



## The Effect of *Sargassum angustifolium* Ethanol Extract on Cadmium Chloride-Induced Hypertension in Rat

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### Abstract

**Background and objectives:** *Sargassum angustifolium* is a brown alga in southwestern coastline of Persian Gulf. Regarding the presence of various bioactive compounds and evidence of antihypertensive effects in other species of *Sargassum*, we evaluated the effect of *S. angustifolium* ethanol extract in CdCl<sub>2</sub>-induced hypertension in Wistar rats. **Methods:** Alga extract was prepared by maceration method using 70% ethanol and assessed for total phenolics and salt content. CdCl<sub>2</sub> (1.5 mg/kg/day) was administered intraperitoneally to the rats for two weeks. Treatment groups received *S. angustifolium* extract (20, 40 and 80 mg/kg) or nifedipine (10 mg/kg) orally and simultaneously were given CdCl<sub>2</sub> for two weeks. Systolic blood pressure (SBP) and heart rate were measured using tail-cuff method. Total antioxidant capacity, urea, creatinine, electrolytes including sodium, potassium, calcium and chloride were estimated in blood samples. The weight and histopathology of kidney tissues were also evaluated. **Results:** The content of total phenolic as gallic acid equivalent and the salt as NaCl was 67.42 ± 9.5 mg/g and 6.9 g/100 g in dried ethanol extract, respectively. CdCl<sub>2</sub> caused significant increase in SBP, kidney/body weight ratio, serum sodium and urea level and decrease in plasma total antioxidant capacity, and also histopathological alterations in kidney tissues. Treatment with *S. angustifolium* extract at the doses of 40 and 80 mg/kg significantly reversed hypertension and improved kidney weight, urea level and electrolyte changes, and enhanced antioxidant capacity and prevented histopathological changes of kidney. **Conclusion:** Findings of the present study indicated antihypertensive and antioxidant effects of *S. angustifolium* extract against CdCl<sub>2</sub>-induced hypertension in rats.

**Keywords:** antioxidants; cadmium chloride; hypertension; *Sargassum*

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### Introduction

Hypertension or high blood pressure as the leading cause of cardiovascular death, affects one billion people worldwide [1]. This disorder is one of the most important risk factors for endothelial dysfunction, kidney failure, coronary artery disease and stroke [2].

The oceans are rich sources of wide range of new substances, foods and drugs that have been less used in medicine and pharmacy. Seaweed or algae

are one group of the most important marine organisms with many pharmacological and biological properties [3]. A variety of algal species has been found in Persian Gulf. *Sargassum angustifolium* C. Agardh is a brown alga from the southwestern coastline of Persian Gulf belonging to the *Sargassaceae* family [4]. Phytochemical studies have displayed the existence of saponins, flavonoids, glycosides, sterols, terpenoids and

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high amounts of total phenolic compounds in this alga [5]. Pharmacological assessments have shown antioxidant, antimicrobial, anti-inflammatory, antihyperlipidemic, anti-diabetic, hepatoprotective, antineoplastic, neuroprotective, anticoagulant, and antihypertensive activities for different algae from *Sargassum* sp. [6-11]. Several natural compounds with valuable effects in lowering blood pressure were isolated from some species of this genus such as *S. siliquastrum*, *S. micracanthum* and *S. maclurei* [11-13]. Regarding the presence of various active compounds with possible cardiovascular beneficent properties and also the evidence of antihypertensive effects in other species of the genus, this study aimed to investigate the effect of ethanol extract of *S. angustifolium* on cadmium chloride ( $\text{CdCl}_2$ )-induced hypertension in rats.

## Materials and Methods

### Ethical considerations

The experimental procedure was conducted according to the international guidelines for laboratory animal use and care (European Directive 2010/63/EU) [14] and approved by the Biomedical Researches Ethics Committee of Isfahan University of Medical Sciences (ethical approval ID: IR.MUI.RESEARCH.REC.1398.196).

### Chemicals

The assay kits for evaluation of urea, creatinine, calcium and chloride levels were purchased from Pars Azmoon Co. (Iran). The kit for ferric reducing antioxidant power (FRAP) assay was prepared from Hakiman Shargh Research Co. (Iran). Folin-Ciocalteu reagent and all other chemicals were purchased from Merck Co. (Germany).

