IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
September 2022 Vol.:25, Issue:2

Evaluation of Acute and Sub-Chronic Toxicity of *Salvia cabulica* Extract

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
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ISSN 2349-7203
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Submitted: 25 August 2022
Accepted: 31 August 2022
Published: 30 September 2022

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Acute Toxicity, Sub-Chronic Toxicity, *Salvia cabulica* Extract

ABSTRACT

The present study was carried out to determine the acute and sub-chronic toxicity of *S. cabulica* plant on Swiss albino mice and rabbits. For this purpose, two experiments were conducted. Acute toxicity of *S. cabulica* extract was determined in male and female Albino Swiss mice and sub chronic toxicity on rabbits. Mice was grouped into (nine) experimental and one control group for LD50 purpose, single oral dose from (100, 200, 300, 500, 800, 1000, 1300, 1500, 2000mg/kg/day) was administered. Sub chronic toxicity test was evaluated according to WHO guidelines of OECD in albino rabbits. All experimental rabbits were divided into 03 groups and each group was containing 5 rabbits. In this study, the doses of methanolic *S. cabulica* extracts were 250 and 500mg/kg/day. The extracts were dissolved in distilled water and given to every group of rabbit daily orally for 28 days, while the other group was controlled. Body weight of rabbit of each group was measured just before and after 28 days of experiment. Blood was collected to determine Hb hemoglobin, RBC Red blood cell count, Hematocrit HCT/PVV, MCV, MCH, MCHCH, LDH, CK-M, calcium serum, total bilirubin, direct bilirubin, alkaline phosphate, albumin, globulin, A/G ratio, cholesterol, blood glucose, triglycerides, WBC white blood cell count, platelets, SGOT serum glutamate oxaloacetate transaminase, urea, total protein, creatinine, and uric acid levels. All the biochemical and Hematological parameters have slightly changes which results that ethanolic extract of *S. cabulica* is safe to use orally and have not toxicological effects on biochemical and hematological parameters. The mice survived on 1000mg/kg dose quantity thus, the lethal dose (LD50) of *S. cabulica* is more than1000mg/kg.

BACKGROUND

In ancient civilizations, medicinal plants were frequently employed by people, from the beginning of the world man has been in search of medicinal plants for healing purpose, that's why there is various evidence about it, written documents, preserved monuments, and even original plant medicines. Man has been searching for different techniques and methods for pursuing medicines from barks roots, leaves and seeds of different medicinal plants. Modern science has brought modifications in the use of active ingredients and it has brought a revolution in pharmacotherapy which has been fetched by the ancient civilizations used during periods (Petrovska 2012).

Traditional Medicine is being used worldwide in developing countries and instantly having an economical importance. Traditional Medicine is often convenient and affordable for treatment regimens in developing countries. The 80% population of Africa is using traditional medicines for health care. Allopathic doctors in Japan prescribe 60-70% traditional medicines for their patients. In the united kingdom mostly 40% of the allopathic practitioners are prescribing traditional medicines (Bussmann and Sharon 2006).

Pakistan's total area is about to 881,913 square kilometers, and it has great altitude and longitude ranges from 0 to 8611 meter, so therefore it possesses many climatic zones and a unique biodiversity. 6,000 species of higher plants are present in Pakistan. It has been reported that 600 to 700 species are being used as medicinal plant. 70% of them are from same region and the remaining 30% are different regions. The main medicinal plant research activities in Pakistan are documentary. In universities the researches are being conducted mainly are ethanol/methanol botanical resources. In Pakistan these plants are found in local areas and the people have an old knowledge regarding traditional use of medicinal plants. Different diseases are being treated by using these plants. The important plants have many active ingredients so they are commercially collected to extract them. The application of traditional information also degrades the values lie in traditions having by old people, especially about the medicine. Only few institutes are there in which the practical use of medicinal plants are studying. Due to synergistic and less unwanted effects the medicinal plants are used as medicine. Plants also have harmful effect due to synthetic therefore, trends leading towards natural remedies. Many people use the medicinal plants as a main source of their income. In Pakistan they just export it but don't cultivated (Shinwari 2010).

