

The Reno and Hepatoprotective Effects of SAMWA Plant (*Cleome droserifolia*) Methanolic Extract against Adrenaline-Induced Adverse Effect to Male Rats

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Abstract

Adrenaline is widely used drug to combat several conditions such as allergy and anaphylaxis. The current work was to investigate the renal and hepatic complications following adrenaline injection, in addition, the impact of *Cleome* (SAMWA) methanolic extract on adrenaline-induced renal and hepatic alterations. Twenty-four male Wister rats were divided equally into four groups; Normal control group received oral distilled water for 30 consecutive days and administered subcutaneous saline on the 31st and 32nd days. The *Cleome* extract (200 mg/kg) group received *Cleome* methanolic extract (200 mg/kg, P.O) for 30 consecutive days and administered subcutaneous saline on the 31st and 32nd days. The adrenaline group received distilled water orally for 30 consecutive days and administered subcutaneous adrenaline (2 mg/kg, s.c.) divided into two doses (1 mg/kg, s.c) each on the 31st and 32nd days. *Cleome* extract (200 mg/kg)/ adrenaline received *Cleome* methanolic extract (200 mg/kg, P. O) for 30 consecutive days and administered subcutaneous adrenaline (2 mg/kg, s.c.) divided into two doses (1 mg/kg, s.c) each on the 31st and 32nd days. Liver and kidney function biomarkers in addition to histopathological analyses were evaluated. Adrenaline caused alteration in liver and kidney function biomarkers without affecting the histological structure of the liver and the kidney. SAMWA methanolic extract pretreatment significantly decreased serum urea, uric acid, aspartate aminotransferase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP). SAMWA ameliorated serum albumin reduction and total protein induced by adrenaline injection. SAMWA methanolic extract could protect liver and kidney of rats exposed to adrenaline.

KEYWORDS

Adrenaline, Hepatic function, Histopathology, Renal function, SAMWA.

INTRODUCTION

Kidney and the liver are vital organs of human body performing the detoxification needs and protection for healthy life (Legallais *et al.*, 2018). Adrenaline is best known to pharmacologists as a substance that has profound effects on the cardiovascular system, narrows the blood vessels and opens airways in the lungs (Fischer *et al.*, 2003). An injection of adrenaline is used to treat severe allergic reactions to insect stings or bites, foods, drugs, and other allergens (Kemp *et al.*, 2008). Adrenaline is excreted as metabolites in urine (Moleman *et al.*, 1992). The plasma half-life of the adrenaline injection is about 2-3 minutes. However, when given by subcutaneous or intramuscular injection, local vasoconstriction may delay its half life time (Gu *et al.*, 1999). It causes constriction in many networks of minute blood vessels and dilates the blood vessels in the skeletal muscles and the liver (Kim *et al.*, 2010). In the liver, adrenaline stimulates the breakdown of glycogen to glucose, resulting in an increase in glucose levels in the blood. It also acts to increase the level of circulating free fatty acids. The extra amounts of glucose and fatty acids can be used by the body as fuel in times of stress or danger, when increased alertness and exertion are required (Kolnes *et al.*, 2015). Abdel

Salam *et al.* (2021) found that adrenaline protecting the liver with decreasing the oxidative stress and liver histological damage following lipopolysaccharide administration in rats. Ntchapda *et al.* (2022) stated that the histological examination of kidney when adrenaline applied in the form of a subcutaneous retard tablet under short ether anesthesia of rats showed hyalinization of the glomeruli and decreased the kidney function parameters.

Renewed attention to alternative medicines and natural therapies has stimulated a new wave of research interest in traditional practices (Nadro and Onoagbe, 2014). Traditional plants might provide a useful source of antioxidants that prevent tissues damage (Rahimi-Madiseh *et al.*, 2016). *Cleome droserifolia* (SAMWA) is used as a traditional medicine in Sinai by Bedouins for treatment of many disease (Moustafa and Mahmoud, 2023). SAMWA leaves and stems extracts are rich in bioactive compounds as flavonoids, glycosides, alkaloids, tannins and steroids (Surendra, 2009). Evidence suggests that certain phytochemicals found in SAMWA plant, played an essential role in treating or retarding a wide spectrum of diseases and reported to possess anti-oxidative, anti-atherosclerotic, anti-inflammatory, antitumor, anti-thrombogenic, antiosteoporosis and antiviral properties (Naga and Ahmed, 2015).

