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Research Article
Protective Role of Aerial Parts of *Silene villosa* Alcoholic Extract Against CCl_4-Induced Cardiac and Renal Toxicity in Rats

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Abstract

Background and Objective: *Silene villosa* (Family-Caryophyllaceae) is used traditionally in different part of Asian continents for the treatment of various illnesses. Recently, *S. villosa* has been tested and confirmed for anti-inflammatory and antioxidant activities. Therefore, the present study was carried out to evaluate cardiac and renal protective effects of *S. villosa* extract (SVE) against CCl_4-induced toxicity. **Materials and Methods:** The herbs of *S. villosa* were collected, authenticated, coarsely powdered and extracted in Methanol using percolation method. Wistar albino rats (≈200 g) of either sex were randomly divided into five groups. Group I (normal control) and Group II (toxic control) received normal saline (1 mL/100 g, p.o.) for 7 days. Groups III (positive control), IV and V (Test groups) were received Silymarin (10 mg kg^{-1}, p.o.), SVE at doses of 250 and 500 mg kg^{-1}, p.o., respectively for 7 days. On the 8th day, except normal group (Group I), all Groups were administered with CCl_4 (1.0 mL kg^{-1}, i.p). After 24 h of CCl_4 administration, the serum cardiac function parameters such as (LDH, CK and Albumin) and the serum renal function parameters such as creatinine, urea and uric acid, electrolytes and tissue total proteins were measured as a marker of cardiac and renal toxicity. The cardiac and renal tissue parameters such MDA and NP-SH were measured for the *in vivo* antioxidant activities. Further, the biochemical studies were followed by histopathological studies of heart and kidney tissues. **Results:** The treatment of CCl_4 in rats, significantly altered the cardiac and kidney function test limitation. Administration of SVE at two different doses of 250 and 500 mg kg^{-1} with CCl_4 showed a significant ($p<0.01$-0.001) protective ability against CCl_4 intoxication by repairing the cardiac and kidney function abnormalities. The protective ability of SVE was further confirmed by the histological study of cardiac and renal tissues. **Conclusion:** The results led us to the conclusion that SVE ameliorate the cardiac and renal dysfunction.

Key words: *Silene villosa* extract (SVE), cardiac dysfunction, kidney failure, histopathology, carbon tetrachloride

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The kidneys are accountable for regulating homeostasis through balancing of electrolytes in the blood and the vital role of the cardiovascular system in maintaining homeostasis by pumping blood. One of the animal study observations has strong support that renin-angiotensin system (RAS) maintain cardiovascular homeostasis in acute liver failure[1]. The present acute kidney injury is very common in the thirty years before synthetic drug users, at present, in addition to the liver injury they had also cardiovascular, diabetes and other incurable diseases[2,3]. Cardiovascular disease, the foremost cause of the death, is mostly triggered by the chronic kidney disease. Both cardiovascular and kidney ailments are closely interrelated and illness of one organ cause dysfunction of the other, finally leading to the failure of both organs. Patients with end-stage renal disease are at higher risk of death due to cardiovascular disease[4].

Traditional herbal drugs due to their safety and efficacy and long history, day by day becoming popular for the treatment of various chronic and acute ailments, nephrotoxicity and cardiac dysfunctions are among them. There are various lines of indication which implicated oxidative stress in the etiology of cardiovascular and kidney diseases[5,6]. The efficacy of natural products is still functioning and up to 50% of the approved drugs in the last 30 years are from the natural sources either directly or indirectly[7]. Recently, for investigation of immunomodulatory and antioxidant activities, RAW 264.7 cells are employed through multiple factor analysis and the extract of *S. villosa* showed a significant cytotoxic effect on RAW cells[8]. In recent finding, alcoholic extract of *S. villosa* aerial part showed anti-inflammatory and hepatoprotective properties (under publication) and wound healing[9]. A single dose of carbon tetrachloride (CCl_4) produces centrilobular necrosis and fatty degeneration of the liver in rats. CCl_4 causes metabolic activation in the liver endoplasmic reticulum by trichloromethyl peroxy free radical (CCl_3O_2). All the free radical species produced by CCl_4 contributes significantly to the biological disorder. CCl_4usually used as a solvent for the generation of hepatic damage by producing reactive free radicals and is responsible for kidney failure and cardiovascular dysfunction[10]. CCl_4-intoxication in the animals cardiac cells increases LDH, creatine kinase (CK) and decreases albumin levels[11] and in kidney cells, increases creatinine, Na, K, Ca, Urea and Uric acid[12]. There is strong evidence of each other dependency of cardiac and kidney organs for the controlling of mortality due to kidney failure and cardiac dysfunction. Extensive search of literature revealed that, in-spite of good medicinal values of *S. villosa*, there is no such report till now, which support the defensive work of this plant on kidney failure and cardiac dysfunction. So, the present study was aimed to examine the possible protective effects of SVE on kidney failure and cardiac dysfunction using Wistar and albino rats.

