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Antihypertensive Activity of Fruit Juice, Peel, and Seed Extracts of Local Pomegranate (*Punica granatum* L.) Cultivars

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Abstract The present study evaluated the antihypertensive activity of fruit juice, peel, and seed extracts obtained from selected local pomegranate (*Punica granatum* L.) cultivars. The extracts exhibited significant dose-dependent antihypertensive activity within the dose range of 100–500 mg kg^{-1}. Overall, the antihypertensive efficacy of the cultivars increased in the following order: «Oq Dona (Tuyatish)» < «Oq Shirin» < «Achchiq Dona» < «Qora Qayim» < «Qizil Anor». Administration of the extracts significantly reduced both systolic arterial blood pressure (SBP) and diastolic arterial blood pressure (DBP) under physiological conditions as well as in rats with adrenaline-induced experimental hypertension 60 min after administration of adrenaline hydrochloride (0.25 mg kg^{-1}). Among the tested cultivars, «Qizil Anor» exhibited the strongest antihypertensive activity. The obtained experimental findings suggest that local pomegranate extracts represent a promising natural source of bioactive compounds for the development of antihypertensive nutraceuticals and phytopharmaceutical preparations.

Keywords *Punica granatum* L., Pomegranate, Antihypertensive activity, Systolic blood pressure, Diastolic blood pressure, Experimental hypertension, Adrenaline-induced hypertension, Plant extracts, Phytotherapy

1. Introduction

Hypertension is currently one of the most prevalent cardiovascular disorders worldwide, affecting approximately 26.4–45% of the global population, and its prevalence is projected to increase to 29–60% by 2025. According to the World Health Organization, hypertension is responsible for approximately 9.4 million deaths annually worldwide [1,2,3]. The pathogenesis of arterial hypertension is a complex, multifactorial process regulated by intricate neurohumoral mechanisms within the human body [4,5,6,7].

Hypertension is generally classified into two major forms: primary (essential) hypertension, which accounts for approximately 90–95% of all cases, and secondary hypertension, which develops as a consequence of other underlying diseases and represents about 5–10% of cases. Both forms are characterized by disturbances in the function of the brain, cardiovascular system, and kidneys, substantially increasing the risk of stroke and ischemic heart [8,9,10,11]. Numerous factors contribute to the development of hypertension, including excessive body weight (obesity), excessive dietary sodium chloride (NaCl) intake, insulin resistance, dysregulation of the renin–angiotensin–aldosterone system (RAAS), hyperactivation of the sympathetic nervous system, endothelial dysfunction associated with impaired endothelin and nitric oxide (NO) biosynthesis, disruption of Ca^{2+} transport homeostasis in vascular smooth muscle cells, elevated angiotensin concentrations, developmental abnormalities during fetal life, and various neurohumoral disorders [12,13,14].

Approximately 60–70% of hypertension cases are associated with overweight or obesity. In obese individuals, enhanced sympathetic innervation, activation of the renin–angiotensin –aldosterone system, and stimulation of peripheral α- and β-adrenergic receptors contribute significantly to elevated arterial blood pressure [15,16,17,18]. Activation of α-adrenergic receptors in vascular smooth muscle cells by the sympathoadrenal system, catecholamines, and angiotensin

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II plays a pivotal role in the development of vasoconstriction -mediated [19,20]. Furthermore, norepinephrine has been reported to participate in vascular smooth muscle contraction through β3-adrenergic receptor-mediated activation of the adenylate cyclase (AC)–cAMP–protein kinase A (PKA) signaling cascade [21,22]. Several studies have demonstrated alterations in erythrocyte membrane ion permeability and impaired functional activity of ion transport systems under hypertensive conditions [23]. In addition, increasing evidence confirms that inflammatory processes at the cellular level are actively involved in the pathogenesis of arterial hypertension [24,25]. Atrial natriuretic peptide (ANP), synthesized by cardiomyocytes, has also been shown to play an important role in the regulation of blood pressure during hypertension [26].