The aim of the present study was to investigate the possible reno and hepatoprotective effects of SAMWA methanolic extract against adrenaline-induced renal and hepatic biochemical and histopathological alterations.

MATERIALS AND METHODS

Plant material

Cleome droserifolia (Family: *Cleomaceae*) aerial parts were gathered from a local herbarium shop. The methanolic extract of the plant was prepared according to Lapornik *et al.* (2005).

Animals

Twenty-four male albino Wistar rats (140–160 g), were got from the National Research Centre's animal house colony (Giza, Egypt). Animals were kept in standardized laboratory settings (25±1°C and 55% humidity) with natural light/dark cycle and fed standard rat pellets with unlimited access to tap water.

Experimental design

Rats were assigned randomly into 4 groups (6 rats/group). Normal control group received oral distilled water for 30 consecutive days and administered subcutaneous saline on the 31st and 32nd days. The *Cleome* extract (200 mg/kg) group received *Cleome* methanolic extract (200 mg/kg, P.O) for 30 consecutive days and administered subcutaneous saline on the 31st and 32nd days. The selection of the *Cleome* extract dose was according to El Naggar *et al.* (2005). The adrenaline group received distilled water orally for 30 consecutive days and administered subcutaneous adrenaline (2 mg/kg, s.c.) that was divided into two doses (1 mg/kg, s.c) each on the 31st and 32nd days according to El-Marasy *et al.* (2020). Adrenaline was obtained from Sigma-Aldrich (St. Louis, MO, USA). The *Cleome* extract (200 mg/kg)/adrenaline group received *Cleome* methanolic extract (200 mg/kg, P.O) for 30 consecutive days and administered subcutaneous adrenaline (2 mg/kg, s.c.) that was divided into two doses (1 mg/kg, s.c) each on the 31st and 32nd days.

Evaluation of body and organs weight

The body weight of experimental rats was assessed using a sensitive balance once before start of dosing and once on the sacrifice day. Calculation of the relative organs (liver and kidney) weights were performed using the subsequent formula [organ weight (g)/body weight (g)×100] according to Buttrick *et al.* (1991).

Blood collection

At the end of experimental duration, blood samples were harvested from the retro-orbital sinus by means of a clean heparinized capillary tube. Blood was placed in plain tubes and centrifuged, after clotting, at 4000 rpm for 15 minutes. Sera samples were stored at -70°C for liver and kidney function biomarkers.

Some kidney function biomarkers

Creatinine (mg/dl) was determined using Wang *et al.* (2022) method. The concentration was measured spectrophotometrically at 492 nm. Urea (mg/dl) was determined using Ceriotti and Spandrio (1963) method. The concentration was measured spec-

trophotometrically at 578 nm. Uric acid (mg/dl) was determined using Liddle *et al.* (1959) method. The concentration was measured spectrophotometrically at 550 nm.

Some liver function biomarkers

AST (U/L) and ALT (U/L) were determined using Huang *et al.* (2006) method. The concentration was measured spectrophotometrically at 340 nm. ALP (U/L) was determined using Ni *et al.* (2019) method. The concentration was measured spectrophotometrically at 405 nm. Serum albumin (g/dl) was determined using Jiang *et al.* (2003) method. The concentration was measured spectrophotometrically at 580 nm. Serum total protein (g/dl) was determined using Zahra (2019) method. The concentration was measured spectrophotometrically at 546 nm.

Histopathological examination

Immediately, after the animals were sacrificed, kidney and liver of each animal was quickly excised, washed with normal saline for the removal of the blood, which might obstruct the process of fixation, then blotted with filter paper, weighted, and rinsed in ice-cold saline and fixed in 10% formaldehyde overnight and they were processed using standard Hematoxylin and Eosin staining histological methods (Fischer *et al.*, 2008). The stained slides were examined and photographed by microscope with camera (Eclipse Ci-L, Nikon, USA).

Statistical analysis

All the values are presented as means ± standard error of the means (SE). Comparisons between different groups were carried out using one-way analysis of variance (ANOVA) followed by Tukey's HSD test for multiple comparisons. The difference was considered significant when $P < 0.05$.

RESULTS

Effects of pretreatment with SAMWA methanolic extract on organs weight to body weight ratio

Kidneys and liver weight /body weight ratio in control and different treated groups were demonstrated in Table 1. Normal relative weights of the kidneys and liver appeared in control rats and rats received methanolic extract of SAMWA. On the other hand, the relative weight of the kidneys and liver of the adrenaline group significantly increased at $P \leq 0.05$ in kidneys and liver by 16.028 and 23.122%, respectively compared to control group.