EXPERIMENTAL

Plant material: The herbs of *S. villosa* were collected during the flowering period from the Al-shadida, Province of Alkharj, Saudi Arabia, in March, 2015 and the plant species were authenticated by Dr. Osman Almekki using morphological features of the plant samples. The voucher specimen was deposited in the Herbarium, College of Pharmacy (PSAU-CPH-7-2015), Prince Sattam Bin Abdulaziz University, Al-Kharj, KSA. The shade and dried herbs (500 g) were coarsely powdered and macerated in 3 L of Methanol for 72 h using percolation method. The methanol was then removed at 50°C under reduced pressure in a rotatory evaporator. The *S. villosa* extract (SVE) was then suspended in distilled water just before its administration to the Wistar albino rats for pharmacological activity in the month of June and July, 2015 which was done in College of Pharmacy, Prince Sattam Bin Abdulaziz University and then samples (serum and tissues) were send to College of Pharmacy, King Saud University for the biochemical estimations.

Animals: Young and healthy rats (~200 g) of either sex, were selected for the present study. Rats (Thirty) were received from the Lab ACU (Animal Care Unit), College of Pharmacy, Prince Sattam Bin Abdulaziz University (PSAU). The rats were randomly divided into 5 groups (n = 6) and were kept in plastic cages with 12 h light and dark cycle in standard laboratory conditions of temperature (25±2°C). All groups of rats were allowed to adapt the laboratory conditions for 1 week earlier to the experiments set up. All rats provided, the standard rodent chow diets and tap water *ad libitum*. The present research plan was approved by the Institutional Animal Ethics Committee (IAEC), College of Pharmacy, PSAU, Al-Kharj, Saudi Arabia.

Experimental procedure: Five groups of rats were notified as, Group I (normal) and Group II (toxic control) received normal saline (1 mL/100 g, p.o.) for seven days. Group III (positive control) was received Silymarin (10 mg kg^{-1}, p.o.) for 7 days. Groups IV and V (Test groups) were received, SVE (250 and 500 mg kg^{-1}, p.o.) each, respectively. On the next day of the

last treatment, except normal group (Group I), all Groups were administered with CCl_4 diluted with liquid paraffin oil (50% v/v, 1.0 mL kg^{-1}, i.p). All the assessment studies were performed next day of CCl_4 administration.

Biochemical estimations in serum: For the biochemical assessment, the blood samples were collected from the retro-orbital plexus under light ether anesthesia. By the centrifugation (3000 rpm×10 min, 4°C) process, serum was separated and transferred to prelabeled eppendrof tubes for assessment of various biochemical parameters of cardiac function (LDH, CK and albumin) and kidney function markers such as creatinine, urea, uric acid and electrolyte ions (calcium, sodium and potassium) were examined at College of Pharmacy, King Saud University, Riyadh, KSA, by using different diagnostic kits.

Collection of heart and kidney tissues: Instantly, after blood withdrawal the animals were sacrificed under light ether anesthesia. The heart and kidney samples were then removed, washed with chilled normal saline and fixed with 10% formalin or frozen in liquid nitrogen[13]. The fixed tissues were processed for histological assessment and the frozen tissues were estimated for biochemical evaluation.

Biochemical estimations in heart and kidney homogenate: Specimens from Kidney and heart organs were separated into two parts. Each piece was homogenized independently with a potter- Elvenhjem tissue homogenizer. For the total protein estimation, the first part homogenate was treated with 50 mM phosphate buffer saline (PBS, pH 7.4). The second part homogenate was treated with 10 mM potassium phosphate (pH 7.4) for the estimations of Malondialdehyde (MDA) and Non-protein Sulfhydryls (NP-SH). Both first and second parts homogenates were independently centrifuged at 10,000 rpm, for 15 min and the supernatant was used for the assessment of biochemical parameters. Total Protein contents were measured by the method of Lowry *et al.*[14]. Myocardial and renal MDA and NP-SH were estimated by the method of Utley *et al.*[15] and Sedlak and Lindsay[16], respectively. The total protein was expressed in g L^{-1} while, MDA and NP-SH were expressed as nmol mg^{-1}.