Moreover, activation of endothelial nitric oxide synthase (eNOS) in vascular endothelial cells stimulates nitric oxide (NO) production, which is essential for maintaining vascular relaxation through vasodilation. Contemporary clinical management of arterial hypertension relies on both monotherapy and combination therapy using various pharmacological agents, including calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor (AT_1) blockers, diuretics, α- and β-adrenergic blockers, among others [26]. Even a modest reduction of 5 mmHg in systolic or diastolic blood pressure has considerable clinical significance, decreasing the incidence of cardiovascular diseases by 15–20%, reducing stroke risk by 20–40%, and lowering overall mortality by approximately 7% (Whelton et al., 2002; Stockton et al., 2017). Consequently, the development of novel antihypertensive agents has increasingly focused on modulating ion transport systems, particularly calcium channels located in vascular smooth muscle cells [27,28]. In recent years, medicinal plant extracts rich in biologically active compounds have attracted considerable attention as promising alternatives for antihypertensive therapy because of their high therapeutic potential and relatively low toxicity and adverse effects.

Therefore, the present study aimed to evaluate the antihypertensive activity of juice, peel, and seed extracts obtained from five local pomegranate (Punica granatum L.) cultivars— «Qizil Anor», «Qora Qayim», «Oq Shirin», «Oq Dona (Tuyatish)», and «Achchiq Dona» —using in vivo experimental animal models.

2. Materials and Methods

Plant Materials

Five local pomegranate (*Punica granatum* L.) cultivars, namely «Qizil Anor», «Qora Qayim», «Oq Shirin», «Oq Dona (Tuyatish)», and «Achchiq Dona», cultivated in a private orchard located in Halqabod neighborhood, Mirzaobod District, Syrdarya Region, Uzbekistan (40°32′39″N, 68°41′58.9″E), were selected as the experimental materials.

Preparation of Pomegranate Extracts

Fruit juice, peel, and seed extracts of the local pomegranate cultivars were prepared according to previously published standard protocols with slight modifications [29,30].

Briefly, pomegranate peels and seeds were dried in an Orienterm ShS-40-01 drying oven (EltemiksLAB, Russian Federation) at 60 ± 0.5 ℃ for 24 h until the residual moisture content reached approximately 5–10%. The dried materials were mechanically ground using a Polaris PCG 1317 laboratory grinder (CityConsalt Ltd., China). Ten grams of each powdered sample were transferred into extraction flasks and extracted with 70% ethanol at a 1:5 (w/v) ratio by incubation at 75 ± 0.5 ℃ for 48 h.

Subsequently, the extracts were subjected to ultrasonic-assisted extraction using a GT SONIC-D3 ultrasonic water bath (Ultrasonic Cleaner, China; 50 Hz) in two consecutive cycles of 25 min each at 40 ± 0.5 ℃. The ethanol solvent (approximately 50%) was then removed under reduced pressure using a RE100-Pro rotary evaporator (DLab, China) equipped with a vertical condenser at 0.1 MPa, 60 ± 0.5 ℃, for 10 min with a rotational speed of 20–280 rpm.

The concentrated extracts were filtered through Whatman No. 1 filter paper (DV Expert, Russian Federation), transferred into glass flasks, and stored at 4 ± 0.5 ℃ for 24 h. Finally, the samples were freeze-dried by sublimation using a laboratory lyophilizer (Russian Federation) for 10 h to obtain dry powdered extracts.

Fresh pomegranate juice was prepared mechanically using an MJ-M176P Juicer (Panasonic, Japan). The obtained juice was subsequently processed by lyophilization to produce a powdered juice extract following previously described procedures [31,32,33].