### Plant material

*Sargassum angustifolium* was collected in Oct 2018 from Bushehr, a south-western coastal region on Persian Gulf, Iran. The alga was identified by the Agricultural and Natural Resources Research Center of Bushehr and a voucher specimen (No. 2662) was deposited at the Herbarium of School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences.

### Extraction

For preparation of *S. angustifolium* ethanol extract, the algae were first completely washed with running tap water and then air-dried in shade at room temperature. The powdered algae were extracted with 70% ethanol for 72 h, using maceration method three times at room temperature. In order to separate the salts, the hydroalcoholic extract was washed through a reverse phase column chromatography by water and then ethanol. The aqueous phase was isolated and discarded but the ethanol phase was concentrated under vacuum by rotary evaporator and was finally freeze-dried and stored in the refrigerator till used for the experiments.

### Total phenolics content assay

Total phenolics content was assessed using Folin-Ciocalteu reagent in *S. angustifolium* ethanol extract. Briefly, the reagent was diluted and mixed with algae samples. After 5 minutes, sodium carbonate solution (20%) was added to the mixture and stored at room temperature for 2 hours. Afterwards, the absorbance was measured at 765 nm by a UV-visible spectrophotometer [15]. The amount of total phenolic compounds was quantified by a standard curve drawn by different concentrations of gallic acid and expressed as mg of gallic acid equivalents (GAE) per gram of the dried extract.

### Salt content assay

The salt (sodium chloride) content of freeze-dried powder of *S. angustifolium* ethanol extract was determined using Mohr method based on the silver nitrate and potassium chromate titration of the chloride ion [16].

### Animals

Adult male Wistar rats weighing 200 to 220 g were obtained from the animal house of the School of Pharmacy and Pharmaceutical Sciences (Isfahan, Iran). The animals were kept in polypropylene cages under standard laboratory settings of temperature and humidity, with a 12 h light/12 h dark cycle and free access to water and rat pellets diet. Based on the cage size and the space necessities, 3 rats were maintained in each cage. The rats were allowed to acclimatize to the laboratory situation for 1 week before the research.

### Experimental design

Thirty-six rats that were comparable in age and weight were randomly divided to six experimental groups of 6 rats each as follows: Group 1: Saline control, received vehicle (normal saline) orally and intraperitoneally (i.p.) for 2 weeks; Group 2: CdCl<sub>2</sub>-induced hypertensive control, received CdCl<sub>2</sub> (1.5 mg/kg, i.p.) daily for 2 weeks [17]; Groups 3, 4 & 5: Treatment groups received ethanol extract of *S. angustifolium* (20, 40 and 80 mg/kg) by oral gavage and simultaneously were given CdCl<sub>2</sub> for 2 weeks [18]; Group 6: Reference group, received nifedipine (10 mg/kg, orally) and simultaneously CdCl<sub>2</sub> for 2 weeks.

The rats were weighed on alternate days. At the end of the experiments, the animal blood specimens were taken from retro-orbital sinus under general anesthesia by i.p. administration of ketamine (50 mg/kg) and xylazine (5 mg/kg) and serum or plasma samples were isolated for biochemical analysis. Finally, the animals were euthanized with exposure to carbon dioxide and the kidneys were separated.

### Heart rate and blood pressure recording

The heart rate and systolic blood pressure (SBP) were detected at the first day and every week by non-invasive tail-cuff method (AD Instrument PowerLab Data Acquisition System, Australia). The animals were consciously controlled in a clear acrylic restrainer at an ambient temperature of 37-38 °C for 10 minutes. Before initiation of the experiment, a one-week training phase was established for adaptation of rats to the method. At least 5 records for each parameter were used for each rat and averaged to attain a mean data.

### Biochemical analysis

The biochemical parameters of kidney including urea and creatinine were evaluated in blood samples of animals using the commercial kits based on the enzymatic colorimetric assay.

### Electrolytes measurement

Serum electrolytes including sodium and potassium were estimated in rat blood samples by a Corning 480 flame photometer (Corning Co., USA) based on the atomic emission spectrometry. Calcium and chloride levels were also measured by commercial spectrophotometric kits.