Histopathology: In the graded series of solution 60% (absolute alcohol), 30% (formaldehyde) and 10% (glacial acetic acid), the Heart and kidney tissues were fixed and then embedded in paraffin wax[17]. The tissue section (3 μm) was made by rotary microtome (Leitz 1512), mounted on slides and then, placed in an oven with a temperature of 60°C for 15 min and then stained with hematoxylin/eosin dye subsequently and observed under alight microscope.

Statistical analysis: Graph Pad Prism 5.01 Software was used for statistical examination. The relationship between the groups were prepared by means of one way analysis of variance (ANOVA), followed by Dunnett's multiple comparison test. The $p<0.05$-0.001 was measured as significant.

RESULTS

Assessment of cardiac functions: The effects of SVE and Silymarin on cardiac dysfunction was given in Table 1. The serum LDH and creatine kinase levels were significantly ($p<0.001$) increased in the CCl_4 group (Group-II)animals (295.50±7.60 and 396.00±7.74 U L^{-1}, respectively) when compared to the normal control (Group-I) animals (157.16±5.75 and 199.16±4.77, respectively). The SVE treatment, prior to CCl_4 treatment, significantly ($p<0.01$-0.001) protected the elevated serum LDH levels at higher dose (500 mg kg^{-1})and CK levels were protected significantly ($p<0.001$) at both the doses (250 and 500 mg kg^{-1}). The serum albumin was depleted in rats treated with CCl_4 (2.12±0.11 mg dL^{-1}) when compare to normal control animals (5.1±0.17 mg dL^{-1}). Administration of SVE at higher dose significantly ($p<0.001$) uphold the normal albumin levels.

Assessment of kidney functions: The effects of SVE and Silymarin and on the renal function was depicted in Table 2. The kidney function markers such as creatinine, urea and uric acid levels in CCl_4 group (Group II) of rats were found to be significantly increased when compared with the normal control group (group I). The elevated levels of creatinine, urea and uric acid were significantly ($p<0.05$-0.001) uphold with the Silymarin (Group III) and SVE (250 and 500 mg kg^{-1}) treatments (Group IV and V).

The effects of SVE and Silymarin on serum electrolyte disturbances was shown in Table 3. Kidney electrolytes such as sodium (Na), Potassium (K) and Calcium (Ca), disturbances in CCl_4 group (Group II) rats were found to be significantly increased when compared to the normal control group (group I) rats. The elevated levels of serum sodium (Na), Potassium (K) and Calcium (Ca) were significantly

Table 1: Cardiac dysfunction test of Silymarin and SVE in carbon tetrachloride intoxicated rat

		LDH (U L^{-1})		Creatine kinase (U L^{-1})		Albumin (mg dL^{-1})	
Treatments	Dose (mg kg^{-1})	Mean±SEM	Change %	Mean±SEM	Change %	Mean±SEM	Change %
Normal		157.16±5.75		199.16±4.77		5.10±0.17	
CCl_4		295.50±7.60***a		396.00±7.74***a		2.12±0.11***a	
Silymarin+CCl_4	10	200.16±8.61***b	32.26	245.50±4.29***b	38.51	3.66±0.20***b	72.30
SVE+CCl_4	250	280.33±8.56b	50.13	303.83±5.66***b	23.27	2.09±0.09b	10.53
SVE+CCl_4	500	253.33±7.98**b	14.26	274.50±6.86***b	30.80	2.90±0.11***b	36.92

Data are expressed as Mean±SEM (n = 6), **p<0.01, ***p<0.001, statistically significant when compare CCl_4 intoxication to a normal control group. When compared CCl_4 group with SVE (250 and 500 mg kg^{-1}) and Silymarin (10 mg kg^{-1}), showed statistically significant via Dunnett's multiple comparison test

Table 2: Kidney function test (Creatinine, urea and uric acid) of Silymarin and SVE in carbon tetrachloride intoxicated rats