Experimental Animals

Experiments were carried out using healthy adult outbred white laboratory rats of both sexes (♂/♀), weighing 275–320 g, obtained from the animal facility of the Institute of Bioorganic Chemistry, Academy of Sciences of the Republic of Uzbekistan. Animals were maintained under standard laboratory conditions at 20 ± 5 ℃, 75 ± 10% relative humidity, and a 12 h light/12 h dark photoperiod, with free access to standard laboratory chow and drinking water [34,35].

Blood Pressure Measurement

Systolic arterial blood pressure was measured non-invasively in the tail artery using the SISTOLA blood pressure monitoring system (Neurobotics, Russian Federation). Rats were placed in a restraining chamber maintained at 34 ± 0.5 ℃ to ensure stable peripheral circulation. Blood pressure measurements were performed using an infrared sensor-based tail cuff system by inflating the cuff to 215 mmHg, followed by gradual deflation. The recorded data were analyzed using AcqKnowledge 4.2 for MP150 software [36,37].

Experimental Design

Experimental hypertension was induced by a single administration of adrenaline hydrochloride (0.25 mg kg^{-1})

according to previously described methods [38].

Adrenaline-induced hypertension remained stable for approximately 140 min following injection. Fifteen minutes after adrenaline administration, pomegranate extracts were administered intraperitoneally at doses ranging from 100 to 500 μg kg^{-1}. Changes in arterial blood pressure were monitored throughout the experimental period [39].

Statistical Analysis

Statistical analyses were performed using OriginPro v.8.5 SR1 (OriginLab Corporation, Northampton, MA, USA). Experimental results are presented as mean ± standard error of the mean (M ± m) obtained from n independent experiments, where *M* represents the arithmetic mean and *m* represents the standard error of the mean (SEM).

Statistical significance between experimental and control groups was evaluated using Student's *t*-test, and differences were considered statistically significant at $P < 0.05$ and $P < 0.01$.

3. Results and Discussion

Under physiological conditions (control group), the mean systolic arterial blood pressure (SBP) of the experimental rats was 123 ± 3.25 mmHg, whereas the mean diastolic arterial blood pressure (DBP) was 84 ± 3.36 mmHg. Following induction of experimental hypertension by intraperitoneal administration of adrenaline hydrochloride (0.25 mg kg^{-1}), blood pressure was measured after 30 min, at which time SBP and DBP increased significantly to 164 ± 2.38 mmHg and 116 ± 4.18 mmHg, respectively. These values are consistent with previously reported findings for adrenaline-induced hypertension models [40]. As described above, the pathogenesis of arterial hypertension involves activation of the sympathoadrenal system through α- and β-adrenergic receptors, which represent important pharmacological targets for antihypertensive therapy. Additional mechanisms include activation of the renin–angiotensin–aldosterone system (RAAS), disturbances in renal Na^+, Ca^{2+}, and K^+ transport, enhanced sodium reabsorption, endothelial dysfunction resulting in reduced synthesis of bradykinin, nitric oxide (NO), and prostacyclin, together with increased production of angiotensin II and endothelin, all of which contribute to elevated vascular resistance and blood pressure [25,1]. Experimental hypertension induced by stress factors or pharmacological agents such as adrenaline is considered a reliable, reproducible, and widely accepted model for evaluating the antihypertensive activity of biologically active compounds because it closely mimics the sympathetic overactivation observed in human hypertension [11,12,33].

Mechanistically, adrenaline activates α-adrenergic receptors located on vascular smooth muscle cell membranes, leading to stimulation of phospholipase C through G-protein signaling. This subsequently increases the production of inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 activates IP_3 receptors located on the sarcoplasmic reticulum, resulting in intracellular Ca^{2+} release and elevation of cytosolic calcium concentration. Simultaneously, stimulation of β-adrenergic receptors increases intracellular cyclic AMP (cAMP), thereby contributing to vascular smooth muscle contraction and the development of hypertension [21,12,13]. The present study demonstrated that fruit juice extracts obtained from local pomegranate (*Punica granatum* L.) cultivars exhibited dose-dependent antihypertensive activity at doses ranging from 100 to 500 mg kg^{-1}. Overall antihypertensive efficacy increased in the following order: «Oq Dona (Tuyatish) » < «Oq Shirin » < «Achchiq Dona » < «Qora Qayim » < «Qizil Anor ».

