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ANTI-INFLAMMATORY, ANTIHYPOXANT AND ANTIOXIDANT ACTIVITY OF PRODUCTS ISOLATED FROM CAPER CULTIVATED IN UZBEKISTAN

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ABSTRACT

Caper extracts have been reported to possess antibacterial, antifungal, analgesic, antitumor, hepatoprotective, antioxidant, anti-inflammatory, and neuroprotective effects.

We have isolated polysaccharide and protein sums from buds and fruits of *C.spinosa* L. cultivated in Uzbekistan. The goal of this research was to investigate anti-inflammatory activity of isolated sums in comparison with ketoprofene. The experiments were made using the formalin-induced paw edema in mice in three variations, at first the investigated substances were introduced to rats *per os* once, and at the second and third experiment the investigated substances were introduced to the animals for five and ten days. On hemic hypoxia model the investigated substances shown high antixypoxic effects close to Mildronate neo drug (70.7%) at doses of 25 mg/kg for PPSCB (67%) and 150 mg/kg for PPSCF (64.2%). On cytotoxic hypoxia model the effects of both investigated substances also were relatively high and close to Mildronate neo (61%), PPSCB – 56% at a dose of 50 mg/kg, and PPSCF – 58% at a dose of 150 mg/kg. In normobaric hypoxia effects of all investigated substances were less, including the etalon drug (25.4%), PPSCB – 25.5% at dose of 150 mg/kg and PPSCF at 100 mg/kg – 29%. The influence of investigated substances on SOD activity has been investigated. It was established that the both investigated sums at first minute of the test increase SOD activity for PPSCB at a dose of 50 mg/kg by 2.28 times, and PPSCF at a dose of 150 mg/kg by 2.26 times in compare to the control. These results indicated on the increasing of antioxidant protection and improving the oxidative status of experimental animals. Thus, the carried out investigation results shown the high anti-inflammatory, antihypoxic and antioxidant potential of PPSCF and PPSCB products. In combination with their low toxicity these properties make them good candidates for development of effective therapeutic remedies and food additives.

INTRODUCTION

Capparis spinosa L. belongs to the family Capparaceae, endemic to Mediterranean countries. Caper extracts have shown to possess antibacterial, antifungal, analgesic, antitumor, hepatoprotective, antioxidant, anti-inflammatory, and neuroprotective effects[1]. It is called the "Plant of the Millennium", and it has a great value in folk medicine like Iranian, Unani, Chinese, Ayurvedic and Greco-Arabi systems[2].

Azhary et al. showed that *C.spinosa* leaves extract operated by inhibiting cytokine gene expression including IFNγ, IL-17 and IL-4. Hexane fraction exhibited the similar anti-inflammatory effect, and would likely contain the bioactive molecules[3].

The anti-inflammatory activities of *C. spinosa* L. fruit aqueous extract effectively inhibited the carrageenan-induced paw edema in mice. Its systematic fractionation and isolation led to the identification of 13 compounds belong to flavonoids, indoles, and phenolic acids[4]. Two biflavonoids, isoginkgetin, and ginkgetin, together with three other flavonoids, were isolated from caper fruits. The anti-inflammatory effects of the flavonoids from caper fruits were evaluated by secreted placental alkaline phosphatase (SEAP) reporter assay, which was designed to measure nuclear factor-kappa B (NF-κB) activation[5].

Polysaccharide of *C. spinosa* L. leaf was obtained by Mazarei et al. [6]. It was established its antioxidant and antimicrobial activity. The fruit of this species is reported to contain 5.8% protein[7]. Hydrophilic polysaccharides, hemicelluloses and pectin compounds have also been extracted with water, base and oxalic acid/ammonium oxalate, respectively from the roots of *C. spinosa*. The important monosaccharides detected in the roots of *C. spinosa* were xylose, arabinose and galactose[8].

Cellular hypoxia can trigger the expression of several inflammatory mediators which signal tissue damage and initiate survival responses[9].

The aim of this work was isolation of biologically active products containing polysaccharide and protein sums from buds and fruits of *C.spinosa* L. and investigation of their biological activity.

Materials and Methods

The buds and fruits of *C. spinosa* L. cultivated in Uzbekistan were collected in the Tashkent region in the Okhangaran and Kibray districts in 2017.