The largest province of Pakistan is Baluchistan and smallest in population but representing 44% of the land area of the country that is 34.7 million hectares. Climate of the province is dry to semiarid, from ranges of cool temperate in the north to coastal tropical area. And it has the ecological zones which are mixed desert, deciduous forest, dry temperate forest, sub-tropical forest, tropical dry and mangrove forest. Because of environmental changes Baluchistan has blessed with different medicinal plants and animals (Anonymous, 2009).

SALVIA CABULICA

Salvia, is a genus of Lamiaceae family which have approximately 900 different species distributed all over the globe. It composed of aromatic and ornamental herbs and shrubs present in tropical and temperate areas. This genus has 2 main centers in America and in South West Asia. The main center for the genus Salvia with a different number of endemic species in turkey. Pakistan has 16 species of this genus. This plant has an important value from the ancient age. Some species of salvia has a curative property. This species comprises antiseptic such as terpenes, flavones, anthocyanin's and proanthocyanins, which used as antispasmodic, antiseptic, astringent as well as anti-neurasthenic insomnia, anti-cancerous. It is also reported that has other biological effects such as, antibacterial, cytostatic, anti-tuberculosis, antiviral and antioxidant actions. It has glandular hairs that are composed of fragrant ether like essential oils, which are the characteristic feature of most of them. So, therefore it can be widely used in perfumes and as sweetening agent for food. *S. cabulica* is full of lilac flowers in their aromatic shrubs, stem, leaves, and branches and contain hair like projections. This genus is found in dry stony mounts at 1600 – 2400 meters of altitude. It is mainly found in Afghanistan and Pakistan, besides this different district of Baluchistan like Hanna Urrak, Walitangi (Quetta), Mach Bolan, Loralli, Ziarat, and in the Murdar mountain range has this plant too. It is reported that *S. Cabulica* is used in the treatment of common cold and lung disorder in folk medicines (Rashid, Farah *et al.* 2009).

Methodology

Medicinal Plant Collection

The samples of *S. cabulica* plant was collected from Hanna Urrak, Quetta and brought to the department and identified by pharmacognosy department chairperson and plant specimen no. MD 191/2019.

Animals

Swiss albino mice of both sex of different weights (25gm to 30gm) was included in this study and rabbits.

Dosage formulation

The weight of *S. cabulica* plant extract was measured and dissolved into distilled water for oral administration on two dosage quantities i.e. 250mg /kg and 500mg/kg rabbits for sub-Chronic toxicological studies.

Plant Extraction

S. cabulica plant was assembled from Hanna Urrak District Quetta of Baluchistan, Pakistan. The concerned plant was identified. The extraction of the plant was performed by soaking in Methanol from seven to fifteen days with rotary evaporator under reduced pressure. After the evaporation of solvent, residue was obtained for Pharmacological studies(Abdul Jabbar, Razaque *et al.* 2021).

Toxicological Studies

Acute toxicity

This study was carried out by LD_{50} to determine. The animals used for this study was male and female both Albino Swiss mice weighing (25-35g). The mice were adjusted in a laboratory condition for a week before the experiment. Mice was grouped into (nine) experimental and one control group for LD_{50} purpose, single oral dose from (100, 200, 300, 500, 800, 1000, 1300, 1500, 2000 mg/kg/day) was administered (Lorke 1983).

Sub-Chronic toxicity

Sub chronic toxicity test was conducted according to WHO guidelines of OECD. Rabbits will be divided into 03 groups and 05 in each group. In this study, the doses of methanolic *S. Cabulica* extracts were 250 and 500 mg per kg per day. The extracts were dissolved in distilled water and given to every group of rabbit daily orally for 28 days, while the other control group in water vehicle. Rabbit was in fasting overnight, halothane anesthesia was used and forfeit after the 29th day. Samples of pair, heparinized and non-heparinized, was collected for hematological and serum biochemical assays (Olorunnisola, Bradley *et al.* 2012).