### Ferric reducing antioxidant power (FRAP) assay

The FRAP assay was used for determining the

total antioxidant capacity of plasma by a commercial kit. Briefly, the plasma samples (10 µL) were mixed with FRAP reagent (200 µL) which contained ferric-tripyridyl triazine and ferric chloride/acetate buffer and incubated in 37 °C. After 40 min, the absorbance was read at 570 nm by a microplate reader/spectrophotometer (Bio-Tek, PowerWave XS, USA). The FRAP value in each sample was estimated as FeSO<sub>4</sub> equivalents using its standard curve [19].

### Histopathological evaluation

The fixed kidney tissues in 10% neutral buffer formalin solution were embedded in paraffin block and cut to 5 µm thickness sections. Then they were stained with hematoxylin and eosin (H&E) for evaluation of histological changes by light microscopy.

### Statistical analysis

The results were expressed as the mean ± SEM and statistically analyzed by one-way analysis of variance (ANOVA) followed by Tukey post-hoc test using SPSS software version 25.0. P value < 0.05 was considered as the significance level.

### Results and Discussion

In the present study, high amount of total phenolic compounds as 67.42 ± 9.5 mg GAE in one g of dried *S. angustifolium* ethanol extract was determined using Folin-Ciocalteu assay and a standard curve of gallic acid ( $y = 1.1642x - 0.0251$ ,  $R^2 = 0.9945$ ). Farvin et al evaluated several species of *Sargassum* and reported a wide range of total phenolics content from 10.2 ± 1.3 to 175.5 ± 53.4 mg GAE/g in different extracts which was higher in ethanol extracts of *S. boveanum*, *S. oligocystum*, and *S. angustifolium* than the hydroalcoholic or water extracts and in other species [20]. Various factors including geographical sites, season, process of preparations and type of extraction may prominently affect the amounts of phenolic content in each extract [21,22].

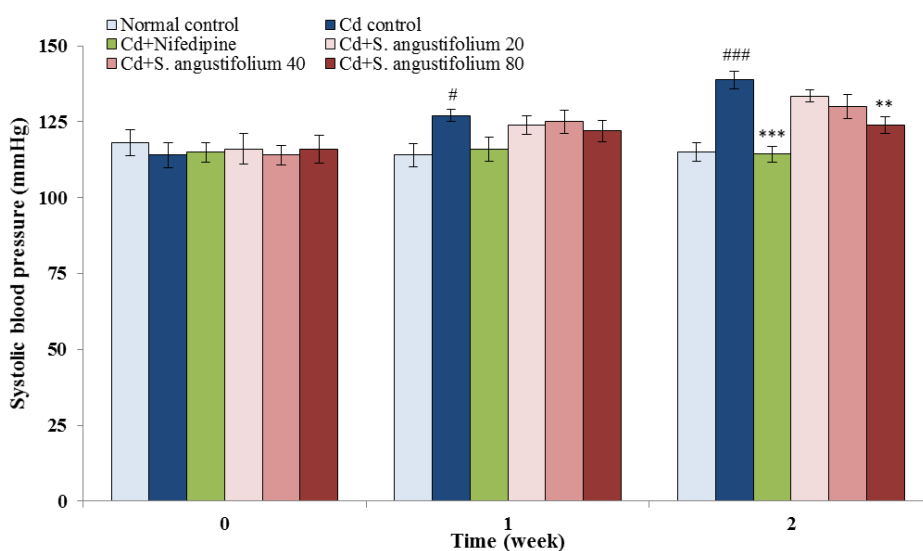
The content of salt as NaCl was 6.9 g/100 g in dried ethanol extract of *S. angustifolium* based on Mohr assay. Although seaweeds have been suggested as the substitute for salt particularly in hypertensive patients because of natural salty taste and containing high amount of healthy mineral salts including potassium and magnesium, small amounts of seaweed should be consumed as

food to prevent excessive salt intake [23,24].