Experimental chemical part

The isolation of water-soluble polysaccharides and pectin substances was carried out as described by Yili et al.[9].

The plant organs (buds and fruits) were crushed and inactivated separately with a boiling mixture of chloroform-methanol (1:1) to remove non-carbohydrate components and pigments. Alcohol-soluble sugars were extracted twice with boiling 82% alcohol (ethanol). The combined alcohol extracts were thickened and analyzed by paper chromatography. The rest of the raw material was successively extracted with cold water, then with a mixture of 0.5% solutions of oxalic acid and ammonium oxalate, and water-soluble polysaccharides and pectin substances were obtained.

To determine the qualitative and quantitative characteristics of monosaccharides, chromatographic studies were carried out on a gas-liquid chromatograph GC 2010 Plus, Shimadzu with a flame ionization detector of APC type (Det3ch). Chromatography was carried out using a Rxi-624Sil MS glass capillary column of 30.0 m length with inner diameter 0.25 mm and film thickness of 1.40 microns. Nitrogen was used as the carrier gas with flow speed of 30 ml/min. The flow through the column was 0.71 ml/min, evaporator temperature - 290°C, column temperature - 280°C, and detector temperature - 300°C. 1 µl of a solution containing 10 mg/ml (0.01%) aldonitrile acetates was introduced into the chromatograph evaporator. Chromatograms were recorded on a computer with fixation of the retention time of components and composition of mixture.

Aqueous extracts were evaporated on a rotary evaporator at 40±50°C. Descending paper chromatography was carried out on Filtrak-FN 13.18 paper in the solvent system "butanol-1-pyridine-water" (6:4:3). Acid aniline phthalate was used to indicate spots.

The IR spectra of the samples were recorded on a 2000 FT-IR spectrometer (Perkin Elmer) in KBr pellets. The viscosity of polysaccharide solutions was measured on an Ostwald viscometer with a capillary diameter of 0.82 mm.

Determination of the composition of product isolated from caper buds shown, that it contains 25-30% polysaccharides, 17-25% proteins and 5-10% flavonoids, and the product isolated from caper fruits contains 30-35% polysaccharides, 25-30% proteins and 5-10% flavonoids.

Experimental pharmacological part

Albino Wistar male rats (weighing between 150 - 200 g) were maintained under normal laboratory condition of humidity (50%), temperature (23 ± 2°C) and a 12-hour light/dark cycle, and allowed free access to food and water *ad libithum*.

Anti-inflammatory activity was evaluated in formalin test[10]. The animals were randomly allocated into 4 groups (n = 6). The first group served as a negative control (normal saline 0.2 mL) while the second and third groups received different doses (25, 50, 100, 150 and 200 mg/kg p.o.) of polysaccharide and protein sums from buds and fruits of *C.spinosa*, and the forth group received ketoprofene (1, 5 and 10 mg/kg p.o.) as a positive control group, respectively. Edema was induced on the right hind paw of the rat by a subplantar injection of 0.1 mL of formalin (2.5 %) 60 minutes after investigated substances administration. Swelling of formalin-injected foot was measured oncometrically. The ability of anti-inflammatory agents to suppress paw inflammation was expressed as a percent inhibition of paw edema and calculated according to the following equation:

Relative Paw Edema=$[(v_2-v_1)/v_1]\times100$,

where v_1 = the animal paw volume before formalin injection and v_2 = the paw volume after drugs and formalin injection at different time points.

Hemic hypoxia model was achieved by intraperitoneal introduction to mice of sodium nitrite at a dose of 300 mg/kg, cytotoxic hypoxia – by subcutaneous introduction of 20 mg/kg sodium nitroprusside. Investigated substances were introduced *per os* at doses of 25-200 mg/kg and etalon drug Mildronate neo (meldonium) (Latvia). Normobaric hypoxia with hypercapnia was modelled in mice using special chamber. Criterion for investigated substances effectiveness was increasing of animal survival period.