		Creatinine (mg dL^{-1})		Urea (nmol L^{-1})		Uric acid (mg dL^{-1})	
Treatments	Dose (mg kg^{-1})	Mean±SEM	Change %	Mean±SEM	Change %	Mean±SEM	Change %
Normal		1.00±0.03		380.28±1.03		2.63±0.14	
CCl_4		2.80±0.08***a		217.16±6.42*** a		6.50±0.19***a	
Silymarin+CCl_4	10	1.93±0.16***b	31.25	107.16±4.39***b	50.65	3.71±0.24***b	42.82
SVE+CCl_4	250	2.45±0.02**b	12.58	195.16±5.39*b	10.13	5.76±0.17*b	11.28
SVE+CCl_4	500	2.21±0.06***b	21.25	177.66±5.18***b	18.18	4.56±0.15***b	29.74

Data are expressed as Mean±SEM (n = 6), *p<0.05, **p<0.01, ***p<0.001, statistically significant when compare CCl_4 intoxication to a normal control group. When compared CCl_4 group with SVE (250 and 500 mg kg^{-1}) and Silymarin (10 mg kg^{-1}), showed statistically significant via Dunnett's multiple comparison test

Table 3: Kidney electrolyte test of Silymarin and SVE in carbon tetrachloride intoxicated rats

		Sodium (mEq L^{-1})		Potassium (mEq L^{-1})		Calcium (mg dL^{-1})	
Treatments	Dose (mg kg^{-1})	Mean±SEM	Change %	Mean±SEM	Change %	Mean±SEM	Change %
Normal		114.14±1.36		4.25±0.19		5.28±0.24	
CCl_4		147.00±1.89***a		12.93±0.34***a		22.56±0.39***a	
Silymarin+CCl_4	10	123.40±0.80***b	16.09	6.96±0.20***b	46.13	7.09±0.26***b	68.55
SVE+CCl_4	250	147.10±1.53b	-	11.25±0.39*b	13.01	20.90±0.47*b	7.32
SVE+CCl_4	500	135.42±1.00***b	7.91	8.68±0.13***b	32.86	18.02±0.47***b	20.09

Data are expressed as Mean±SEM (n = 6), *p<0.05, **p<0.01, ***p<0.001, statistically significant when compare CCl_4 intoxication to a normal control group. When compared CCl_4 group with SVE (250 and 500 mg kg^{-1}) and Silymarin (10 mg kg^{-1}), showed statistically significant via Dunnett's multiple comparison test

(p<0.05-0.001) uphold with the Silymarin (Group III) and SVE (250 and 500 mg kg^{-1}) treatments (Group IV and V).

Estimation of heart homogenate: The effects of SVE and Silymarin on total protein, MDA and NP-SH were shown in (Fig. 1a-c), respectively. The levels of total proteins and NP-SH in CCl_4 only treated group (Group II), were found to be substantially attenuated with increased levels of MDA, when compared to the normal control group (group I). Whereas, rats pretreated with SVE at higher dose and Silymarin (10 mg kg^{-1}) showed the significant (p<0.001) improvement in the total protein (Fig. 1a) and NP-SH level (Fig. 1c). SVE treated groups at both doses (250 and 500 mg kg^{-1}) and Silymarin (10 mg kg^{-1}) treatments were also showed significant (p<0.05-0.001) improvement in the MDA level (Fig. 1b).

Estimation of kidney homogenate: The effects of SVE and Silymarin on total protein, MDA and NP-SH of kidney tissues were shown in (Fig. 2a-c), respectively. The levels of total protein and NP-SH were found to be significantly decreased with increased levels of MDA in CCl_4 only treated group (Group II) rats when compared to the normal group (group I) rats. Meanwhile, the pretreatment of CCl_4 intoxicated rats with SVE at higher dose (500 mg kg^{-1}) and Silymarin (10 mg kg^{-1}) showed the significant (p<0.05-0.001) improvement in the total protein (Fig. 2a) and NP-SH level (Fig. 2c). The levels of MDA in the groups pretreated with SVE at both the doses (250 and 500 mg kg^{-1}) and Silymarin (10 mg kg^{-1}) were found to be significantly (p<0.05-0.001) improved (Fig. 2b).

Histopathological studies: The histopathological appraisal of the heart and kidney tissues were given in Fig. 3 and 4, respectively. The photomicrograph of heart of normal rats (Fig. 3a) showed no histopathological changes. The CCl_4-intoxicated group confirms myocardial infraction on the basis of dilatation and congestion of myocardial blood vessels, (Fig. 3b) and myolysis of sporadic myocytes (Fig. 3c). Treatment with Silymarin (Fig. 3d), SVE, 250 mg kg^{-1} (Fig. 3e) and 500 mg kg^{-1} (Fig. 3f) respectively, showed the improvement or reversal of myocardial changes.

