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Calcium-channel blockade-mediated blood pressure-lowering and vasorelaxant effects of *Brassica oleracea*

Mahwish Haroon[1], Mueen Ahmad Chaudhry[2*], Munnaza Ambreen[2] and Muhammad Sajjad Haider[3]

[1]Faculty of Pharmacy, The University of Lahore, Lahore, 54000-Pakistan
[2]Department of Pharmacy, Green International University, Lahore, 54000-Pakistan
[3]School of Pharmacy, Multan University of Science and Technology, Multan, 60600-Pakistan

Abstract: **Background**: *Brassica oleracea* L. (Brassicaceae), commonly known as cabbage, is usually used for dietary purposes and is also known for many medicinal uses, including blood pressure. **Objectives**: The current research study aimed to authenticate the traditional claims of B. oleracea L. for hypertension on a scientific basis using *in vivo* and *in vitro* pharmacological techniques. **Methods**: Crude extract of *B. oleracea* L. was evaluated for its hypotensive and vasorelaxant effects in normotensive anesthetized wistar rats using an invasive blood pressure-measuring technique and isolated rat thoracic aorta, respectively. **Results**: Normotensive anaesthetized rats used in experiments showed a gradual decrease in blood pressure parameters and heart rate when treated with Bo.Cr (0.1–100 mg/kg) comparable to verapamil (0.01–30 mg/kg). Whereas, in isolated aortic tissue, Bo.Cr (0.01-3 mg/ml) exhibited complete relaxation on high K^+ [80 mM] and phenylephrine (1 µM)-mediated contractions. Crude extract at doses of 0.3 and 1 mg/ml also showed a reduction in response to Ca^{2+} concentration-response curves. **Conclusion**: Results indicate calcium channel-blocking activity, a possible cause of the blood pressure-lowering and vasodilator effects of *B. oleracea.*

Keywords: *Brassica oleracea*; Hypotension; Phenylephrine; Vasodilation; Verapamil

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INTRODUCTION

Cardiovascular diseases (CVD) are among the leading global cause of death. Most of these deaths attributed to hypertension that majorly affect low- and middle-income countries (Al-Makki *et al*., 2022). 1.4 billion adults aged 30–79 have hypertension worldwide (2024 data) (Celora *et al*., 2025). The global epidemiology of hypertension shows that hypertension prevalence increased in low- and middle-income countries (Mills *et al*., 2020). In Pakistan factors associated with hypertension includes socio-demographic, lifestyle and health-related risk factors contributing to hypertension (Riaz *et al*., 2021). According to two enormous studies, the prevalence of hypertension in Pakistan is about 26% (Elahi *et al*., 2023, Ajani *et al*., 2021).

In low-income countries, the poor adherence and discontinuation of antihypertensive treatment, often due to perceived side effects, drug costs, lack of understanding of the need for lifelong medication and general mistrust or lack of information (Jeemon *et al*., 2021). In recent years, the search for safer, more affordable antihypertensive agents has spurred scientific exploration of commonly consumed vegetables and traditionally used medicinal plants.

Brassica oleracea L. (Brassicaceae), commonly known as cabbage (Lucic *et al*., 2023), is usually used for dietary purposes but is also known for many medicinal uses, some of which have been reported; however, the effectiveness regarding blood pressure has not been evaluated to date. The current research study aimed to authenticate the traditional claims about the medicinal use of B. oleracea L. on a scientific basis using *in vivo* and *in vitro* pharmacological techniques (Piragine *et al*., 2022).

MATERIALS AND METHODS

Plant material and extraction

B. oleracea L. bulbs were purchased locally and identified (GC.Herb.Bot. 2939). Fresh leaves were separated from the bulb, dried in a shed and then coarsely powdered for maceration. The crude extract was prepared in 70% aqueous ethanolic solution via cold maceration and concentrated using a rotary evaporator (Mahmood *et al*., 2017). The extract yield 9% approx. that was stored in airtight amber glass containers at 4°C and protected from light. For each rat dose of crude extract of *B. oleracea* (Bo.Cr) was freshly dissolved in normal saline and passed through sterilized filter (0.22 µm) before injection. All chemicals used in experimental work were of lab grade and acquired from an authentic source. Verapamil (Sigma-Aldrich, St. Louis, MO 63103, USA) was used as the standard drug and stock solution (10^{-2} M) was prepared in distilled water and stored at -20°C. Dilutions of the standard drug and crude extract were prepared freshly for each protocol.