Among the tested cultivars, the «Qizil Anor » fruit juice extract showed the strongest antihypertensive activity. At the highest tested dose (500 mg kg^{-1}) under physiological conditions, the extract significantly reduced SBP and DBP by 7.32% and 10.71%, respectively, corresponding to blood pressure values of 114 ± 3.17 mmHg (SBP) and 75 ± 2.09 mmHg (DBP) compared with the control group (Table 1).

Furthermore, administration of the «Qizil Anor » fruit juice extract (500 mg kg^{-1}) to rats with adrenaline-induced experimental hypertension produced a pronounced antihypertensive effect. Sixty minutes after adrenaline injection (0.25 mg kg^{-1}), SBP and DBP were reduced by 9.15% and 12.07%, respectively, compared with the hypertensive control group, reaching values of 149 ± 3.31 mmHg (SBP) and 102 ± 4.67 mmHg (DBP) (Table 1).

These findings indicate that the antihypertensive efficacy of «Qizil Anor »is superior to that of the other local cultivars tested and suggest that its biologically active constituents may effectively attenuate adrenaline-induced increases in arterial blood pressure. The observed activity may be attributed to the high abundance of polyphenols, flavonoids, anthocyanins, ellagitannins, and other antioxidant phytochemicals known to improve endothelial function, enhance nitric oxide bioavailability, suppress oxidative stress, and modulate vascular smooth muscle contractility.

In the subsequent experiments, the antihypertensive activity of peel extracts obtained from five local pomegranate (*Punica granatum* L.) cultivars, namely «Qizil Anor », «Qora Qayim », «Oq Shirin », «Oq Dona (Tuyatish) », and «Achchiq Dona », was evaluated under both physiological conditions and adrenaline-induced experimental hypertension. The extracts were administered at doses of 100, 250, and 500 mg kg^{-1}.

The peel extracts exhibited dose-dependent antihypertensive activity, with increasing efficacy observed as the dose increased from 100 to 500 mg kg^{-1}. Among the tested cultivars, the «Qizil Anor »peel extract demonstrated the most pronounced antihypertensive effect. At the highest dose (500 mg kg^{-1}) under physiological conditions, the extract reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) by 17.07% and 25.00%, respectively, compared with the control group, corresponding to values of 102 ± 3.89 mmHg (SBP) and 63 ± 4.13 mmHg (DBP) (Table 2).

Table 1. Antihypertensive activity of fruit juice extracts obtained from local pomegranate (*Punica granatum* L.) cultivars at doses of 100, 250, and 500 mg/kg (Mean ± SEM)

