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Therapeutic Efficacy of *Cissus rotundifolia* as Antiurolithiasis and Antihypertensive Agent in Albino Rats

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Abstract:
The present work was undertaken to evaluate the efficacy of the methanolic leaves extract of *Cissus rotundifolia*, as an anti-urolithic and antihypertensive agent in albino rats by measuring the biochemical parameters, enzyme immunoassay, and free radical scavenging activity using DPPH assay. Twenty four male albino rats were divided into 4 groups (n = 6) as G1 (negative control) received a normal diet, G2 (positive control) received EG (0.75%) and 1% aluminum chloride; G3 was given 200 mg/kg of CR extract daily via a gastric tube for 28 days, G4 was orally given 400 mg/kg of CR extract for 28 days. All the tested samples showed a significant antioxidant DPPH radical scavenging activity in doses of 200 and 400 mg/kg, b.w. A notifiable decrease in serum urea and creatinine levels were also, observed. The present study emphasizes the safe herbal remedies of *C. rotundifolia* as anti-hypertensive and antioxidants as well as anti-urolithiatic.
Keywords: *Cissus rotundifolia*; antiurolithiatic; antihypertensive; antioxidant.

INTRODUCTION

Urolithiasis (UL) or Kidney stones (renal calculi) is one of the oldest known and widespread diseases that greatly affects a massive number of patients worldwide (López and Hoppe 2010; Rajat *et al.,* 2011). UL means the accretion of a solid, hard mass of nonmetallic minerals inside the urinary tract. Stone formation is the culmination of a series of physicochemical events like super-saturation, nucleation, growth, and aggregation of the crystal (Yashir and Waqar, 2011). It is considered as a global problem across a wide geographical scale, in developing and under developed countries (Moe, 2006; Agarwal *et al.,* 2014). The stone disease varies with age, gender, ethnicity, and season. Fifty to seventy-five percent of patients will have recurrent stone disease within 20 years of urolithiasis (Pearle *et al.,* 2005), consequently, it can be considered as a disease for life (Srinivasa *et al.,* 2013). The stones may cause various symptoms, including pain and urinary tract infection (UTI) that represent the second most common symptom. About 150 million people were diagnosed with UTI each year (Akram et *al.,* 2007). Obstruction of urinary tract and hemorrhage are other common symptoms. The study of Shashi et al. (2013) revealed that calcium oxalate stones represent up to 80%, calcium phosphate account for 15-25%, while 10- 15% are mixed stones. Struvite, cysteine, and uric acid stones are existing in low percent.

Hypertension is a risk factor for developing cardiovascular diseases such as coronary heart disease, and heart failure (Kokubo and Matsumoto, 2017; Iqbal *et al.,* 2016, 2018). Being the largest cause of death worldwide, cardiovascular diseases are responsible for 17.3 million deaths per year globally (Knowlin *et al.,* 2017). Epidemiologic data indicate that approximately 40% of the human population aged above 25 years is affected by hypertension (Garfinkle, 2017). In the last few decades, childhood hypertension is constantly increased and has become a major health problem in children (Karatzi *et al.,* 2017). Almost 90–95% of all the hypertensive patients are of unknown causes (Kearney *et al.,* 2004). In addition to the antihypertensive drugs, changes the lifestyle, weight loss, reducing sodium, and increasing potassium intake, limiting alcohol consumption, avoiding smoking, and regular physical activities are advised for preventing and management of blood pressure **(**Wu *et al.,* 2016; McDonough *et al.,* 2017). The Renin-angiotensin-aldosterone system (RAAS) is a well-known mechanism that controls blood pressure by regulating body fluid volume. Angiotensin-converting enzyme (ACE) is a crucial factor in RAAS pathway. Although, ACE inhibitor drugs are much successful in reducing the blood pressure, yet food-derived antihypertensive peptides are safe and free from any side effects (Wu *et al.,* 2017).