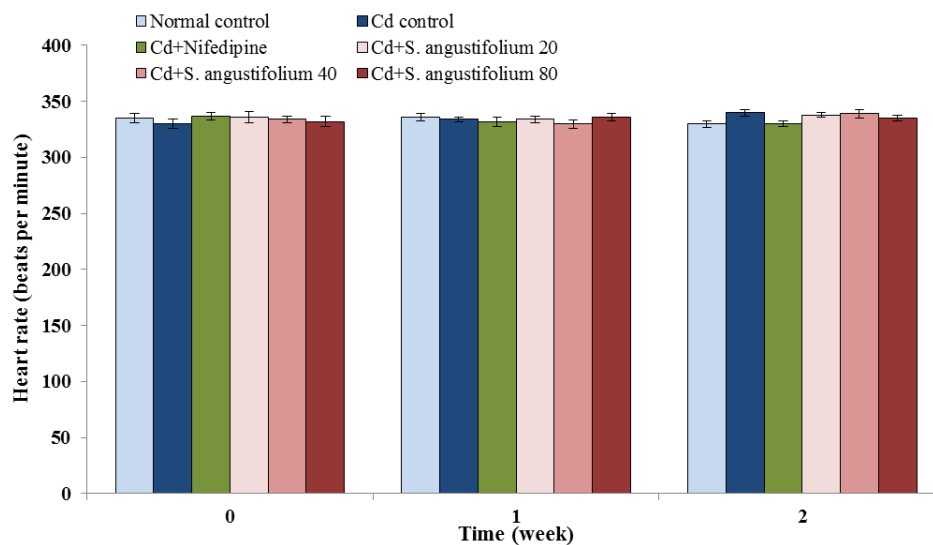
In this study, CdCl<sub>2</sub> was used for induction of an animal model of hypertension. Exposure to Cd is associated with development of hypertension and vascular dysfunction through induction of oxidative stress, inflammation, injuring tissues in kidney, heart and vascular systems, decreasing availability of nitric oxide, reduction of endothelium-dependent relaxation, stimulating renin-angiotensin system and calcium related contractile activity [25-27]. After 2 weeks exposure of rats to CdCl<sub>2</sub> (1.5 mg/kg, i.p.), SBP significantly elevated from 114.3 ±2.5 to 138.3 ±5.4 mmHg) compared to the saline control group (116.1 ±4.7 mmHg) (p<0.001). Figure 1 shows the effect of oral administration of *S. angustifolium* extract (20, 40 and 80 mg/kg) and nifedipine (10 mg/kg) on SBP in CdCl<sub>2</sub>-induced hypertensive rats. Nifedipine as a reference antihypertensive drug resulted in a notable decrease in SBP near to the normal value (p<0.001). Treatment with *S. angustifolium* extract significantly lowered the CdCl<sub>2</sub>-induced hypertension in rats at the doses of 40 and 80 mg/kg after 2 weeks of administration (p<0.05 and p<0.01, respectively). No change was observed between the heart rate on 15<sup>th</sup> day and initial heart rate in different groups (Figure 2).

Investigations on other species of *Sargassum* have revealed helpful effects in reducing blood pressure. Sargachromenol D and farnesylacetone are natural

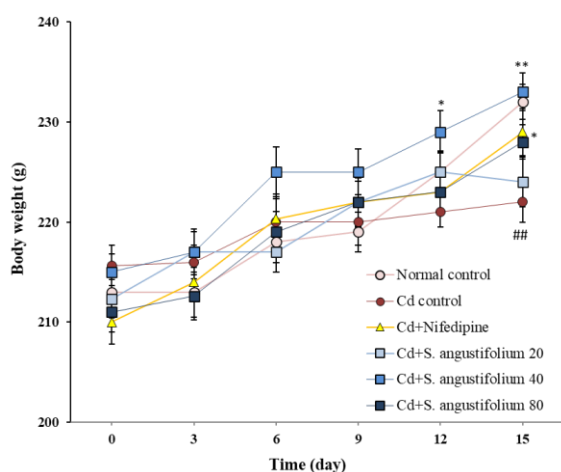
compounds isolated from *S. siliquastrum* which have shown notable vasodilatory effects. Sargachromenol D acts through blocking an L-type calcium channel and antagonizing the endothelin A/B2 receptors [11]. Farnesylacetone has displayed long-term antihypertensive effect via blocking an L-type calcium channel in spontaneous hypertensive rats without altering the heart rate [12]. Sargahydroquinoidic acid isolated from *S. micracanthum* has also shown high vasodilatory activity on the basilar arteries of rabbit [28]. A new peptide with suppressing effect on endothelin-1 and inhibitory activity on angiotensin I-converting enzyme (ACE) has recently isolated from *S. maclurei* [13]. Exposure to CdCl<sub>2</sub> (1.5 mg/kg) resulted in a significant decrease in body weight gaining in hypertensive rats when compared to saline control group (p<0.01) during the experimental period. While administration of *S. angustifolium* extract at the doses of 40 and 80 mg/kg and also nifedipine significantly prevented body weight loss induced by CdCl<sub>2</sub> (Figure 3). Dzobo et al also reported remarkable decrease in body weight gaining in male rats receiving CdCl<sub>2</sub> at the dose of 1.67 mg/kg while no significant change in body weight gaining has been observed after administration of 1 mg/kg CdCl<sub>2</sub> in the study of Yadav et al and Liu et al [29-31].