Antioxidant activity was determined by the reaction of autoxidation of adrenaline in an alkaline medium in the presence of SOD due to the dismutation of superoxide anion radicals. The investigated substance was introduced to rats one hour before the determination of antioxidant activity. 50 µl of serum and 450 µl of distilled water cooled to 0°C were added to the test tube. 250 µl of ethanol-chloroform mixture was added to eliminate the interfering effect of hemoglobin. Next, the samples were mixed and left to incubate at room temperature for 10 minutes. The resulting suspension was stirred and centrifuged for 10 min. at 6000 g. The supernatant was used to determine SOD. 0.15 ml of adrenaline solution was added to the samples before determination of optical density. The change in optical density was recorded for 3 min. every 30 sec. at a wavelength of 347 nm in a cuvette with a layer thickness of 1 cm. To calculate the activity, the absorption values of the control and experimental samples were used.

The calculation was carried out according to the formula:

SOD/t=(Ex-E0/Ex) x 100%/50 x F x V x 1000/5- x v x d, where

(Ex-E0/Ex) x 100%/50 - activity unit, 50% inhibition of adrenaline oxidation reaction

V is the total volume of the incubation sample

F - dilution factor (15)

v is the volume of the supernatant used to determine the activity of SOD,

d is the length of the optical path of the cell (1 cm).

The experiments were made in three modifications, at first the investigated substances were introduced to rats *per os*

once, and at the second and third experiment the investigated substances were introduced to the animals for five and ten days.

Data were shown as mean ± SD of different groups. The data of this study were statistically analyzed using OriginPro 9.0 (MicroCal Software, Northampton, MA). The $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

In subplantar injection of 0.1 ml of 2.5% formalin solution, experimental rats developed pronounced paw edema, as evidenced by a significant increase in hind paw volume. 3 hours after the administration of formalin, the volume of the paw in the experimental animals of the control group increased by an average of 57% (Table 1).

Table 1. Comparison of reduction of formalin-induced paw edema in rats between different doses of investigated substances

No.	Group	Dose, mg/kg	The average volume of liquid displaced by the rat paw, mL		Increase of the rat hind paw volume		Anti-inflammatory effect, %
			Intact	In 3 hours after formalin injection	mL	%	
1	Control	0.2 mL normal saline	0.9±0.19	1.25±0.47	0.35±0.05	38.8	-
2	PPSCB	25.0	0.92±0.37	1.23±0.53	0.31±0.25	33.6	**13.4**
		50.0	0.7±0.02	1.02±0.28	0.32±0.17	45.7	**17.7**
		100.0	0.68±0.27	0.90±0.75	0.22±0.11	32.3	**16.7**
		150.0	0.73±0.33	0.89±0.41	0.16±0.05	21.9	**43.5**
		200.0	0.64±0.67	0.97±0.04	0.33±0.19	51.5	**32.7**
3	PPSCF	25.0	0.88±0.61	1.02±0.29	0.14±0.16	15.9	**59.0**
		50.0	0.82±0.73	1.1±0.12	0.12±0.31	14.6	**62.3**
		100.0	0.76±0.52	0.88±0.09	0.16±0.05	21.0	**45.8**
		150.0	0.9±0.19	1.08±0.05	0.18±0.16	20.0	**48.4**
		200.0	0.73±0.44	0.93±0.31	0.20±0.19	27.3	**29.6**
4	Ketoprofene	1.0	0.78±0.75	0.94±0.11	0.16±0.04	20.5	**47.1**
		5.0	0.86±0.35	0.95±0.09	0.09±0.38	10.4	**73.1**
		10.0	0.74±0.72	0.86±0.48	0.12±0.56	16.2	**58.2**

Note: *P=0.05 in compare to the control

The polysaccharide and protein sum from caper buds (PPSCB) most effectively showed anti-inflammatory and anti-edematous effects at a dose of 150 mg/kg (43.5%). The sum of polysaccharides and proteins (PPSCF) from caper fruits shows the highest anti-inflammatory effect at a dose of 50 mg/kg (62.3%).

The reference drug ketoprofene at a dose of 5 mg/kg exhibits an anti-inflammatory effect of more than 70%. It was shown that 25 mg/kg PPSCF was as efficient as 10 mg/kg of ketoprofene in attenuating formalin-induced edema. PPSCB was not so efficient as PPSCF.