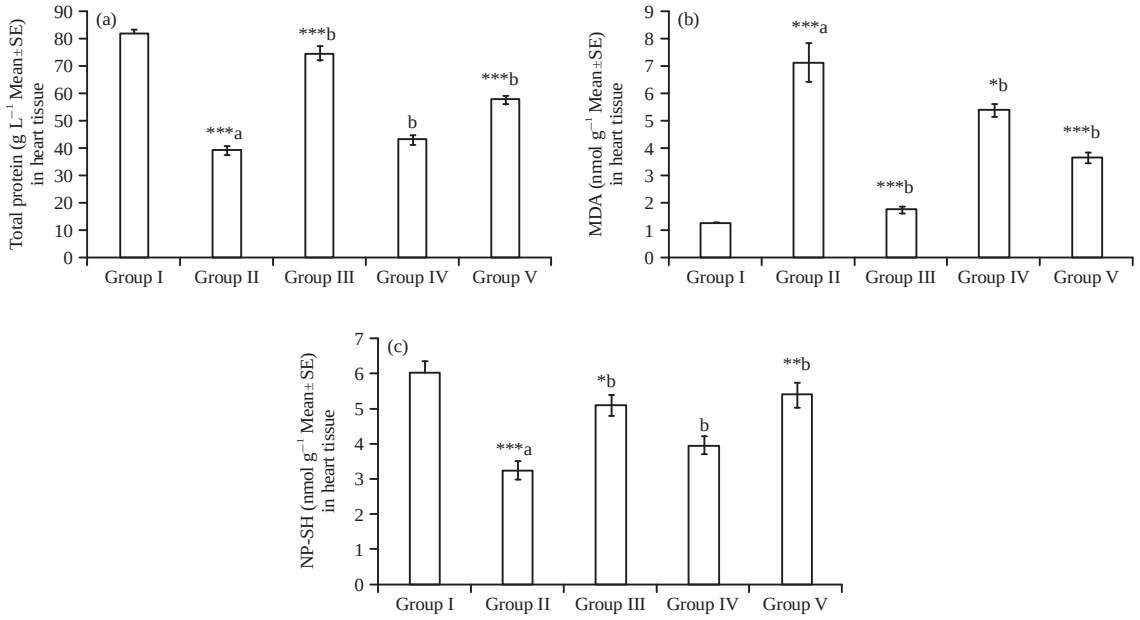

Fig. 1(a-c): Effect of SVE on cardiac (a) Total protein (b) MDA and (c) NP-SH in the CCl_4-intoxicated cardiac injury (n = 6), All values represent Mean±SEM. Where'a' as compared with control group and'b' as compared with CCl_4 group. * p<0.05, **p<0.01, ***p<0.001, ANOVA, followed by Dunnett's multiple comparison test