No	Extract		Baseline blood pressure (mmHg)					
	Pomegranate cultivar	Dose (mg/kg)	Extract		Experimental hypertension + extract			
					30 min after administration		60 min after administration	
			SBP	DBP	SBP	DBP	SBP	DBP
1.	Qizil anor	100	118 ±3,05	80 ±3,12	159 ±3,18	110 ±4,19	150 ±4,46*	109 ±4,83*
		250	115 ±4,52*	76 ±3,63	158 ±3,02	109 ±3,18	152 ±4,11**	108 ±3,89*
		500	114 ±3,17**	75 ±2,09*	156 ±4,14*	108 ±4,72*	149 ±3,31**	102 ±4,67**
2.	Qora Qayin	100	119 ±4,68	82 ±3,73	160 ±3,44	115 ±3,85	153 ±4,10*	113 ±3,74*
		250	118 ±4,24	78 ±4,27	159 ±3,12	113 ±4,45	152 ±4,27**	107 ±4,35*
		500	116 ±3,01*	76 ±3,14	158 ±3,15	110 ±4,51*	150 ±3,13**	101 ±4,67**
3.	Oq Shirin	100	121 ±3,18	83 ±4,02	162 ±4,16	113 ±3,80	157 ±4,18*	112 ±3,16
		250	120 ±4,53	80 ±3,19	162 ±4,05	112 ±3,51	155 ±4,10*	110 ±3,42
		500	118 ±3,28	78 ±4,05	161 ±3,15	110 ±4,15*	153 ±3,12*	106 ±4,11*
4.	Oq Dona (Tuyatish)	100	122 ±2,40	83 ±4,18	163 ±3,50	115 ±3,19	161 ±3,57*	113 ±4,76
		250	121 ±4,56	81 ±4,55	163 ±4,87	114 ±3,55	158 ±3,00*	113 ±3,48
		500	120 ±3,11	79 ±3,31	162 ±3,15	112 ±4,16	154 ±4,19*	107 ±3,52*
5.	Achchiq Dona	100	120 ±3,65	82 ±2,96	161 ±3,45	114 ±4,17	155 ±3,42*	110 ±4,04
		200	119 ±4,01	79 ±3,09	161 ±4,16	114 ±3,40	153 ±4,16*	108 ±4,13
		300	117 ±3,08*	77 ±3,12	160 ±3,17	111 ±4,15*	152 ±3,07**	103 ±3,46**

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure. In the normotensive control group, SBP and DBP were 123 ±3.25 mmHg and 84 ±3.36 mmHg, respectively. In the experimental hypertension group, SBP and DBP were 164 ±2.38 mmHg and 116 ±4.18 mmHg, respectively. Data are presented as mean ±SEM (n = 3–5). P < 0.05 and P < 0.01 indicate statistically significant differences compared with the control group.

Table 2. Antihypertensive activity of peel extracts obtained from local *Punica granatum* L. cultivars at doses of 100–500 mg/kg (Mean ± SEM)

No	Extract		Baseline blood pressure (mmHg)					
	Pomegranate cultivar	Extract	Extract		Extract			
					30 min after administration		60 min after administration	
			SBP	DBP	SBP	DBP	SBP	DBP
1.	Qizil anor	100	104 ±3,47*	65 ±3,48*	145 ±3,23*	101 ±3,33*	144 ±4,23**	100 ±4,17**
		250	105 ±3,18*	65 ±3,74*	144 ±4,82*	97 ±3,16**	141 ±4,87**	99 ±3,10**
		500	102 ±3,89*	63 ±4,13*	142 ±3,12*	94 ±4,45**	138 ±3,16**	90 ±3,57**
2.	Qora Qayin	100	105 ±4,18*	67 ±4,05*	146 ±4,01*	102 ±3,05*	145 ±3,12**	101 ±3,08**
		250	106 ±4,83*	66 ±4,23*	145 ±3,07*	98 ±4,13**	142 ±4,15**	101 ±4,54**
		500	104 ±4,66*	64 ±3,08*	144 ±4,10*	96 ±3,05**	141 ±3,80**	95 ±4,60**
3.	Oq Shirin	100	108 ±3,17*	69 ±4,11*	148 ±4,79*	104 ±4,82*	148 ±3,81**	102 ±3,22**
		250	108 ±4,46*	68 ±4,41*	147 ±3,50*	100 ±4,17*	144 ±4,17**	103 ±4,47*
		500	106 ±4,35*	66 ±3,42*	146 ±4,32*	98 ±3,18**	143 ±3,11**	97 ±4,43**
4.	Oq Dona (Tuyatish)	100	110 ±3,14*	70 ±3,29*	150 ±3,18*	106 ±3,27*	150 ±4,16**	103 ±4,08*
		250	109 ±4,16*	69 ±3,15*	149 ±4,57*	101 ±3,32*	145 ±3,16**	104 ±3,14*
		500	107 ±3,15*	67 ±4,90*	147 ±3,21*	100 ±4,20**	144 ±4,96**	98 ±3,15**
5.	Achchiq Dona	100	106 ±4,54*	68 ±3,16*	147 ±3,19*	103 ±4,18*	146 ±4,11**	100 ±4,46**
		200	107 ±3,75*	67 ±3,41*	146 ±4,65*	99 ±3,10**	143 ±3,75**	102 ±3,40**
		300	105 ±3,63*	65 ±4,14*	145 ±3,12*	97 ±4,53**	142 ±4,83**	96 ±3,65**