**Figure 1.** Effects of *Sargassum angustifolium* extract (20, 40 and 80 mg/kg) and nifedipine (10 mg/kg) on systolic blood pressure in CdCl<sub>2</sub>-induced hypertension. Values are means±SEM (n=6). <sup>#</sup>p<0.05 and <sup>###</sup>p<0.001 versus normal control; <sup>\*\*</sup>p<0.01 and <sup>\*\*\*</sup>p<0.001 versus CdCl<sub>2</sub> control



**Figure 2.** Effects of *Sargassum angustifolium* extract (20, 40 and 80 mg/kg) and nifedipine (10 mg/kg) on heart rate in CdCl<sub>2</sub>-induced hypertension. Values are means±SEM (n=6)



**Figure 3.** Effects of *Sargassum angustifolium* extract (20, 40 and 80 mg/kg) and nifedipine (10 mg/kg) on body weight in CdCl<sub>2</sub>-induced hypertension. Values are means±SEM (n=6). ###p<0.01 versus normal control; \*p<0.05 and \*\*p<0.01 versus CdCl<sub>2</sub> control

The kidney/body weight ratio was increased in CdCl<sub>2</sub>-induced hypertensive rats ( $p<0.05$ ). Treatment with nifedipine and *S. angustifolium* extract (40 and 80 mg/kg) prevented kidney weight gaining ( $p<0.05$ ) (Table 1).

As shown in Table 1, significant increase in serum sodium and urea level was observed in CdCl<sub>2</sub>-induced hypertension group ( $p<0.05$ ). Supplementation with *S. angustifolium* extract at the dose of 80 mg/kg brought back these markers toward normal level. However, there was no statistically significant difference between groups in terms of serum potassium, calcium, chloride

and creatinine levels. Histopathological evaluation of kidney tissues in animals which were exposed to CdCl<sub>2</sub> for 2 weeks showed mild tubular swelling compared to the normal architecture in saline control group (Figure 4A and 4B). The mild tubular swelling was also found in rats' kidney that were treated with 20 mg/kg *S. angustifolium* extract. The architecture of kidney tissues was normal in all other treated animals (Figure 4C-4F).

It is well known that CdCl<sub>2</sub> toxicity is associated with renal damage in a dose dependent manner through induction of oxidative stress, apoptosis and disordered iron absorption [31]. Liu et al also reported slightly swelling and hyperemia in the interstitium of kidney tissues after 3 weeks exposure to CdCl<sub>2</sub> at the dose of 1 mg/kg. Moreover, they observed obvious swelling in glomerular and renal tubules and damage in kidney structure including narrowing of lumens, necrosis in the epithelial cells, congestion and infiltration of inflammatory cells in the interstitium after exposure to higher doses of CdCl<sub>2</sub> including 2.5 and 5 mg/kg [31]. On the other hand, protective effect of ethanol extract of some *Sargassum* sp. has been reported in kidney dysfunction by reducing renal biomarkers towards normal values [32].