Despite drugs are used to prevent and treat diseases; almost all synthetic drugs cause adverse reactions; that motivated humans to return to phytotherapy (Chitme *et al.,* 2010). About 80% of the population living in developing countries relies almost on traditional medicine (Saad and Said, 2011). Medicinal plants have a vast potential in the treatment of various disorders due to the presence of therapeutically important phytochemicals (Ashraf *et al.,* 2020; Hussain *et al.,* 2016; Iqbal and Ashraf, 2018; Iqbal and Ashraf, 2019a,b; Iqbal *et al.,* 2019; Kalim *et al.,* 2016; Shahzad *et al.,* 2017). Proteomics studies have also revealed the importance of herbal plants in curing diseases (Zaynab *et al.,* 2018). Yemen is very rich in medicinal plants and still among the traditional communities that use plants for a wide variety of purposes (Coskun *et al*., 2005). Halas; *Cissus rotundifolia* (CR) (family Vitaceae) is one of the medicinal plants found in Yemen. It is a climbing prostrate shrub found throughout Africa, Egypt, and the Arabian Peninsula (Al Zandi *et al.,* 2019). The leaves of CR contain an appreciable amount of nutritional components like proteins, fats, minerals, and unsaturated fatty acids; while the non-nutritional elements are present at very low concentrations (Ali *et*

al., 2004; Korish, 2016). So, CR leaves can be considered as a potential source of nutritional components (Korish, 2016). Halas is used traditionally in Yemen for the treatment of gastrointestinal troubles (Geissler *et al*., 2002), in loss of appetite and fever, antimalarial, antioxidant and antimicrobial (Al-Fatimi *et al.,* 2007; Alshawsh *et al.*, 2009, Said *et al*., 2015; Wael *et al.,* 2019). Whereby, Raslan (2015) found that the alcoholic extract of Halas has antiulcer, anti-inflammatory, hepato-protective, and analgesic activity. While, water extract of Halas leaves has antidiabetic activity (Al-Mehdar and Al-Battah, 2016; Wael *et al.,* 2019). As safety and efficacy data are not available for most medicinal plants, the objective of this study was to assess and evaluate the efficacy and safety of CR as anti-urolithic and antihypertensive agent in albino rats by measuring the biochemical parameters, enzyme immunoassay, and free radical scavenging activity using DPPH assay.

MATERIALS AND METHODS

Twenty-four male albino rats *Rattus rattus* (*Rattus norvegicus albinus)* weighing about 200 - 250g/each was used in this study. The rats were reared in the animal house of Sana'a University, Biology Department. The rats were housed in a standard metallic cage under the same environmental conditions with an alternate 12 h light-dark cycle at room temperature (20±2°C). The animals had *ad libitum* access to a commercial diet and water. The bedding of the animal cages was changed every 48hrs. Animals were left seven days before the experiment for adaptation. Then rats were randomly divided into 4 groups (6 animals/each):

Group I: was fed with a normal diet and left as a negative control (Co)**.**

Group II: administered EG (0.75%) and 1% aluminum chloride and serves as a positive control (Po).

Group III: were given 200 mg/kg of CR extract daily via a gastric tube for 28 days.

Group IV: were orally given 400 mg/kg of CR extract for 28 days

Preparation of extract*:*

Leaves of Halas; CR were collected from Taiz governorate in Yemen and were identified and authenticated at Botany Department, Faculty of Science, Sana`a, University. The plant was carefully washed with tap water, rinsed with distilled water, chopped into small pieces, and shade dried at room temperature, and then they were grinding into a fine powder. The extraction of a bioactive material from the powder was carried out with 70% methanol using the Soxhlet apparatus. The extract was concentrated by a rotary evaporator and subjected to freeze-drying in a freezer (Jimoh *et al*., 2013).

Chemicals and dosages

Stone induction

In this study, hyperoxaluria was induced by administration of ethylene glycol (EG)v/v (0.75% in drinking water) for 21 days and1% ammonium chloride (AC) v/w AC (1%) was given only for the first 7 days, as the administration of for more than 7 days led to the death of the rats (Fan *et al.*, 1999; Khan *et al.,* 2011). Alcoholic extract of CR was completely dissolved in distilled water at a dose of 200 and 400 mg/kg body weight (b.w.)/rat.

Blood collection

Blood samples were collected from the orbital vein of all specimens after the first and last day of the experimental period. The serum was separated by centrifugation at 3,000×*g* for 15 mins.

Biochemical analysis

The serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), lactate dehydrogenase

(LDH), creatinine and urea were measured by kinetic UV assay colorimetric methods using kits supplied by Roche diagnosis attached with Roche/Hitachi analyzer machine according to the method obtained by Chen et al. (2010) and Rock et al. (1987).