Adult male albino wistar rats (200–250 g) were maintained at controlled housing conditions and provided with standard diet and filtered water in animal house of the Faculty of Pharmacy, The University of Lahore, Lahore, Pakistan. Before experimental work animals were

*Corresponding author: e-mail: mueen.ahmad@giu.edu.pk

keept for overnight fasting but provided with filtered water *ad libitium.* All experiments were conducted according to the guidelines of the Laboratory Animal Resources of the National Research Council, as previously followed by Qureshi *et al*. (2015).

Invasive measurement of blood pressure in rats

Adult male albino rats (n=18) were randomly segregated in three groups with n=6 in each groups and taged as normal control, test group and positive control goup, used to test the effect of vehicle, crude extract and standard darug (verapamil), respectively. Blood pressure in anesthetized rats was evaluated using an invasive blood pressure measurement method previously described by Chaudhry *et al*. (2021b). Each rat was anesthetized via intraperitoneal injections of diazepam (5 mg/kg) and ketamine (80-100 mg/kg) and fixed in the spine position. Blunt dissection was performed to catheterize blood vessels. The drug was administered through the jugular vein and effects were observed via a carotid artery connected to a pressure transducer (MLT0699) and a Power Lab data acquisition system (AD Instruments, Australia).

Vasorelaxation on isolated rat thoracic aorta

Albino rats (n=24) were randomly segregated in four groups with n=6 for each protocol of vasorelaxnt effect of crude extract and the standard drug. The vasorelaxant effect of *B. oleracea* was assessed using the method previously described by Chaudhry *et al*. (2021a). Thoracic aorta from the descending zone was quickly detached and placed in Petri dish, already filled with Kreb's solution. A tissue ring with a length of 2-3 mm was fixed at one end and attached to an isometric force transducer (TRI201AD Instrument, Australia) at the other end under 1g resting tension in a 20 ml organ bath comprising Kreb's solution, continually oxygenated and maintained at 37°C. Vasorelaxant effects of *B. oleracea* was evaluated in cumulative concentrations on sustained aortic contractions mediated by potassium chloride; (KCl; 80 mM) and phenylephrine (PE; 1 µM) (Hu *et al*., 2018). To ensure the calcium channel blockade activity, Ca^{2+} concentration-response curves (CRC) were also built. After the equilibrium period (50-60 min), the response of the aortic ring was stabilized by repeated exposure to high K^+ (80 mM) until homogeneous responses were achieved. Now Krebs solution was replaced with Ca^{2+} free Kreb's solution containing EDTA (0.1 mM) for 20-30 min to eliminate the tissue's calcium. In the next step, the former solution was again switched to another Krebs solution, enriched with K^+ and free of Ca^{2+} and allowed for 40-50 min to achieve the baseline tension (1 g). Control CRCs were prepared with CaCl2 to assess the tissue response to Ca^{2+}. After taking two comparable control CRCs of Ca^{2+}, the whole procedure was repeated, followed by a 40-50 min incubation with ascending concentrations of crude extract/control drug. A shift toward the right in the Ca^{2+} curve would ensure calcium-blocking activity.

Statistical analysis

Results are presented as mean ± standard error of the mean (SEM). Statistical analyses were performed using GraphPad Prism software. One-way ANOVA followed by Dunnett's post hoc test was applied and differences were considered statistically significant at a 95% confidence level when $p < 0.05$. Levels of significance are indicated as $*p < 0.05$, $**p < 0.01$ and $***p < 0.001$.

RESULTS

Effects on blood pressure in anesthetized rats

After intravenous administration of Bo.Cr (0.1-100 mg/kg) in normotensive anesthetized rats, a dose-dependent decrease was seen in systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) (Fig. 1A). Whereas decrease in heart rate (HR) was trailed by increase at higher doses (30 and 100 mg/kg) (Fig. 1B). A significant decrease in SBP (mean + SEM) (65.55±2.07%), DBP (65.80±2.49%) and MAP (65.79±2.42%) was started at 30 mg/kg and on heart rate it was found as 66.34±20.34% at 3 mg/kg (n=6) (Fig. 2). No considerable changes were seen on BP or HR in vehicle control rats (data not shown).