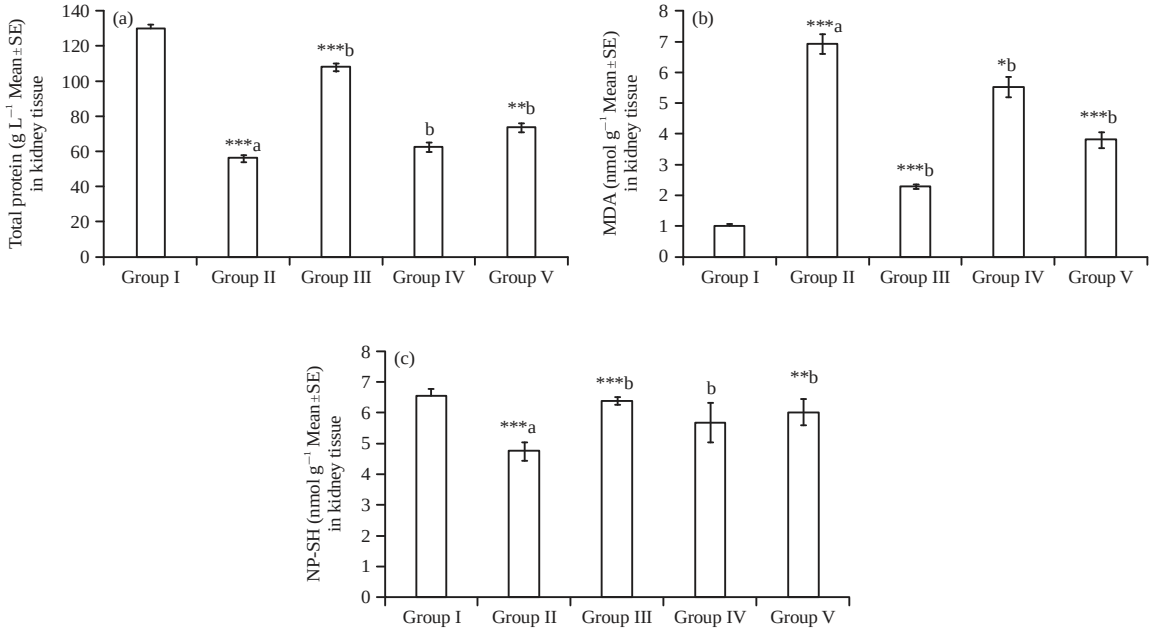

Fig. 2(a-c): Effect of SVE on kidney (a) Total protein (b) MDA and (c) NP-SH in the CCl_4-intoxicated nephrotoxicity (n = 6), All values represent Mean±SEM. Where'a' as compared with Control group and 'b' as compared with CCl_4 group. *p<0.05, **p<0.01, ***p<0.001, ANOVA, followed by Dunnett's multiple comparison test

Similarly, the photomicrograph of kidney tissue of normal rats was shown in Fig. 4a, confirms, there was no histopathological changes take place. The CCl_4-treated kidney tissue showed cytoplasmic vacuolization and congestion of glomerular tuft as well as in the renal tubular epithelium (Fig. 4b, c). Treatment with Silymarin (Fig. 4d), showed the improvement or reversal of kidney tissue changes. Treatment with SVE, 250 mg kg^{-1}, showing cytoplasmic

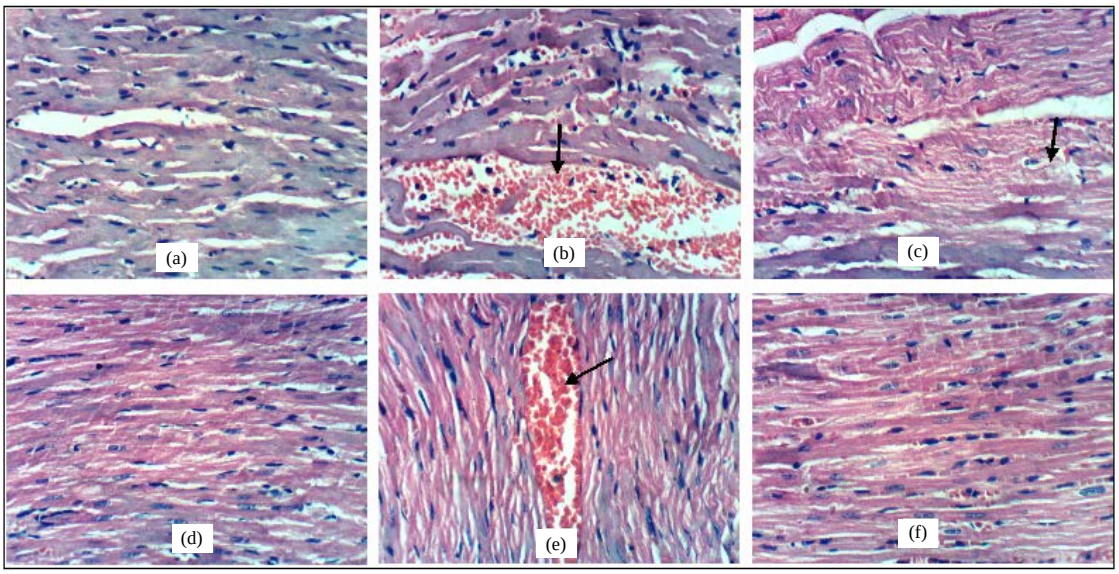

Fig. 3(a-f): Histopathological photomicrograph of cardiac tissues (H and E×400), Section of normal (Group-1) rat, showing no histopathological changes (a). A section of CCl_4 intoxicated group (Group-II) showing dilatation and congestion of myocardial blood vessels (b) and myolysis of sporadic myocytes (c). Section of Silymarin+CCl_4 (Group-III), showing no histopathological changes (d). Section of SVE (250 mg kg^{-1})+CCl4 (Group-IV) showing congestion of myocardial blood vessels (e) and SVE (500 mg kg^{-1})+CCl_4 (Group-V) showing no histopathological changes (f)

