animals on the fifteenth day. For haematological and biochemical examination, blood samples were obtained by heart puncture and placed into tubes containing EDTA and non-heparinized tubes. Upon blood collection, the rats were euthanized, and their internal organs, like kidneys, liver, spleen, and lungs, were removed, weighed, and checked for any noticeable lesions.

Blood analysis

Utilizing Enzo Life Sciences diagnostic kits, biochemical analysis was performed on liver function markers (AST, ALT), total bilirubin, and nephrotic markers (urea, creatinine, and uric acid). Robonik semi-auto analyzer was used to quantify the results. Red and white blood cells, haemoglobin, haematocrit, and platelets were among the haematologic parameters measured.

Antioxidant parameters

Estimation lipid peroxidation

The basis of this procedure is the formation of malondialdehyde (MDA) by lipid peroxidation, which combines with thiobarbituric acid (TBA) to produce thiobarbituric acid reactive substances (TBARS), a complex that takes on a pink colour. This complex's absorbance can be determined spectrophotometrically at 532 nm. A standard curve was created using MDA[13] to compare sample readings. The final volume was adjusted to 4 mL with water after combining 0.2 mL of tissue homogenate, 0.2 mL of SDS, 1.5 mL of acetic acid, and 1.5 mL of TBA. The mixture was placed in a water bath and heated to 95°C for 60 minutes. Following cooling, a vigorous shake was performed before adding 1 mL of water and 5 mL of a combination ofn-butanol and pyridine. The mixture was then centrifuged at 4000 rpm for 10 minutes, and the absorbance of the organic layer was measured at 532 nm. MDA levels were expressed in nmol per mg of protein.

Estimation of reduced glutathione

The Sedlak and Lindsay (1968) method measured reduced glutathione. After adding 0.2 M Tris buffer (pH 8.2) to 0.5 mL of tissue homogenate, the mixture was combined with 0.1 mL of Ellman's reagent (0.01 M) (5,5′-dithiobis-(2-nitro-benzoic acid)) (DTNB), and centrifuged for 15 minutes at 3000 g. 412 nm was the absorbance measured. Several similar standards are also used to ascertain the glutathione content. Glutathione content is given as µM of GSH/mg protein.

Assay of superoxide dismutase

The superoxide dismutase assay used Misra and Fridovich's (1972) protocol. The tissue homogenate (0.1 mL) was combined with reaction solutions containing hydroxylamine hydrochloride (0.2 mL, 0.1 mM), sodium carbonate (1 mL, 50 mM), and nitroblue tetrazolium (0.4 mL, 25 µm). Using a UV spectrophotometer (MINDRAY 91), the combination was detected at 560 nm.

Assay of catalase

Takahara et al. (1978) developed the technique to measure catalase activity. After combining 1.2 mL of phosphate buffer with 0.2 mL of tissue homogenate, 1.0 mL of H_2O_2 solution was added to initiate the reaction. For three minutes, the absorbance was measured at 240 nm at intervals of 30 seconds. Hydrogen peroxide was swapped out for distilled water to create the enzyme blank. The enzyme's activity was expressed in units of µM of H_2O_2 decomposed/min/mg of protein.

Histopathological examinations

The vital organs that were removed from the sacrificial rats were embedded in paraffin wax after being treated with 10% formalin. At a thickness of 5 µm, paraffin slices were prepared and stained using eosin and haematoxylin. The slides were examined with an Olympus model light microscope, which produced enlarged photographs of the tissue structure for additional research (Figure 1) .

Statistical analysis

Mean ± SD was used to express values. One-way ANOVA and Post Hoc t-tests were performed to assess the significance of intergroup differences. A statistical significance level of $P < 0.05$ was applied.