Table 2. Comparison of reduction of formalin-induced paw edema in rats between different doses of investigated substances at five-day administration

No.	Group	Dose, mg/kg	The average volume of liquid displaced by the rat paw, mL		Increase of the rat hind paw volume		Anti-inflammatory effect, %
			Intact	In 3 hours after formalin injection	mL	%	
1	Control	0.2 mL normal saline	0.7±0.24	1.1±0.13	0.4±0.67	57.1	-
2	PPSCB	25.0	0.8±0.14	1.14±0.19	0.34±0.09	42.5	25.5
		50.0	0.88±0.17	1.2±0.11	0.32±0.11	36.3	36.4

		100.0	0.83±0.21	1.1±0.05	0.27±0.24	32.5	43.0
		150.0	0.9±0.05	1.14±0.17	0.24±0.21	26.6	**46.5**
		200.0	0.76±0.32	1.11±0.21	0.35±0.23	46.0	19.4
3	PPSCF	25.0	0.74±0.24	1.0±0.11	0.26±0.15	35.1	38.5
		50.0	0.92±0.11	1.1±0.27	0.18±0.20	19.5	**65.8**
		100.0	0.88±0.20	1.07±0.12	0.19±0.16	21.5	62.3
		150.0	0.85±0.05	1.05±0.24	0.2±0.12	23.5	58.8
		200.0	0.89±0.01	1.2±0.17	0.31±0.15	34.8	39.0
4	Ketoprofene	1.0	0.88±0.12	1.12±0.16	0.24±0.24	27.2	52.3
		5.0	0.96±0.08	1.12±0.15	0.16±0.27	16.6	**70.9**
		10.0	0.88±0.04	1.13±0.20	0.25±0.21	28.4	50.2

Note: *P=0.05 in compare to the control

A five-day administration showed the same trend in the manifestation of anti-inflammatory activity by the investigated substances. PPSCB shown the best anti-inflammatory effect at a dose of 150 mg/kg (46.5%), and PPSCF – at 50 mg/kg (65.8%). Ketoprofene at a dose of 5 mg/kg exhibits an anti-inflammatory effect of 70.9% (Table 2). Usually, NSAIDs are prescribed to apply for 7-14 days to avoid development of their side effects. Ten-day administration of investigated substances shown relatively high activity of PPSCF with the best value (61.4%) at a dose of 100 mg/kg. PPSCB activity was highest at a dose of 150 mg/kg (52.3%). Ketoprofene at a dose of 5 mg/kg exhibits an anti-inflammatory effect of 62.1% (Table 3).

Table 3. Comparison of reduction of formalin-induced paw edema in rats between different doses of investigated substances and ketoprofene at ten-day administration

No.	Group	Dose, mg/kg	The average volume of liquid displaced by the rat paw, mL		Increase of the rat hind paw volume		Anti-inflammatory effect, %
			Intact	In 3 hours after formalin injection	mL	%	
1	Control	0.2 mL normal saline	1.02±0.11	1.5±0.64	0.48±0.16	47.0	-
2	PPSCB	25.0	1.08±0.13	1.47±0.52	0.39±0.14	36.1	23.1
		50.0	1.1±0.24	1.4±0.40	0.3±0.11	27.2	42.1
		100.0	1.06±0.10	1.34±0.37	0.28±0.15	26.4	43.8
		150.0	0.98±0.19	1.2±0.32	0.22±0.11	22.4	**52.3**
		200.0	1.0±0.15	1.33±0.45	0.33±0.13	33.0	29.7
3	PPSCF	25.0	1.1±0.16	1.38±0.37	0.28±0.16	25.4	45.9
		50.0	0.98±0.23	1.21±0.33	0.23±0.05	23.4	50.2
		100.0	1.1±0.11	1.3±0.27	0.2±0.16	18.1	**61.4**
		150.0	1.0±0.13	1.24±0.32	0.24±0.21	24.0	48.9
		200.0	1.1±0.24	1.42±0.43	0.32±0.13	29.0	38.2
3	Ketoprofene	1.0	1.05±0.10	1.29±0.23	0.24±0.32	22.8	48.5
		5.0	0.95±0.23	1.12±0.09	0.17±0.15	17.8	**62.1**
		10.0	1.01±0.27	1.21±0.16	0.2±0.11	19.8	57.8

Note: *P=0.05 in compare to the control

On hemic hypoxia model the investigated substances shown high antixypoxic effects close to Mildronate neo drug (70.7%) at doses of 25 mg/kg for PPSCB (67%) and 150 mg/kg for PPSCF (64.2%) (Table 4).