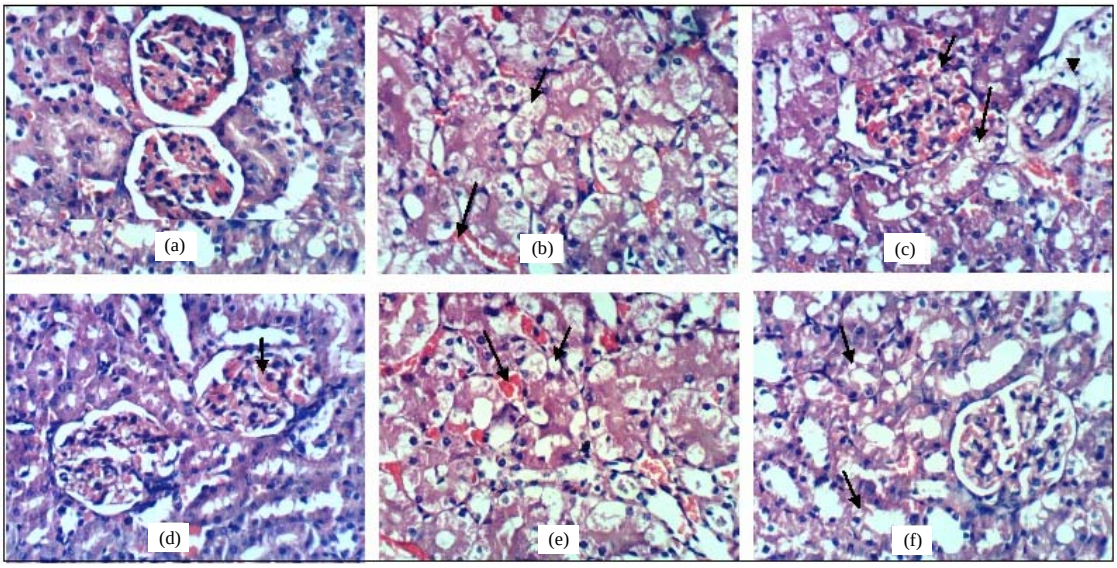

Fig. 4(a-f): Histopathological photomicrograph of Kidney tissues (H and E×400), Section of normal (Group-1) rat, showed the normal histological structure of renal parenchyma (a). A section of CCl_4 intoxicated group (Group-II), showing cytoplasmic vacuolization of epithelial lining renal tubules (Small arrow) and congestion of intertubular blood capillaries (b) and congestion of the glomerular tuft (small arrow) and cytoplasmic vacuolization of epithelial lining renal tubules (c). Section of Silymarin+CCl_4 (Group-III), showing congestion of glomerular tuft (d). Section of test drug SVE (250 mg kg^{-1})+CCl_4 (Group IV), showing cytoplasmic vacuolization of epithelial lining renal tubules (small arrow) and congestion of intertubular blood capillaries (e) and SVE (500 mg kg^{-1})+CCl_4 (Group V) showing cytoplasmic vacuolization of epithelial lining renal tubules (f)

vacuolization of epithelial lining renal tubules (small arrow) and congestion of intertubular blood capillaries (Fig. 4e) and SVE, 500 mg kg^{-1}, showed cytoplasmic vacuolization of epithelial lining renal tubules (Fig. 4f).

DISCUSSION

Serum LDH levels are amplified in patients exhibiting heart failure or a risk factor for death in patients with idiopathic pulmonary arterial hypertension (IPAH)[18]. Among the various cardiac markers, serum CK, myocardial creatine, LDH and albumin are used for early diagnosis of cardiac injury, tissue ischemia and myocardial infarction (MI)[19]. Due to cytochrome P_{450}, cardiac tissue has affinity towards CCl_4 intoxication and resulting in oxidative damage to lipids and proteins and the disturbed cardiac cell membrane integrity causing leakage of enzymes from tissue to plasma. This accounts for the decreased activities of these enzymes in cardiac tissue and increasing their concentration in the serum as an indicator of myocyte injury[20,21]. Albumin synthesis is extremely sensitive to CCl_4 intoxication because it inhibits the production of albumin due to marked desegregation of the endoplasmic membrane-bound polysome[22]. The significant reduction in the serum levels of LDH and CK and the increment in the serum albumin level in experimental groups treated with SVE confirm improvement of cardiac function in CCl_4-treated group. The findings of serum studies have an outstanding correlation with histological assessment of cardiac tissue.