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure. In the normotensive control group, SBP and DBP were 123 ±3.25 mmHg and 84 ±3.36 mmHg, respectively. In the experimental hypertension control group, SBP and DBP were 164 ±2.38 mmHg and 116 ±4.18 mmHg, respectively. Data are expressed as mean ±SEM (n = 3–5). P < 0.05 and P < 0.01 indicate statistically significant differences compared with the experimental hypertension control group.

Similarly, administration of the «Qizil Anor» peel extract (500 mg kg⁻¹) significantly attenuated adrenaline-induced hypertension. Sixty minutes after injection of adrenaline hydrochloride (0.25 mg kg⁻¹), SBP and DBP were reduced by 15.85% and 22.41%, respectively, compared with the hypertensive control group, reaching 138 ± 3.16 mmHg (SBP) and 90 ± 3.57 mmHg (DBP) (Table 2).

In the subsequent experiments, the antihypertensive activity of seed extracts obtained from five local pomegranate (*Punica granatum* L.) cultivars, namely «Qizil Anor», «Qora Qayim», «Oq Shirin», «Oq Dona (Tuyatish)», and «Achchiq Dona», was evaluated under both physiological conditions and adrenaline-induced experimental hypertension. The extracts were administered at doses of 100, 250, and 500 mg kg⁻¹.

The seed extracts exhibited dose-dependent antihypertensive activity, with increasing efficacy observed as the dose increased from 100 to 500 mg kg⁻¹. Among the tested cultivars, the «Qizil Anor» seed extract demonstrated the greatest antihypertensive effect. At the highest dose (500 mg kg⁻¹) under physiological conditions, the extract significantly reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) by 12.20% and 19.05%, respectively, compared with the control group, corresponding to values of 108 ± 4.74 mmHg (SBP) and 68 ± 3.18 mmHg (DBP) (Table 3).

Furthermore, administration of the «Qizil Anor» seed extract (500 mg kg⁻¹) significantly attenuated adrenaline-induced hypertension. Sixty minutes after administration of adrenaline hydrochloride (0.25 mg kg⁻¹), SBP and DBP were reduced by 10.97% and 13.79%, respectively, compared with the hypertensive control group, reaching 146 ± 3.12 mmHg (SBP) and 100 ± 4.33 mmHg (DBP) (Table 3).

Arterial hypertension is a multifactorial disorder characterized by complex molecular and neurohumoral regulatory mechanisms. The elevation of vascular pressure is primarily mediated through the coordinated activation of the hypothalamus, reticular formation, peripheral sympathetic ganglia, sympathetic nerve fibers, adrenal medulla, and the adrenaline-dependent sympathetic system, together with the renin–angiotensin–aldosterone system (RAAS) and modulation of nitric oxide (NO) production by vascular endothelial cells. Activation of these pathways stimulates sympathetic neurotransmission, resulting in the release of norepinephrine, which activates α_1-adrenergic receptors on vascular smooth muscle cells and initiates a cascade of vasoconstrictor signaling events [1,2,3].

Previous studies have demonstrated that pomegranate peel extract administered at 400 mg kg⁻¹ exhibits significant antihypertensive activity in vivo and potent vasorelaxant effects in vitro in rats with norepinephrine-induced experimental hypertension [5,16]. Similarly, pomegranate seed extract has also been reported to possess marked antihypertensive activity in experimental animal models [7,9].