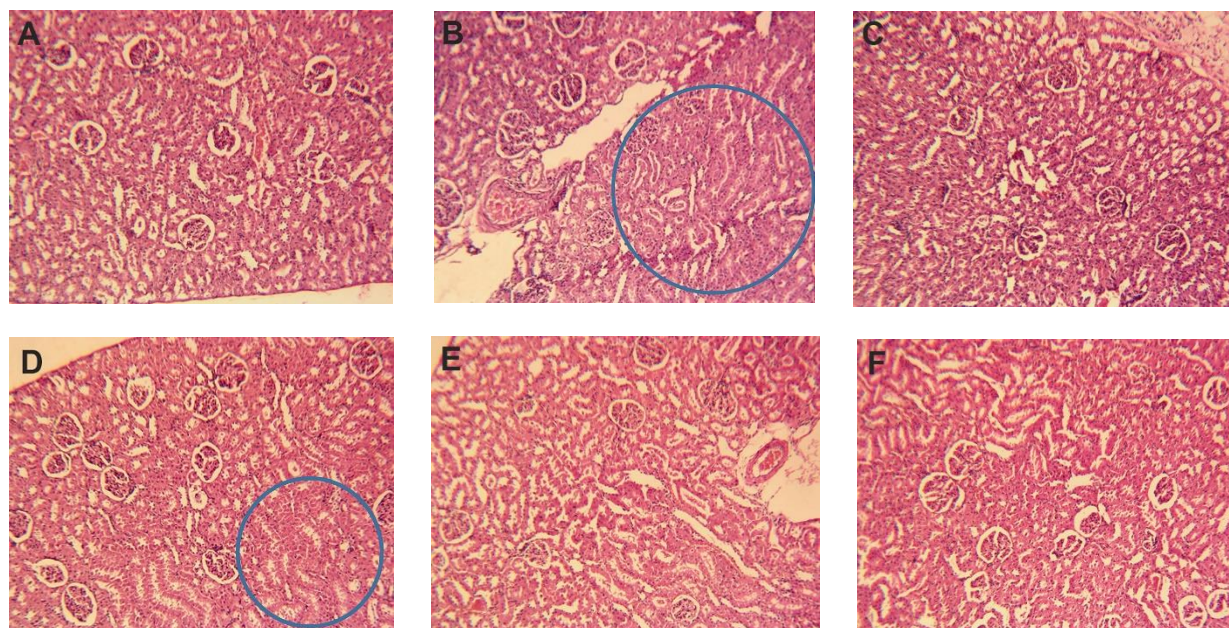
Two weeks exposure to CdCl<sub>2</sub> resulted in a notable decrease in the FRAP value as the total antioxidant capacity in plasma samples of CdCl<sub>2</sub>-induced hypertensive animals compared with normal control rats ( $p<0.001$ ). All treatments largely raised the serum FRAP value (Figure 5).



**Table 1.** Effect of *Sargassum angustifolium* extract and nifedipine on organ weight, serum electrolytes and biochemical parameters of kidney in CdCl<sub>2</sub>-induced hypertensive rats

Parameter		Groups					
		Normal control	Cd control	Cd + Nifedipine (10 mg/kg)	Cd + <i>S. angustifolium</i> (20 mg/kg)	Cd + <i>S. angustifolium</i> (40 mg/kg)	Cd + <i>S. angustifolium</i> (80 mg/kg)
Organ weight	Kidney (BW%)	0.51 ± 0.005	0.55±0.009 <sup>#</sup>	0.51±0.007*	0.53 ± 0.007	0.50 ± 0.004*	0.51 ± 0.003*
	Sodium (mEq/L)	140.90±0.15	143.70±0.13 <sup>#</sup>	140.50±0.09*	140.20± 0.11*	141.90 ± 0.17	140.6±0.08*
Electrolytes	Potassium (mEq/L)	4.73 ± 0.11	4.60 ± 0.19	4.81 ± 0.08	4.80 ± 0.09	4.68 ± 0.17	4.80 ± 0.10
	Calcium (mEq/L)	10.37±0.031	10.21±0.052	10.27±0.031	10.22±0.056	10.28±0.018	10.25±0.036
	Chloride (mmol/L)	97.48 ± 0.30	99.25 ± 0.37	97.95 ± 0.26	98.71 ± 0.25	99.10 ± 0.32	97.67 ± 0.58
Kidney markers	Urea (mg/dL)	31.50 ± 0.96	38.52±1.24 <sup>#</sup>	32.42±1.48*	35.33± 1.76	34.67 ± 1.62	32.55 ± 1.18*
	Creatinine (mg/dL)	0.51 ± 0.02	0.54 ± 0.06	0.52 ± 0.03	0.54 ± 0.06	0.54 ± 0.02	0.53 ± 0.05