Chronic kidney disease, the ninth foremost cause of death in the United States[23], is associated with an increased risk of cardiovascular disease and chronic renal failure. Among the various kidney disease markers, serum creatine, urea, uric acid and electrolytes, used for routine investigation for early diagnosis of CKDs[24,25]. Increased creatinine levels have been reported in serum of CKD patients. The present study also revealed that the administration of CCl_4 caused marked impairment in kidney disease markers, serum creatine, urea, uric acid and electrolytes, supported by earlier work[26]. Serum creatinine, urea and uric acid concentrations were significantly higher in CCl_4-treated rats and caused alteration of kidney function. The significant reduction in the levels of serum creatinine, urea and uric acid concentrations in experimental groups treated with various doses of SVE, confirm improved kidney function in CCl_4-treated group. Electrolytes are separated in the solution and have the capability to perform an electrical current. These electrolytes play a vital role in sustaining homeostasis[27]. Sodium is primarily responsible for maintaining osmotic pressure[28]. An increased plasma sodium caused renal water retention because of shift of water from intracellular to extracellular space. Regulation of the retained body sodium is maintained by the kidneys, with the excess excreted in the urine and by tubular reabsorption. An abnormal Na^+ levels in CKD patients, is accountable for a higher risk for progression to the risk of end-stage renal disease (ESRD), whereas both lower and higher sodium levels were associated with a higher risk of mortality. While caring for CKD patients, clinicians must give larger attention towards serum sodium levels, this might be helpful in progress and patient outcomes[21]. Serum potassium is the most convincing electrolyte marker of renal failure[25] and also one of the key elements in cardiac function. Hyperkalemia caused by poor kidney function and can results in abnormal and sometimes fatal cardiac arrhythmia[29]. Hypocalcemia is a contributory risk factor for the bone ailment, development of secondary hyperparathyroidism and/or increased risk of death. Hypercalcemia poses a risk for kidney patients and the finding of hypocalcemia and its suitable treatment is essential for management of patients with CKDs[30]. In the present experiment, serum electrolytes (Na, K and Ca) concentrations were significantly higher in CCl_4-treated rats and caused alteration of kidney function, supported by earlier study[31,32]. The significant reduction in the levels of serum electrolytes in the experimental groups treated with various doses of SVE, also confirm the improved kidney function in the CCl_4-treated group.

One of the study suggests, renal oxidative stress marker, malondialdehyde (MDA) may be a useful for the prediction of the development of ARF (Acute Renal Failure)[33] and about one-quarter of cases of CKD cause congestive heart failure[34]. The present finding also showed the decrease in total protein, NP-SH and increased in MDA level in the hearts and Kidney tissues in the CCl_4-treated rats, representing that the heart and kidney was the target organs affected by carbon tetrachloride toxicity and these findings are in agreement with previous findings[35-37]. The significant enhancement in the levels of total protein, NP-SH and control in the level of MDA in experimental groups treated with various doses of SVE, confirm protection in the CKDs and cardiac function. These tissue studies have an outstanding correlation with histological assessment of cardiac tissue of rats but not a satisfactory result in the kidney tissue histological assessment.

CONCLUSION

The preclinical study showed that SVE at both dose levels (250 and 500 mg kg^{-1}) could improve the cardiac and renal dysfunction possibly due to the protective nature on both

heart and kidney function biomarkers and improving the antioxidant status. Histological texture of the heart was further confirmed the protective nature of SVE in the cardiac disease but like kidney biomarker, histological study did not show total reversal of histological texture. So, furthermore animal studies are required to evaluate the detailed mechanism underlying the protective effect of the SVE.

SIGNIFICANCE STATEMENTS

The present preclinical study discovers the noval cardio and hepatoprotective agent as SVE that can be beneficial for the cardiac and renal dysfunction against the CCl_4 induced toxicity model. The present study may help the researchers to discover the important area of the cardiac and renal toxicities that many researchers were not able to explore. Thus, a new theory on treating cardiac and kidney disorders, SVE with available marketed standard drugs may be effective in treating other cardiac and kidney related problems.

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