Table 3. Antihypertensive activity of seed extracts obtained from local *Punica granatum* L. cultivars at doses of 100, 250, and 500 mg/kg (Mean ± SEM)

No	Extract		Baseline blood pressure (mmHg)					
	Pomegranate cultivar	Extract	Extract		Pomegranate cultivar			
					30 min after administration		60 min after administration	
			SBP	DBP	SBP	DBP	SBP	DBP
1.	Qizil anor	100	111 ±3,57*	72 ±4,90*	151 ±4,80*	107 ±4,42*	153 ±3,09*	105 ±3,04*
		250	110 ±3,42*	70 ±3,17*	150 ±3,40*	102 ±4,02*	149 ±4,17**	106 ±4,45*
		500	108 ±4,74*	68 ±3,18*	148 ±4,12*	101 ±3,18*	146 ±3,12**	100 ±4,33**
2.	Qora Qayin	100	112 ±4,40*	74 ±4,10*	152 ±3,41*	108 ±3,35*	154 ±3,57*	106 ±4,50*
		250	110 ±4,12*	72 ±3,27*	151 ±3,47*	106 ±3,47*	150 ±3,18**	108 ±3,13*
		500	109 ±4,78*	70 ±4,14*	150 ±4,67*	104 ±4,15*	147 ±4,32**	102 ±3,47**
3.	Oq Shirin	100	116 ±4,42	76 ±4,17	155 ±3,14	112 ±3,28	158 ±3,32*	110 ±4,12*
		250	113 ±3,15*	73 ±3,25*	154 ±4,12*	110 ±3,24	154 ±3,27*	111 ±3,43*
		500	112 ±4,01*	72 ±3,04*	153 ±4,55*	108 ±4,75*	150 ±4,11**	104 ±3,17*
4.	Oq Dona (Tuyatish)	100	115 ±4,42	78 ±3,45	157 ±4,11	114 ±4,10	160 ±4,68*	111 ±3,16*
		250	112 ±3,15*	75 ±4,60	156 ±4,16	113 ±4,17	156 ±4,12*	112 ±4,35*
		500	110 ±3,54*	74 ±3,16*	154 ±3,17*	110 ±3,32	153 ±3,83*	105 ±4,10*
5.	Achchiq Dona	100	116 ±3,87	73 ±4,19*	152 ±3,26*	110 ±4,37*	155 ±4,16*	108 ±3,56*
		200	114 ±3,15*	71 ±4,47*	153 ±4,42*	108 ±4,51*	152 ±4,14*	110 ±4,73*
		300	113 ±4,36*	69 ±3,86*	152 ±3,18*	106 ±3,19*	148 ±3,16**	103 ±4,05*

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure. In the normotensive control group, SBP and DBP were 123 ±3.25 mmHg and 84 ±3.36 mmHg, respectively. In the experimental hypertension control group, SBP and DBP were 164 ±2.38 mmHg and 116 ±4.18 mmHg, respectively. Data are expressed as mean ±SEM (n = 3–5). P < 0.05 and P < 0.01 indicate statistically significant differences compared with the experimental hypertension control group.

Several investigators have suggested that the antihypertensive effects of plant-derived extracts against adrenaline-induced hypertension may, at least in part, be mediated through α_2-adrenergic receptor blockade [40,33]. In addition, pomegranate peel extract has been shown to significantly reduce systolic blood pressure in vivo [15,17,20]. Clinical evidence further supports these findings. Daily consumption of pomegranate juice for 4 weeks has been reported to reduce systolic blood pressure from 120.3 mmHg to 115.6 mmHg [8].

Likewise, supplementation with Pomanox® (ProbelteBio, Spain), a standardized pomegranate extract rich in punicalagin, flavonoids, and ellagic acid, for 8 weeks significantly decreased both systolic and diastolic blood pressure in human subjects [9].