Enzyme immunoassay:

Serum aldosterone was estimated by microplate enzyme immunoassay, a colorimetric technique using the Aldosterone Test System Product that was reported by Carlos et al. (2000).

Angiotensin-converting enzyme (ACE) was estimated by commercially kits using a different factor calculation by the method of Harjanne (1984).

Free radical scavenging activity using DPPH assay.

The antioxidant activity of the methanolic extract was assessed by measuring their ability to scavenge DPPH (2,2-diphenyl-1-picrylhydrazyl) free radicals compared to ascorbic acid as a standard. Radical scavenging activity of plant extract against (DPPH) was determined at wavelength 517 nm on a UV visible light spectrophotometer. 3 ml of freshly prepared methanolic DPPH solution (6×10-5 M) was mixed with 100 µgm/ml concentration of the plant extract. The samples were kept in the dark for 15 mins at room temperature then the UV absorbance was measured. The measurements were repeated in triplicate (Pal *et al*., 2011).

Radical scavenging activity was calculated by the formula

$$\% \text{ Inhibition} = [(A\ B - A\ A)/A\ B] \times 100$$

Where A B = absorption of blank sample (t= 0 min)

A A = absorption of test extract solution (t=15 mins)

Statistical analysis

The results are expressed as mean± S.E. The statistical analysis was carried out using (ANOVA). Statistical P-value <0.05 was considered to be significant.

RESULTS

Free radical scavenging activity (DPPH assay) of CR extract

The free radical scavenging activity of CR extract in contrast with ascorbic acid (As A) as standard antioxidant is represented in table1 and showed a statistically significant at p<0.05.

Table 1. Free radical scavenging activity of the CR.

Parameters	DPPH (%)
Ascorbic acid	93.89 ±4.842
C. rotundifolia	80.58±1.840

Values are expressed in mean ± SE of 3 times repeated for each set of CS extract.

Effect of CR alcoholic extract on serum aldosterone level:

Table 2 indicated that aldosterone level significantly increased in urolithiatic group II when compared with negative control group I.; whereas serum aldosterone concentration significantly decreased in CR treated groups (III, IV). Moreover, the decrease was significant between CR treated group IV and non-significant in CR treated group III when compared to normal control group.

Table 2. Effect of methanolic extract of CR on serum aldosterone level concentration pg/ mg

Groups	Parameters
	Serum aldosterone level
I negative control	98.25±19.15
II positive control	534.25± 10.74a****
III (200mg/kg)	66.54± 4.84b***
IV (400mg/kg)	38.10± 2.68a**b****

Effect of CR extract on serum ACE level

As shown in table 3, there was a significant increase in the ACE concentration in group IV when compared with other treated groups. Meanwhile, this increase in II group was not statistically significant.

Table 3. Effect of alcoholic extract of CR on serum ACE concentration.

Groups	Parameters
	Serum ACE level U/ L
I	96.70 ± 3.64
II	102±5.09
IV	116± 1.92 a** b*

Significant difference group as compared to negativecontrol (I). , b- Significant difference group as compared to positive control (II).

Effect of CR extract on the serum level of creatinine and urea

As seen in table 4 both urea and creatinine levels in serum were significantly decreased in treated specimens of group (III) and (IV), whereas the parameters were significantly increased in group (II).

Table 4. Effect of methanolic extract of CR on serum urea and creatinine levels in experimental groups.

Group	Parameters	
	Urea	Creatinine
I	10.20±0.68	28.28±1.31
II	12.14±0.41	39.22±2.12 a**
III	9.02±0.30 b***	29.78±1.63 b**
IV	7.94±0.30 a* b****	26.70±2.02 b***

a- Significant difference as compared to negative control (group I). b- Significant difference as compared to positive control (group II)

Effect of CR extract on AST, ALT and LDH levels

The data in table 5 showed that liver enzymes (AST, LDH and ALT) are significantly decreased in urolithiatic group (group II). On the contrary these values noticeably increased in CR extract treated groups (group III and IV) except for LDH which slightly decreased (group IV)