RESULTS

Acute toxicity study

The hydroalcoholic root extract was calculated using the limit test dose of 3200 mg/kg by OECD guideline 423. Following oral administration of hydroalcoholic root extract at doses of 800, 1600, and 3200 mg/kg,

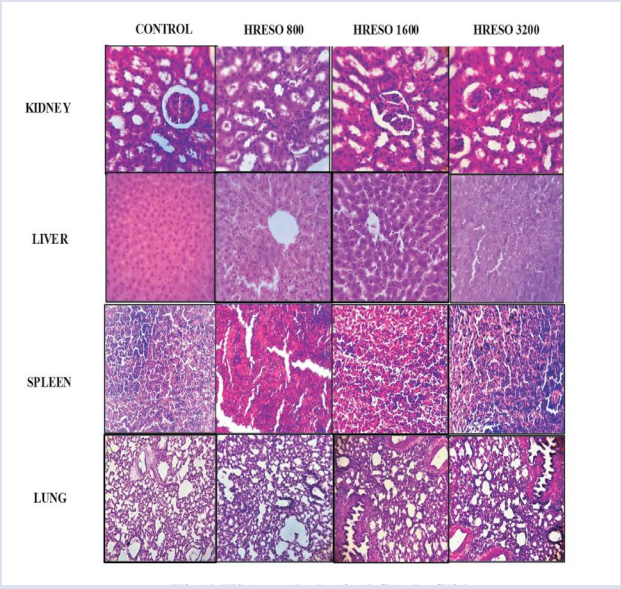


Figure 1. Histopathological study slides

no treatment-related adverse symptom or death was noted. The general conduct of the animals in the extract-treated and the control groups was initially studied for a brief 4-hour period and then for a longer 72-hour period. Compared to the control group, the animals treated with extract did not exhibit any alterations in behaviour, breathing, skin effects, water consumption, impairment in food intake, or temperature. As a result, the LD_{50} was determined to be >3200 mg/kg and the extract appears safe at a dose level of 3200 mg/kg.

Effect of HRESO on Relative Organ and Body Weight

The experimental animals showed no signs of poisoning in their skin, fur, eyes, salivation, diarrhoea, or behaviour, and the experimental rat did not die. During the study, the HRESO-treated rats did not exhibit any discernible variations in their consumption of food or water in comparison to the control group. When comparing the body weight of the HRESO-administered groups to the control group after 14 days, there was a minor rise in body weight ($p<0.05$). There was no discernible difference in the relative organ weights between the experimental and control groups. Graph 1 and Graph 2 illustrate the effect of the extract on the weight of the body and the organs.

Effect of HRESO-induced Changes on Hematological Parameters

The RBC count shows a modest reduction after 14 days with increasing dosages of HRESO, with 1600 mg showing the lowest result. The WBC count varies very little amongst all groups and stays largely constant. The platelet count in the HRESO (800 mg) group is noticeably lower than in the other groups, which is a striking difference. Furthermore, Haemoglobin levels slightly decline as the HRESO dosage rises, reaching its lowest value at the highest dose (3200 mg). The effect of the plant-tested extract on haematological parametersis shown in Table 1.

Effect of HRESO-induced changes on kidney and liver markers

There is no discernible dose-dependent trend in the minor fluctuations of AST and ALP. As the dose of HRESO is increased, ALT exhibits a slight increase. For all categories, GGT stays comparatively constant. At increasing HRESO doses, LDH decreases; the lowest result is observed at 3200 mg. With an HRESO dosage, bilirubin increases slightly, although not significantly. At higher HRESO dosages, there is a small

TABLE 1. Effect of oral administration of hydroalcoholic root extract of Salvia officinalison haematological parameters of the rat.

BLOOD PARAMETERS	Control	HRESO (800mg)	HRESO (1600mg)	HRESO (3200mg)
RBC (10^6 / L)	7.84 ± 0.03	7.89 ± 0.04	7.11 ± 0.07	7.49 ± 0.11
WBC (10^9 / L)	7.48 ± 0.14	7.46 ± 0.03	7.44 ± 0.05	7.49 ± 0.07
PLATELETS(10^3/µl)	231.00 ± 2.94	234.58 ± 3.92	233.00 ± 2.83	236.75 ± 1.71
Hb (g/dl)	15.38 ± 0.19	15.62 ± 0.70	15.21 ± 0.45	14.26 ± 0.12

Values are expressed as mean ± STD. P < 0.05 when compared to the control group.
HRESO- Hydroalcoholic Root Extract of *Salvia Officinalis.*

TABLE 2. Effect of oral administration of hydroalcoholic root extract of Salvia Officinalison biochemical parameters of the rat.