Methanolic extract of SAMWA plant significantly $P \leq 0.05$ decreased kidneys and liver weight/body weight ratios by -12.836 and -14.394%, respectively compared to adrenaline control group.

Table 1. Effects of pretreatment with SAMWA on liver and kidney weights to body weights ratio in adrenaline administered rats.

Treatment	Kidney (g%)	Liver (g%)
Normal control	0.705±0.0059 ^b	3.408±0.0055 ^b
SAMWA control	0.703±0.0028 ^b	3.373±0.0082 ^b
Adrenaline control	0.818±0.007 ^a	4.196±0.0274 ^a
SAMWA+ Adrenaline	0.713±0.0091 ^b	3.592±0.0055 ^c

Data are presented as mean±SEM. Statistical analysis are carried by one way ANOVA followed by Tukey's multiple comparison test. Means followed by different letters in the same column are significantly different according to one-way ANOVA test followed by Post Hoc Tukey's test.

Effects of pretreatment with SAMWA methanolic extract on kidney function biomarker

The mean values of creatinine, urea, and uric acid of adrenaline group significantly $P \leq 0.05$ increased by 28.205%, 82.666 and 87.5%, respectively as compared to control group. On the other hand, pretreatment with SAMWA methanolic extract showed non-significant decreases in creatinine, urea and uric acid level by -6.0%, -30.170 and -21.568%, respectively comparing to adrenaline group (Table 2).

Table 2. Effects of pretreatment with SAMWA on serum urea, uric acid and creatinine in adrenaline administered rats.

Treatment	Creatinine (mg/dl)	Urea (mg/dl)	Uric acid (mg/dl)
Normal control	0.78±0.02 ^b	45.00±0.97 ^b	2.72±0.09 ^b
SAMWA control	0.75±0.05 ^b	45.75±1.11 ^b	2.58±0.10 ^b
Adrenaline control	1.00±0.02 ^a	82.20±3.02 ^a	5.10±0.28 ^a
SAMWA+ Adrenaline	0.94±0.02 ^a	57.40±3.01 ^c	4.00±0.18 ^c

Data are presented as mean±SEM. Statistical analysis are carried by one way ANOVA followed by Tukey's multiple comparison test. Means followed by different letters in the same column are significantly different according to one-way ANOVA test followed by Post Hoc Tukey's test.

Effects of pretreatment with SAMWA methanolic extract on liver function.

As demonstrated in Table 3, adrenaline injection exhibited significant $P \leq 0.05$ increases in ALT, AST and ALP activities by +67.213%, +185.714% and +73.645%, respectively compared to normal rats. On the other hand, pretreatment with SAMWA methanolic extract significantly decreased $P \leq 0.05$ ALT, AST and ALP activities by -27.941%, -43.333 and -16.737%, respectively compared to adrenaline group.

The adrenaline group showed non-significant $P \geq 0.05$ decrease in albumin and total protein levels by -16.666 and -15.584%, respectively compared to control rats. Moreover, pretreatment of SAMWA methanolic extract non-significantly $P \geq 0.05$ increased albumin and total protein levels by 18.518 and 16.153%, respectively compared to adrenaline administered rats.

Effects of pretreatment with SAMWA methanolic extract on histopathological study.

Kidney

Section of renal tissue of rat (Fig. 1) from control group, SAMWA methanolic extract group, adrenaline group and SAMWA+ Adrenaline group showed normal structure being formed of glomeruli embedded in between different types of tubules (proximal convoluted tubules and distal tubules). The proximal convoluted tubules are lined with cuboidal epithelium with rounded nuclei.