The antihypertensive activity of extracts derived from both vegetative and reproductive organs of pomegranate is believed to be largely attributable to their high polyphenol and flavonoid contents, which improve vascular endothelial function [21,25,30]. Moreover, pomegranate juice has been shown to inhibit platelet aggregation and reduce arterial blood pressure, effects that have been associated primarily with its polyphenolic [21,2,13]. The antihypertensive mechanisms of flavonoids and other dietary polyphenols have now been extensively documented [22,26].

Oxidative stress is another central mechanism involved in hypertension. Excessive production of reactive oxygen species (ROS) reduces nitric oxide bioavailability and promotes endothelial dysfunction. Polyphenolic compounds have been reported to exert antihypertensive effects by scavenging ROS, preserving endothelial nitric oxide synthase (eNOS) activity, and restoring NO-mediated vascular relaxation [23,25,28].

Recent studies have further demonstrated that the antihypertensive activity of pomegranate extracts involves activation of AMP-activated protein kinase (AMPK) and modulation of the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2). These signaling pathways improve mitochondrial function, attenuate oxidative stress, and enhance vascular homeostasis [1]. Both experimental and clinical investigations have also confirmed that pomegranate extracts significantly reduce systolic and diastolic blood pressure by inhibiting the activity of angiotensin-converting enzyme (ACE), a key regulator of the renin–angiotensin system [5,6]. Furthermore, pomegranate juice exhibits broad pharmacological activity by suppressing ACE activity under both physiological and hypertensive conditions while simultaneously modulating intracellular signaling pathways involved in blood pressure regulation [11,23]. The antihypertensive effects of pomegranate extracts have therefore been attributed to a combination of mechanisms, including inhibition of ACE activity, enhancement of nitric oxide production, improvement of endothelial function, and antioxidant protection mediated by polyphenolic constituents [25,30,40]. Clinical studies have reported that consumption of 150 mL day^{-1} of pomegranate juice by patients with arterial hypertension reduced systolic and diastolic blood pressure by approximately 7% and 6%, respectively. These beneficial effects are believed to result from enhanced endothelial NO production together with potent antioxidant activity [31,32,33].

4. Conclusions

Overall, the available evidence indicates that the antihypertensive activity of plant-derived extracts is mediated through multiple complementary mechanisms. These include blockade of voltage-dependent Ca^{2+} channels, activation of Ca^{2+}-activated K^+ (KCa) channels, inhibition of α- and β-adrenergic receptors, stimulation of endothelial nitric oxide synthase (eNOS) and NO production, activation of endogenous antioxidant defense systems, and suppression of ACE activity and endothelin synthesis [35].

The present study demonstrated that juice, peel, and seed extracts obtained from five local pomegranate (*Punica granatum* L.) cultivars («Qizil Anor», «Qora Qayim», «Oq Shirin», «Oq Dona (Tuyatish)» and «Achchiq Dona») possess significant in vivo antihypertensive activity.

The antihypertensive effects of the extracts were dose-dependent over the range of 100–500 mg kg^{-1}, with the overall efficacy increasing in the following order:

«Oq Dona (Tuyatish)» < «Oq Shirin» < «Achchiq Dona» < «Qora Qayim» < «Qizil Anor».

The extracts significantly reduced both systolic and diastolic blood pressure under physiological conditions as well as in rats with adrenaline-induced experimental hypertension measured 60 min after administration of adrenaline hydrochloride (0.25 mg kg^{-1}).

These findings provide experimental evidence supporting the therapeutic potential of local pomegranate cultivars as a valuable natural source of antihypertensive bioactive compounds. The results may serve as a scientific basis for the future development of functional foods, nutraceuticals, dietary supplements, and novel antihypertensive phytopharmaceuticals derived from pomegranate extracts.

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