Body weight

Body weight of rabbit of each group was measured just before and after 28 days of treatment.

Hematological parameters

Blood was collected to estimate of Hb hemoglobin, RBC Red blood cell count, Hematocrit HCT/PVV, MCV, MCH, MCHCH, LDH, CK-M, calcium serum, total Bilirubin, direct bilirubin, alkaline phosphate, albumin, globulin, A/G ratio, cholesterol, blood glucose, triglycerides, Platelets and WBC white blood cell count also done.

Biochemical parameters

To estimate serum biochemical parameters, serum biochemical parameters were employed. SGOT serum glutamate oxaloacetate transaminase, urea, total protein, creatinine, and uric acid levels can be determined.

RESULTS

Acute toxicity

Results indicates that LD_{50} doses of *Salvia cabulica* extracts caused mortality rate in group A (33.33%), B (33.33%), C (50.00%), D (50.00%), E (66.66%), F (83.33%), G (100%), H (100%) and I (100%), respectively. Body weight was linearly decreased after acute and sub chronic doses of *Salvia cabulica* extracts in Swiss albino mice and rabbits in all treatment groups which is shown in Table No 1.

Sub chronic toxicity of *Salvia cabulica* extract on rabbits

Kidney function test

Urea Level (mg/dL) was 79.8±2.603 for control group and 80.6±2.916 for drug treated with 250mg/kg and 500 mg/kg. Creatinine Level was 1.38±0.18 for control group and for treated with 250mg/kg drug were 1.54±0.275 and 500 mg/kg 1.68±0.150 rabbit. Uric acid for control group was 0.42±0.049 and for 250, 500mg/kg were 0.54±0.051, 0.64±0.060 respectively. Urea level shows no significance while creatinine has highly significant (P<0.01) at 500mg/kg shown in Table No. 2.

Random Blood Glucose

Random Blood Glucose for control group was 96.4±7.034 and for 250,500mg/kg were 15.66±0.647, 15.62±0.682 respectively and there was not any efficacy.

Cardiac Enzymes

LDH Level for control group was 797.6±80.112 and for 250,500mg/kg were 798.6±69.267, 835±75.869 respectively. LDH has significant (P<0.05) at dosage of 250mg/kg.

Calcium Serum

Calcium Serum for control group was 15.1±0.531 and for 250,500mg/kg were 15.66±0.647, 15.62±0.682 respectively. Calcium serum has no significance.

Hematological parameters

Hb (g/dl) for control group was 11.44±0.5235 and for 250, 500mg/kg were 12.46±0.431, 11.84±0.346 respectively. Red blood cell Count (million/ul) for control group was 6.378±0.326 and for 250, 500mg/kg were 5.49±0.149, 5.00±0.066 respectively. Hematocrit (HCT/PCV) % for control group was 39.37±2.420 and for 250, 500mg/kg were 38.03±2.706, 37.05±2.729 respectively. MCV (fl) for control group was 68.72±1.044 and for 250,500mg/kg were 67.26±1.181, 66.24±1.215 respectively.

MCH (pg) for control group was 21.12±0.395 and for 250, 500mg/kg were 19.74±0.649, 18.88±0.724 respectively. MCHC (g/l) for control group was 30.92±0.661 and for 250,500mg/kg were 29.54±0.871, 28.66±0.853 respectively. Total White blood cell Count for control group was 9.91±0.547 and for 250,500mg/kg were 9.16±0.424, 8.8±0.304 respectively. Platelet (×10^9/L) for control group was 289.4±40.373 and for 250,500mg/kg were 286.8±39.78, 284.8±39.76 respectively. HB shows no significance at dosage of 500mg/kg, Hematocrit HCT/PCV and RBC shows Significant (P<0.05) at a dosage of 250mg/kg. Other all hematological effects have highly significant (P<0.01) at a dosage of 250mg/kg.