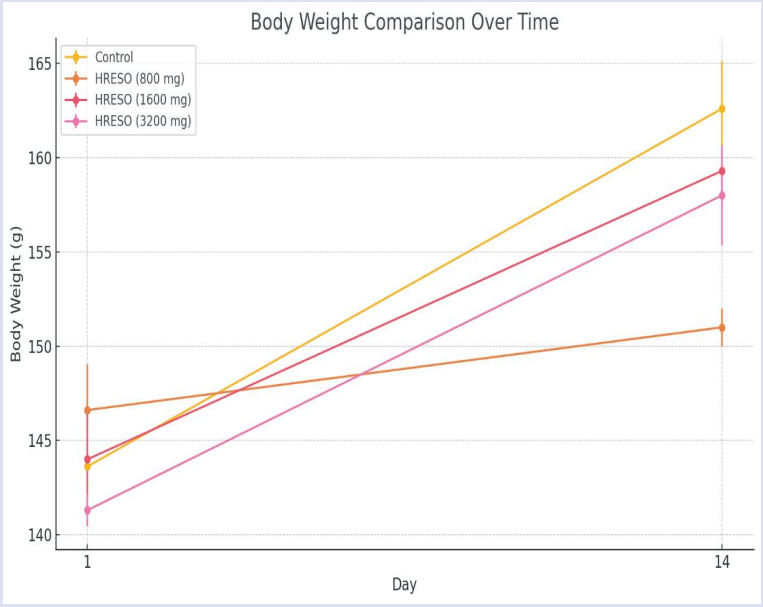
PARAMETERS	Control	HRESO (800mg)	HRESO (1600mg)	HRESO (3200mg)
AST (IU/L)	70.54 ± 0.78	68.83 ± 2.75	66.79 ± 6.49	69.41 ± 4.07
ALP(IU/L)	134.97± 1.91	133.09 ± 3.31	136.48 ± 2.86	132.60 ± 3.01
ALT(IU/L)	74.09 ± 2.14	74.67 ± 2.07	76.15 ± 1.15	78.42 ± 2.60
GGT(IU/L)	30.08 ± 1.15	31.03 ± 1.85	31.05 ± 1.35	30.23 ± 1.11
LDH(IU/L)	222.03±11.98	238.08 ± 4.87	212.65 ± 6.52	201.95 ± 22.41
BILIRUBIN (mg/dl)	0.75 ± 0.04	0.76 ± 0.14	0.78 ± 0.07	0.78 ± 0.04
PROTEIN (g/dl)	7.92 ± 0.19	7.97 ± 0.09	7.46 ± 0.62	7.51 ± 0.46
GLUCOSE (mg/dl)	116.88 ± 6.15	118.48 ± 6.51	107.93 ± 13.73	111.18 ± 11.32
UREA(mg/dl)	19.04 ± 0.28	20.28 ± 1.11	20.19 ± 0.38	23.58 ± 1.33
URIC ACID (mg/dl)	2.20 ± 0.26	2.20 ± 0.22	2.00 ± 0.43	2.10 ± 0.26
CREATININE(mg/dl)	0.50 ± 0.04	0.50 ± 0.07	0.54 ± 0.05	0.55 ± 0.05

Values are expressed as mean ± STD. P < 0.05 when compared to the control group
HRESO- Hydroalcoholic Root Extract of *Salvia Officinalis*