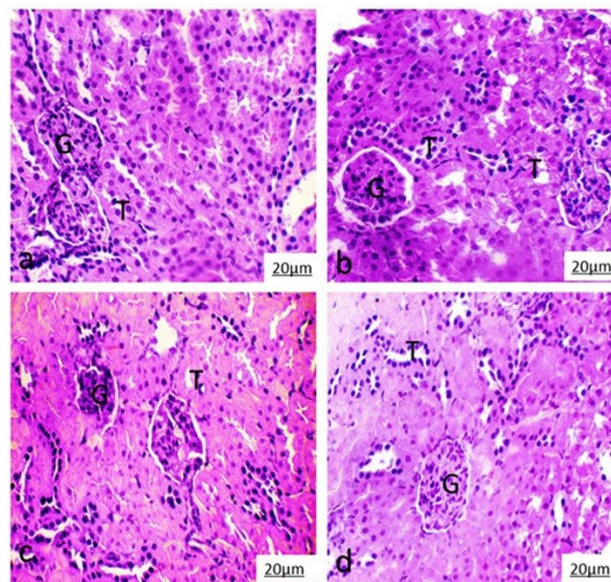


Fig. 1. Photomicrograph of a section of renal tissue of rat (a) from control group, (b) SAMWA methanolic extract group, (c) adrenaline group and (d) SAMWA+ Adrenaline group showed normal structure being formed of glomeruli (G) embedded in between different types of tubules (T). (H&E, 400 X).

Liver

Section of liver tissue (central vein and portal area) of rat (Figs. 2 and 3) from control group, SAMWA methanolic extract group, adrenaline group and SAMWA+ Adrenaline group showed normal organization structure without injury. The liver showed hexagonal lobules are centered on the central vein and have a portal triad area containing branches of the portal vein, hepatic artery, and bile duct.

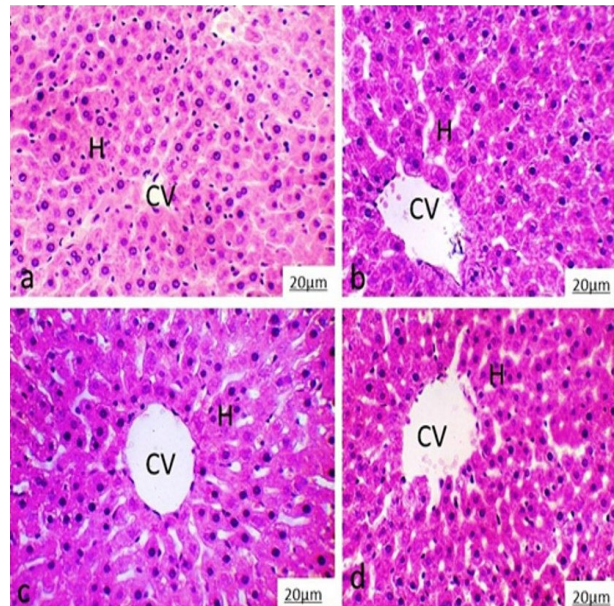


Fig. 2. Photomicrograph of a section of central vein (CV) of liver tissue from (a) control group, (b) SAMWA methanolic extract group, (c) adrenaline group and (d) SAMWA+ Adrenaline group showed normal organization structure without injury. The liver showed normal hepatocytes (H) surrounded the central vein (CV) (H&E, 400 X).

Table 3. Effects of pretreatment with SAMWA on liver function parameters in adrenaline administered rats.

Treatment	ALT (U/L)	AST (U/L)	ALP (U/L)	Albumin (g/dl)	Total protein (g/dl)
Normal control	48.80±1.16 ^b	50.40±1.69 ^b	81.20±3.25 ^b	3.24±0.14 ^a	6.16±0.22 ^{ab}
SAMWA control	47.75±3.82 ^b	49.25±3.07 ^b	81.50±1.66 ^b	3.25±0.08 ^a	6.60±0.11 ^a
Adrenaline control	81.60±4.41 ^a	144.00±7.83 ^a	141.00±4.37 ^a	2.70±0.20 ^a	5.20±0.26 ^b
SAMWA+ Adrenaline	58.80±2.78 ^b	81.60±5.61 ^c	117.40±5.11 ^c	3.20±0.04 ^a	6.04±0.20 ^{ab}

Data are presented as mean±SEM. Statistical analysis are carried by one way ANOVA followed by Tukey's multiple comparison test. Means followed by different letters in the same column are significantly different according to one-way ANOVA test followed by Post Hoc Tukey's test.