Liver function test

Total Bilirubin (mg/dL) for control group was 0.272±0.021 and for 250,500mg/kg were 0.288±0.021, 0.306±0.032 respectively. Direct Bilirubin (mg/dL) for control group was

0.126±0.045 and for 250,500mg/kg were 0.146±0.064, 0.164±0.084 respectively. Alkaline Phosphatase (U/L) for control group was 55.4±3.412 and for 250, 500mg/kg were 57±3.4003, 59.2±1.754 respectively. SGOT (U/L) for control group was 80.1±3.667 and for 250, 500mg/kg were 81.7±3.440, 81.7±3.440 respectively. Total bilirubin and alkaline phosphate have highly significant (P<0.01) at dosage of 250mg/kg and others have no significance.

Total protein

Total proteins Level (g/dL) for control group was 6.34±0.163 and for 250,500mg/kg were 6.4±0.1228, 5.62±0.2040 respectively. Albumin level (g/dL) for control group was 3.76±0.163 and for 250, 500mg/kg were 3.82±0.2040, 3.68±0.1832 respectively. Globulin (g/dL) for control group was 2.5±0.100 and for 250, 500mg/kg were 2.12±0.037, 2.12±0.058 respectively. A/G ratio for control group was 1.294±0.131 and for 250,500mg/kg were 1.454±0.166, 1.530.1137 respectively. Total protein, A/G ratio has highly significant (P<0.01) at dosage of 500mg/kg, globulin and A/G ratio also at dosage of 250mg/kg. And globulin has Significant (P<0.05) at dosage of 500mg/kg.

Lipid profile

Cholesterol level (mg/dL) for control group was 35.6±2.020 and for 250,500mg/kg were 35.6±2.0204, 34±2.173 respectively. Triglycerides level (mg/dL) for control group was 47.2±4.223 and for 250, 500mg/kg were 44.6±4.5244, 44.4±4.457 respectively. Cholesterol has no significance at 250mg/kg and highly significant (P<0.01) at 500mg/kg, while triglycerides has highly significant (P<0.01) at both dosages.

Table No. 1: Mortality of Swiss Albino mice after acute toxicity of *Salvia cabulica* extracts

S. No	Doses	Mortality	
		Number	Percentage%
1	Control group	0	0
2	Group A 100 mg/kg/day	2	33.33%
3	Group B 200 mg/kg/day	2	33.33%
4	Group C 300 mg/kg/day	3	50.00%
5	Group D 500 mg/kg/day	3	50.00%
6	Group E 800 mg/kg/day	4	66.66%
7	Group F 1000 mg/kg/day	5	83.33%
8	Group G 1300 mg/kg/day	6	100.00%
9	Group H 1500 mg/kg/day	6	100.00%
10	Group I 2000 mg/kg/day	6	100.00%

Table No. 2: Body weight of rabbit before and after administration of *Salvia cabulica* extracts at different doses

Doses	Body weight (kg)	
	Before	After
Group A 300 mg/kg/day	1.11	0.84
Group B 500 mg/kg/day	1.03	0.75
Group Control	1.25	1.88

Table No. 3: Effect of *Salvia cabulica* on Kidney function test on rabbit

S. No.	Test	Control (Mean+ SEM)	Drug treated 250mg/kg (Mean +SEM)	Drug treated 500mg/kg (Mean +SEM)
1	**Urea (mg/dL)**	79.8±2.603	80.6±2.916	81.6±2.916
2	**Creatinine,**	1.38±0.188	1.54±0.275	1.68±0.150**
3	**Uric acid(mg/dL)**	0.42±0.049	0.54±0.051**	0.64±0.060**

Values of the mean ± SEM; n=5; * = Significant (P<0.05), ** =, highly significant (P<0.01).