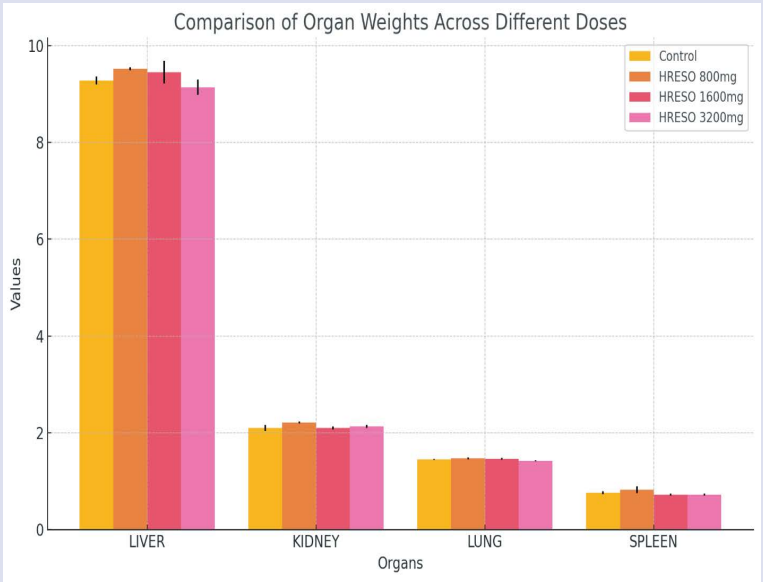
TABLE 3. Effect of oral administration of hydroalcoholic root extract of Salvia officinalis on Oxidative stress in rat liver tissue.

OXIDATIVE STRESS	Control	HRESO (800mg)	HRESO (1600mg)	HRESO (3200mg)
MDA(nmol/mg protein)	1.20± 0.19	1.24 ± 0.36	1.66 ± 0.31	2.24 ± 0.29
SOD(Units/ mg protein)	9.58 ± 0.56	11.53 ± 1.13	11.25 ± 0.70	9.78 ± 0.26
CAT(Units/ mg protein)	82.45± 0.87	83.93 ± 1.22	83.03 ± 1.29	81.85 ± 0.39
GSH(Units/ mg protein)	43.15±0.61	44.88 ± 0.17	47.23 ± 1.38	46.98± 1.20

Values are expressed as mean ± STD. P < 0.05when compared to the control group.
HRESO- Hydroalcoholic Root Extract of *Salvia Officinalis*



GRAPH 1. Effect of oral administration of hydroalcoholic root extract of *Salvia officinalis* on rat's average body weight (g).
Values are expressed as mean ± STD. P < 0.05 when compared to the control group.
HRESO- Hydroalcoholic Root Extract of *Salvia Officinalis*



GRAPH 2. Effect of oral administration of hydroalcoholic root extract of *Salvia officinalis* on average organ weight (g) of rat.
Values are expressed as mean ± STD. P < 0.05 when compared to the control group.
HRESO- Hydroalcoholic Root Extract of *Salvia Officinalis*

decrease in protein. Higher HRESO doses cause glucose to decline slightly, although this decrease is highly variable. The amount of urea increases with the HRESO dose, reaching its maximum at 3200 mg. Roughly unchanged is uric acid. A modest rise in creatinine is observed at higher dosages of HRESO. The effect of the plant-tested extract on kidney and liver markersis shown in Table 2.

Effect of HRESO-induced changes on Oxidative stress

When HRESO is administered, there is a noticeable dose-dependent increase in MDA (malondialdehyde). The maximum dose (3200 mg) significantly doubled the MDA levels compared to the control. SOD (Superoxide Dismutase) rises in comparison to control at lower HRESO doses (800 and 1600 mg). Even at the greatest dosage (3200 mg), it returns to almost control levels. This pattern may suggest that an adaptive response occurs at lower dosages, overpowered at the greatest dose. There is little difference in CAT (catalase) between any two groups. Slight rise at lower HRESO doses, which at the highest dose returns to levels almost exactly under control. Because of their modest size, the modifications might not have much of an impact on biology. When HRESO is administered, GSH (glutathione) generally increases. The highest amounts were seen at dosages of 1600 mg and 3200 mg. This rise could be an adaptive reaction to oxidative stress. The effect of the plant-tested extract on Oxidative stressis shown in Table 3.

The control liver, kidney, lung, and spleen tissues showed normal architecture. Oral HRESO administration had no significant effect on the liver architecture, and the liver tissue showed intact sinusoids and central veins with no inflammatory alterations. The architecture of the kidney tissue was normal, with complete glomeruli and tubules in HRESO-administered rats. The epithelium, smooth muscles, and bronchioles in the lung tissue are all intact even after 14 days of oral HRESO administration. The red pulp in the spleen tissue is normal, with no negative alterations in HRESO-administered rats.