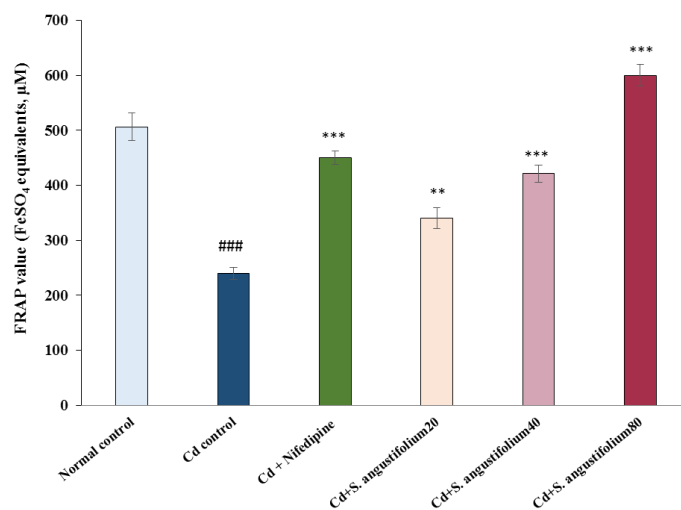
Values are means±SEM (n=6). <sup>#</sup>p<0.05 versus normal control, and \*p<0.05 versus Cd control. BW: body weight



**Figure 4.** Representative H & E histological sections of the kidney tissue of normal control group (A); CdCl<sub>2</sub>-induced hypertensive group (B); nifedipine treated group (C); *Sargassum angustifolium* extract treated groups with doses of 20 mg/kg (D), 40 mg/kg (E) and 80 mg/kg (F), ×40 magnification; Circles indicate the tubular swelling areas

Increased oxidative stress including reduction in catalase, superoxide dismutase, reduced glutathione, and increase in lipid peroxidation has been reported in CdCl<sub>2</sub>-induced hypertension [27]. On the other hand, strong antioxidant activities have been proven for *S. angustifolium* through 2,2-diphenyl-1-picrylhydrazil (DPPH) radical scavenging activity, iron chelating effect, reducing power and inhibition of liposome lipid

oxidation [5,20]. Farvin et al indicated high content of catechin, quercetin and coumarin in ethanol extract of *S. angustifolium* which was higher than other species of *Sargassum* [20]. Babakhani and co-workers also isolated phenolic constituents from *S. angustifolium* including protocatechuic acid, gentisic acid, hydroxy benzoic acid and gallic acid which are involved in its antioxidant properties [33].



**Figure 5.** Effects of *Sargassum angustifolium* extract (20, 40 and 80 mg/kg) and nifedipine (10 mg/kg) on plasma FRAP value in CdCl<sub>2</sub>-induced hypertension. Values are means±SEM (n=6). ###p<0.001 versus normal control; \*\*p<0.01 and \*\*\*p<0.001 versus CdCl<sub>2</sub> control

## Conclusion

In conclusion, the findings of the current study indicated the antihypertensive and antioxidant activities of *S. angustifolium* ethanol extract through attenuating SBP, decreasing serum sodium and urea level, enhancing antioxidant defense, and preventing histopathological alterations of kidney in CdCl<sub>2</sub>-induced hypertensive rats. Additional surveys are still needed to clarify the detail mechanisms of blood pressure-lowering effect of this natural medicine and describe its worth for the clinical uses.

## Acknowledgments

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## Author contributions

Leila Safaeian was responsible for the stereological plan, designing the animal studies, analyzing the data and editing the manuscript; Afsaneh Yegdaneh designed the herbal studies; Masoud Mobasherian was involved in the animal treatments and preparation of the manuscript

## Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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### Abbreviations

FRAP: ferric reducing antioxidant power; GAE: gallic acid equivalents; SBP: systolic blood pressure