Table 5. Effect of methanolic extract of CR on AST, ALT and LDH serum level

Groups	Parameters		
	AST	ALT	LDH
(I)	182.2±8.55	52.24±3.04	1957±148.0
(II)	125.9±10.91 a**	39.6±1.14 a*	1422±110.9 a*
(III)	175±8.56b**	58.34±4.53b**	1862±121.9
(IV)	200±4.65b****	67.4±3.53a*b***	2317±95.6b***

DISCUSSION

The increased renal reactive oxygen species (ROS) impaired antioxidant enzyme activities of the kidney that may inhibit stone formation caused by hyperoxaluria (Huang *et al.,* 2002). In the present study, administration of CR leaves extracts significantly prevented crystal formation in urine may be due to its diuretic effect that increases diuresis (Mikawlrawng *et al.,* 2014). The increase in urine volume decreases the saturation of the salts and prevents the precipitation of the crystals (Michell, 1989). Furthermore, it enhances the entry of extracellular calcium into cells as concluded by Garcia et al. (1997a).

In the present study, DPPH radical scavenging activity showed that CR leaves extract significantly exhibited strong antioxidant activity. This result is in agreement with the findings of Al-Fatimi et al. (2007); Raslan (2015) and Shalabi (2017). The antioxidant activity of CR leaves may be due to its antioxidant constituents as flavonoids (Al-Mamary, 2002). Nevertheless, flavonoids act potentially as antioxidants, scavenging free radicals, RO (Kumawat *et al.,* 2012). Antioxidants play an important role in health-promoting biochemical pathways, so increasing the intake of antioxidant-rich foods can prevent diseases and lower health problems (Duvoix *et al*., 2005).

Renin-angiotensin-aldosterone system (RAAS) is a well-known mechanism that controls urine output and regulating the volume of fluid in the body hence the blood pressure. In the present study, the increase in aldosterone level in urolithiatic group II as well as its decrease in CR treated groups (group III& IV) may explain the diuretic effect of CR extract. Angiotensin-converting enzyme (ACE) is a crucial factor in RAAS that converts angiotensin I to the active vasoconstrictor angiotensin II (Bader, 2010). Due to the important roles of ACE in the regulation of blood pressure, the regulation of this enzyme has been used to treat hypertension (Coppey *et al*., 2006). The increase in the ACE concentration in CR extract administered groups in the present study hence its antiurolithiatic effect and hypertension regulation by vasoconstrictor. This result is in agreement with the findings of Garcia et al. (1997b) who found that the addition of aqueous extract of *Cissus sicyoides* led to smooth muscle contraction of the aorta in guinea pigs.

Serum concentrations of AST, ALT, and LDH are useful in the detection of liver injury. Elevated levels of ALT and AST, of the treated group indicating that CR did not exert any hepatoprotective effect. This finding agreed with Ataa et al. (2015). Whereas, Wanjohi et al. (2020) concluded that leaves extracts are safe when administered orally for a long duration at doses lower than 400 mg/kg body weight. The leaves extract increases urine excretion (Salman *et al*., 2016), consequently, decreasing the calcium and oxalates ions. Moreover, the increased drainage of water and salt (sodium) into the urine causes lowering the resistance of blood flow thus decreases the blood pressure (Yeo *et al.,* 2009). Furthermore, the high vitamin content of CR leaves extract may be useful in treating hypertension (Gholami *et al*., 2012).

Estimation of serum concentrations of protein metabolism end products, (urea and

creatinine), gives a picture of the viability of renal tissue. Our study showed the rise of serum creatinine and urea in urolithiatic group II in contrast to their decrease in treated groups (Group III&IV). This increase was significant but not to the level that causing renal failure which means that the doses of EG/AC used in this study were accepted and not too toxic. The increase in the serum level of these parameters in-group II agreed with (Rathod *et al.,* 2012; Makasanaa *et al.,* 2014). They attributed this elevation to the decrease of glomerular filtration rate caused by tubular obstruction by oxalate crystals hence the retention of urea and creatinine. Furthermore, urolithiasis induced by EG was associated with a marked increase in kidney weight, probably due to hypertrophy of renal papilla. Moreover, EG poisoning can lead to lower in urine volume consequently increase urine concentration, decrease urine pH, and increase in kidney weight (Mandavia *et al.*, 2013; Zhang, 2014).

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CONFLICT OF INTEREST

All the authors have declared that no conflict of interest exists.

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