Table No. 4: Effect of *Salvia cabulica* on (random) Blood Glucose of rabbits

S. No.	Test	Control (Mean + SEM)	Drug treated 250mg/kg (Mean +SEM)	Drug treated 500mg/kg (Mean +SEM)
1	**Blood Glucose Random**	96.4+ 7.034	101.8+9.467	106+10.323

=values of the mean ± SEM; n=5; * Significant (P<0.05), ** = highly significant (P<0.01)

Table No. 5: Effect of *Salvia cabulica* on Cardiac Enzymes of rabbit

S. No.	Test	Control (Mean+ SEM)	Drug treated 250mg/kg (Mean +SEM)	Drug treated 500mg/kg (Mean +SEM)
1	LDH (U/L)	797.6±80.112	798.6±69.267	835±75.869*
2	CK-MB (U/L)	23.4±0.8146	25±0.709**	25.8±0.5846*
3	SGOT (U/L)	83.4±3.364	86.4±3.623**	89.8±3.743*

Values of mean ± SEM; n=5; * = Significant (P<0.05), ** =, highly significant (P<0.01)

Table No. 6: Effect of *Salvia cabulica* on Blood of rabbits

S. No.	Test	Control (Mean+ SEM)	Drug treated 250mg/kg (Mean +SEM)	Drug treated 500mg/kg (Mean +SEM)
1	Hb (g/dl)	11.44±0.5235	12.46±0.431**	11.84±0.346
2	RBC Count (million/ul)	6.378±0.326	5.49±0.149*	5.00±0.066**
3	Hematocrit (HCT/PCV) %	39.37±2.420	38.03±2.706*	37.05±2.729**
4	MCV(fl)	68.72±1.044	67.26±1.181**	66.24±1.215**
5	MCH(pg)	21.12±0.395	19.74±0.649**	18.88±0.724**
6	MCHC (g/l)	30.92±0.661	29.54±0.871**	28.66±0.853**
7	Total WBC Count (×10^9/L)	9.91±0.547	9.16±0.424**	8.8±0.304**
8	Platelet Count (×10^9/L)	289.4± 40.373	286.8±39.78**	284.8±39.76**

Values of mean ± SEM; n=5; * = Significant (P<0.05), ** =, highly significant (P<0.01)

Table No. 7: Effect of *Salvia cabulica* on Serum Calcium

S. No.	Test	Control (Mean + SEM)	Drug treated 250 mg/kg (Mean +SEM)	Drug treated 500mg/kg (Mean +SEM)
1	Calcium-Serum (mg/dL)	15.1±0.531	15.66±0.647	15.62±0.682

Values of mean ± SEM; n=5; * = Significant (P<0.05), ** =, highly significant (P<0.01).

Table No. 8: Effect of *Salvia cabulica* on Liver function test of rabbit

S. No.	Test	Control (Mean+ SEM)	Drug treated 250mg/kg (Mean +SEM)	Drug treated 500mg/kg (Mean +SEM)
1	Total, Bilirubin (mg/dL)	0.272±0.021	0.288±0.021**	0.306±0.032
2	Direct Bilirubin (mg/dL)	0.126±0.045	0.146±0.064	0.164±0.084
3	Alkaline Phosphatase(U/L)	55.4±3.412	57±3.4003**	59.2±1.754
4	SGOT (U/L)	80.1±3.667	81.7±3.440	81.7±3.440

Values of mean ± SEM; n=5; * = Significant (P<0.05), ** =, highly significant (P<0.01)

Table No. 9: Effect of *Salvia cabulica* on Total Protein test of rabbits

S. No.	Test	Control (Mean+ SEM)	Drug treated 250mg/kg (Mean +SEM)	Drug treated 500mg/kg (Mean +SEM)
1	Total proteins (g/dL)	6.34±0.163	6.4±0.1228	5.62±0.2040**
2	Albumin (g/dL)	3.76±0.163	3.82±0.2040	3.68±0.1832
3	Globulin (g/dL)	2.5±0.100	2.12±0.037**	2.12±0.058*
4	A/G ratio	1.294±0.131	1.454±0.166**	1.530.1137**