DISCUSSION

Since ancient times, medicinal plants have been used to treat various diseases[14].Several herbs and their formulations are harmful[15]. Safety testing is required to increase the market's acceptance, standardization, and regulation of herbal medications[16]. Toxicology tests examine products that include single chemicals, mixtures of chemicals, crude extract, medicines, food additives, insecticides, and packaging materials or their chemical constituents[17]. The present study studied the hydroalcoholic extract of Salvia officinalis root using Wistar rats. Numerous themes were evaluated, including behavioural observations, body and organ weight alterations, biochemical and haematological parameters, indicators of oxidative stress, and histological abnormalities in important organs.

The oral dosage of 800 mg/kg, 1600 mg/kg, and 3200 mg/kg of the extract did not result in significant clinical signs or mortality in rats. The extract has a rather high level of safety, with an LD50 > 3200 mg/kg, indicating that at these levels, it is safe for therapeutic use in rats and may even be safe for human use.

The results showed that the body and organ weights of the rats given the extract did not substantially differ from the control group. The extract did not adversely affect the rats' overall growth and health, as seen by the stability of body weight. The fact that there haven't been any noticeable alterations increases the extract's safety because organ weight is a sensitive indicator of toxicity[18].

Haematological indicators are examined to ascertain the level of toxicity of pharmacological chemicals, such as plant extracts[19]. The haematological parameters of animals are sensitive markers of the physiological alterations caused by environmental pollution or toxic stress[20].Haematological investigation revealed that the treatment groups differed somewhat regarding haemoglobin levels, white blood cell (WBC), and red blood cell (RBC) counts. These differences, however, did not depend on dosage and remained within normal bounds, indicating that the extract did not adversely affect the immune system or the blood-forming organs.

Numerous blood indicators are required to assess the health of several organs, including the liver and kidneys, which are vital for metabolic activities[21]. No observable negative effects were discovered when liver and renal function markers like AST, ALT, urea, and creatinine were examined. Despite a few small variations, none of them pointed to liver or renal impairment. This finding suggests that the extract does not impair the regular operation of these vital organs.

The oxidative stress indicators that were examined were MDA (malondialdehyde), CAT (catalase), SOD (superoxide dismutase), and GSH (glutathione). The results showed that MDA increased in a dose-dependent way, suggesting that larger doses (3200 mg/kg) were linked to higher levels of oxidative stress and lipid peroxidation[22]. Particularly at lower doses, the initial spike in SOD and GSH levels indicates that the body is putting up a defence reaction. The greatest dosage appeared to overwhelm the antioxidant defences, suggesting that smaller dosages may induce an adaptive response while greater amounts cause oxidative damage[23].

The liver, kidney, lungs, and spleen are the key organs that any harmful material primarily targets for metabolism[24]. No significant tissue architecture alterations or damage were found during the histological analysis of important organs, such as the liver, kidney, spleen, and lungs. The haematological and biochemical testing outcomes corroborate the extract's non-toxic nature at the administered dosages.

CONCLUSION

Per OECD recommendations, an acute oral toxicity test was performed to confirm the harmless nature of *Salvia officinalis* roots hydroalcoholic extract. The results of this investigation indicate that, even at high dosages, oral administration of Salvia officinalis root hydroalcoholic extract in rats is safe. Higher dosages did cause some oxidative stress, but the rats' physiological systems could compensate, and no significant toxicity resulted. This extract shows promise for therapeutic application if the dosage is properly controlled. Given the lack of significant clinical symptoms, organ damage, or death, Salvia officinalis may be worth exploring in further research and clinical trials for potential medicinal uses. Subsequent research endeavours may develop into the extract's enduring impacts and therapeutic possibilities, particularly emphasizing its pharmacological advantages and chronic toxicity. Further investigation into its antioxidant mechanisms may also shed light on potential applications of the extract to treat diseases associated with oxidative stress.

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Cite this article: Ranjini H S, Kadmad A H M A, Fayazul H S, Prashanthkumar G, Vinodakumar H R, Akash. Acute Oral Toxicity Evaluation of Hydroalcoholic Extract of Salvia Officinalis Roots in Wistar Rats as per OECD 423 TG. Pharmacogn J. 2025;17(5): 577-582.