Table 4. Mice survival period on hemic hypoxia model (M±m, n=10)

No.	Group	Dose, mg/kg	Survival period, min.	Survival period increasing, %
1	Sodium nitrite (control)	300	12.3±0.10	-
2	Mildronate neo	1.0	19.2±0.48	56.0
		5.0	21.0±0.63	**70.7**
		10.0	19.5±0.51	58.5
3	PPSCB	25.0	20.5±0.67	**66.6**
		50.0	19.0±0.34	54.4
		100.0	18.5±0.53	50.4
		150.0	17.8±0.42	44.7
		200.0	16.5±0.65	34.1
4	PPSCF	25.0	16.5±0.53	34.1
		50.0	17.0±0.29	38.2
		100.0	18.7±0.32	52.0
		150.0	20.2±0.14	**64.2**
		200.0	19.2±0.17	56.0

Note: *P=0.05 in compare to the control

On cytotoxic hypoxia model the effects of both investigated substances also were relatively high and close to Mildronate neo (61%), PPSCB – 56% at a dose of 50 mg/kg, and PPSCF – 58% at a dose of 150 mg/kg (Table 5).

Table 5. Mice survival period on cytotoxic hypoxia model (M±m, n=10)

No.	**Group**	**Dose, mg/kg**	**Survival period, min.**	**Survival period increasing, %**
1	Sodium nitroprusside (control)	20	12.8±0.21	-
2	Mildronate neo	1.0	19.0±0.48	48.4
		5.0	20.6±0.36	**60.9**
		10.0	18.8±0.68	46.8
3	PPSCB	25.0	18.7±0.73	46.0
		50.0	20.0±0.37	**56.2**
		100.0	19.7±0.93	53.9
		150.0	19.2±0.39	50.0
		200.0	17.5±0.78	36.7
4	PPSCF	25.0	16.7±0.32	30.4
		50.0	17.0±0.27	32.8
		100.0	18.7±0.52	46.0
		150.0	20.2±0.75	**57.8**
		200.0	18.5±0.29	44.5

Note: *P=0.05 in compare to the control

In normobaric hypoxia effects of all investigated substances were less, including the etalon drug (25.4%), PPSCB – 25.5% at dose of 150 mg/kg and PPSCF at 100 mg/kg – 29% (Table 6).

Table 6. Mice survival period on normobaric hypoxia with hypercapnia model (M±m, n=10)

No.	**Group**	**Dose, mg/kg**	**Survival period, min.**	**Survival period increasing, %**
1	Control (0.9% NaCl)	0.2 ml	20.4±0.94	-
2	Mildronate neo	1.0	24.7±0.47	21.0
		5.0	25.6±0.72	**25.4**
		10.0	24.3±0.28	19.1
3	PPSCB	25.0	24.5±0.31	20.0
		50.0	24.8±0.49	21.5
		100.0	25.3±0.87	24.0
		150.0	25.6±0.24	**25.4**
		200.0	23.7±0.49	16.1
4	PPSCF	25.0	23.5±0.64	15.5
		50.0	25.7±0.27	25.9
		100.0	26.3±0.13	**28.9**
		150.0	24.8±0.21	21.5
		200.0	23.1±0.46	13.2

Note: *P=0.05 in compare to the control

Statistical processing of research results was performed using IBM SPSS Statistics 27 software.

Several studies have been performed that reveal the therapeutic potential and physiological importance of SOD[11]. The enzyme can serve as an anti-inflammatory agent and can also prevent precancerous cell changes[12]. The influence of investigated substances on SOD activity has been investigated. It was established that the both investigated sums at first minute of the test increase SOD activity for PPSCB at a dose of 50 mg/kg by 2.28 times, and PPSCF at a dose of 150 mg/kg by 2.26 times in compare to the control. These results indicated on the increasing of antioxidant protection and improving the oxidative status of experimental animals.

CONCLUSION

Thus, the carried out investigation results shown the high anti-inflammatory, antihypoxic and antioxidant potential of PPSCF and PPSCB products. In combination with their low toxicity these properties make them good candidates for development of effective therapeutic remedies and food additives.

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Conflict of interests

The authors have declared no conflict of interests.

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