Values of mean ± SEM; n=5; * = Significant (P<0.05), ** = highly significant (P<0.01)

Table No. 10: Effect of *Salvia cabulica* on Lipid profile of rabbits

S. No.	Test	Control (Mean+SEM)	Drug treated 250mg/kg (Mean +SEM)	Drug treated 500mg/kg (Mean +SEM)
1	Cholesterol (mg/dL)	35.6±2.020	35.6+2.0204	34+2.173**
2	Triglycerides (mg/dL)	47.2±4.223	44.6±4.5244**	44.4±4.457**

All values are mean ± SEM; n=5; * = Significant (P<0.05), ** = highly significant (P<0.01).

DISCUSSION

Results of this study showed that after the plant administration of formulation, serum creatinine and urea concentration was increased significantly probably due to the extract effect on kidney function but in 500mg/kg animal the creatinine level became highly significant (Safa *et al* 2005). This protective effect may be due to elevated level of total antioxidant contents in this plant. (Al-Soqeer, A. 2011) the current studies show that there are no toxic effects on kidneys. Orally Administration of plant results in non-significant increase in blood glucose level which may be due to carbohydrate content of the plant. It is also known that diagnosis of cardiac enzymes is very important. Serum CK activity is more complex indicator in early stage myocardial ischemia, while significantly increase in LD is rightly proportional to the range of injury in myocardial tissues (Chatterjea *et al* 2002). Oral administration of *Salvia cabulica* also results in non-significant change in the level of SGOT and LDH. The potential of reducing the factors that produce infarction in the myocardium shown due to Level of CKMB was increased highly significant. The results also suggest that *Salvia cabulica* have protective effects on the heart. (Edet, E. *et al* 2009). Oral administration of *Salvia cabulica* also results in non-significant changes in level serum calcium and highly meaningful change in uric acid. In Hematological parameters of rabbit, the administration of *Salvia cabulica* results in highly notable change in the level of RBC Count, Hemoglobin, Hematocrit (HCT/PCV) %, MCH, MC, MCHC, WBCs count. There was also significant increase in the level of blood platelets. According to literature review the ALOX 12 and PTAFR gene leads to arised production of the megakaryocytes and its conversion into platelets, evidence of current research shows that *Salvia cabulica* may raise ALOX 12 activity, and PTFAR activity because of which increase found in platelet production (Yunita F *et al*, 2012). Administration of *Salvia cabulica* in liver function test results in highly notable change in the level of Total Bilirubin and Alkaline Phosphatase. And non-significant change in Direct Bilirubin and SGOT. Globulin, Total proteins and A/G ratio are significant, and Albumin became non-significant which shows that the plant does not contain any toxicity in the liver. Orally administration of my plant results in highly significant change the cholesterol and triglycerides level, results reveals that the *Salvia cabulica* is safe and have non-toxic effects on lipid profile.

CONCLUSION

LD50 doses of *Salvia cabulica* extracts caused mortality rate in group A (33.33%), B (33.33%), C (50.00%), D (50.00%), E (66.66%), F (83.33%), G (100%), H (100%) and I (100%), respectively. Body weight was linearly decreased after acute and sub chronic doses of *Salvia cabulica* extracts in Swiss albino mice and rabbits in all treatment groups; whereas the body weight was remained stable in non-treated group (control). All the biochemical and hematological parameters have slightly changed which results that ethanolic extract of *S. cabulica* is safe to use orally and have not toxicological effects on biochemical and hematological parameters. The mice survived on 1000mg/kg dose quantity thus, the lethal dose (LD50) of *S. cabulica* is more than1000mg/kg.

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