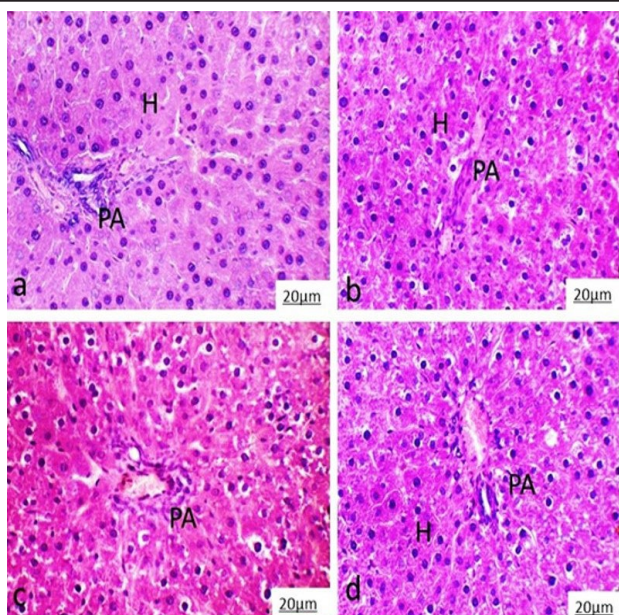


Fig. 3. Photomicrograph of a section of portal area (PA) of liver tissue from (a) control group, (b) SAMWA methanolic extract group, (c) adrenaline group and (d) SAMWA+ Adrenaline group showed normal organization structure without injury. The liver showed normal portal triad area (PA) containing branches of the portal vein, hepatic artery, and bile duct. (H&E, 400 X).

DISCUSSION

Adrenaline injections are used to treat severe allergic reactions to insect stings or bites, foods, medications, and other allergens. The impact of short term of adrenaline injection on the liver and kidney are needed to be investigated (Kowalski *et al.*, 2016). SAMWA extract was one of the traditional plants that showed their hepatorenal protective effects in different research (Abdel Maksoud *et al.*, 2020). In the present study, the possible reno and hepatoprotective effects of SAMWA against adrenaline-induced renal and hepatic complications in albino rats were investigated by using organs/body weight ratio, some kidney and liver function biomarker in addition to the histopathological studies of the liver and the kidney. Injection of adrenaline in the current study generated significant elevation in the liver and kidney weight to body weight ratio which may be associated with adrenaline-induced stress. This outcome is in harmony with prior study of Klein (1999) that found adrenaline injection increased relative organs weight.

Our results showed that the kidney's function biomarker altered as evidenced by the elevation in the serum levels of creatinine, urea and uric acid in adrenaline-treated rats without alteration the histological structure of the kidney. This result is in agreement with Heringlake *et al.* (2007) that showed the adrenaline induced renal complication. Moreover, adrenaline administration induced significant alteration in liver enzymes which are the primary criteria typically used for the diagnosis of hepatic injury. The characteristic findings were a significant increase in serum ALT, AST and ALP. In addition to significant decreased serum albumin and total protein. The absence of histopathological alteration of liver and kidney induced by the adrenaline may be due to the short duration to follow up the histological sample according to Virdi *et al.* (2003).

People in developing countries rely almost entirely on traditional medicine for primary health care. Because medicinal plants are the foundation of traditional medicine, more than 3300 million people use them on a regular basis (Vedavathy, 2003). The growing recognition of natural products being nontoxic and free of side effects is driving up demand for medicinal plants (Arunachalam *et al.*, 2009). However, only a small percentage of hepatoprotective and nephroprotective plants, as well as formulations used in traditional medicine, have been pharmacologically evaluated for use in scientific studies. The protective effect of *Cleome droserifolia* methanolic extracts against adrenaline in-

duced renal and hepatic complications was investigated. Treating experimental animals with SAMWA methanolic extract before induction of adrenaline attenuated the alteration in the liver and kidney body weight ratio. The significant amelioration in relative organs weight may be due to the antioxidant effect of flavonoid and phenolic contents of *Cleome droserifolia* methanolic extract (Hashem and Shehata, 2021). Pretreatment with SAMWA methanolic extract significantly mitigated the perturbed kidney and liver function by decreasing serum creatinine, urea and uric acid. The modulation of the liver function biomarker may be resulted from the stabilizing potential of *Cleome droserifolia* to the liver cell membrane (Lai *et al.*, 2015).

CONCLUSION

Acute adrenaline administration in experimental rats showed only alteration to some renal and hepatic function biomarker without affecting the histopathological change of the liver and the kidney. On the other hand, *Cleome* methanolic extract modulates those alterations. *Cleome* methanolic extract should be recommended for production on a commercial scale in the Egyptian meal, factories, and medicines. Such extract has the capability to reduce the hazards on kidney and liver functions.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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