Similar effects were also observed after the administration of verapamil (0.01-30 mg/kg) in normotensive anesthetized rats, status of blood pressure was observed (Fig. 3) with significant reduction on SBP was found as (mean + SEM) 43.75±4.39%, DBP 45.46±1.46%, MAP 44.89±2.04% started at 3mg/kg and significant effect on heart rate was measured as 68.51±14.12%, started at 30 mg/kg (n=5) (Fig. 4).

Effects on rat's isolated aorta

To evaluate the dilatory effects on blood vessels, crude extract was tried on high K^+ [80 mM] and PE (1 µM) mediated contraction on isolated thoracic aorta of rat. A concentration-dependent (0.01-3 mg/ml) dilation was seen with the percentage relaxation (mean + SEM) 97.09±1.34, 94.95±2.32, 89.91±3.22, 81.82±5.20, 58.64±8.75% and 0.00±0.00% on high K^+ [80 mM] (n=5) and 97.41±2.59, 96.64±3.36, 92.74±1.44, 84.94±8.99, 39.49±11.48% and 0.00±0.00% on phenylephrine (1 µM) mediated contractions at 0.01, 0.03, 0.1, 0.3, 1 and 3 mg/ml, with EC_{50} value of 1.16(95% CI, 0.86 - 1.22, n=5) and 0.74(0.62 - 0.95, n=5), respectively (Fig. 5A). Similar to verapamil with percentage relaxation 83.82±6.71, 74.19±8.64, 56.08±6.09, 36.81±6.00% with EC_{50} value of 0.16(0.08 - 0.15, n=5) on high K^+ [80 mM] induced aortic contraction and 74.42±2.52, 67.79±1.55, 51.70±2.02, 30.53±6.53% with EC_{50} value of 0.12(0.06 - 0.11, n=5) on phenylephrine (1 µM) induced aortic contraction at 0.01, 0.03, 0.1, 0.3 (Fig. 5B).

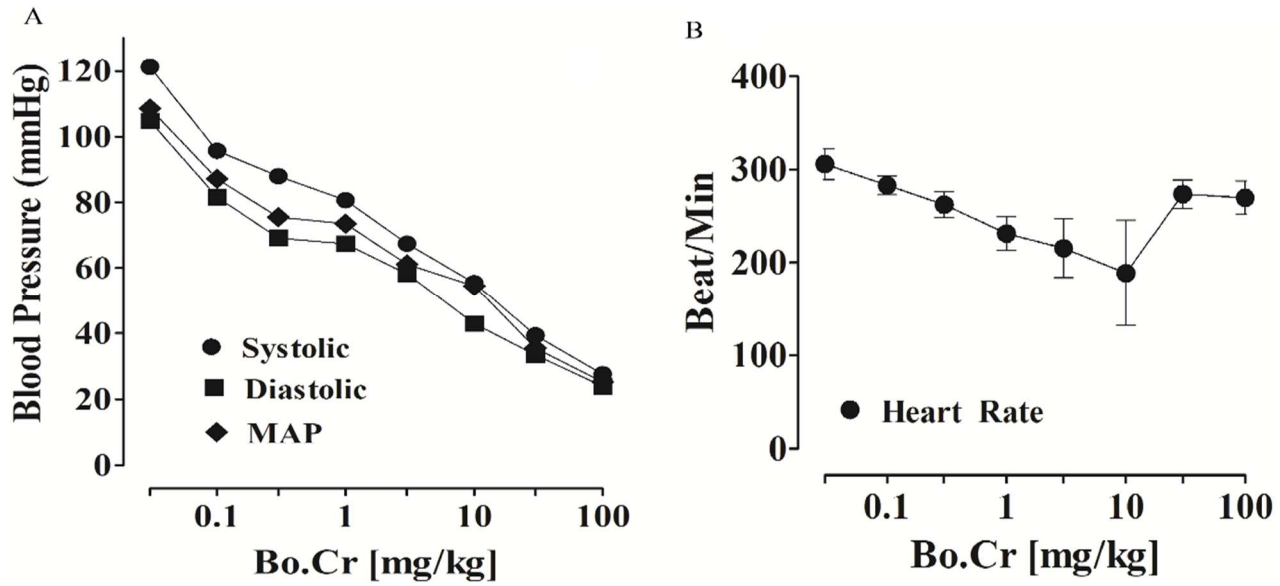

Fig. 1: Dose-dependent effects of aqueous ethanolic extract of B. oleracea (Bo.Cr) on (A) blood pressure and (B) heart rate in normotensive anesthetized rats.

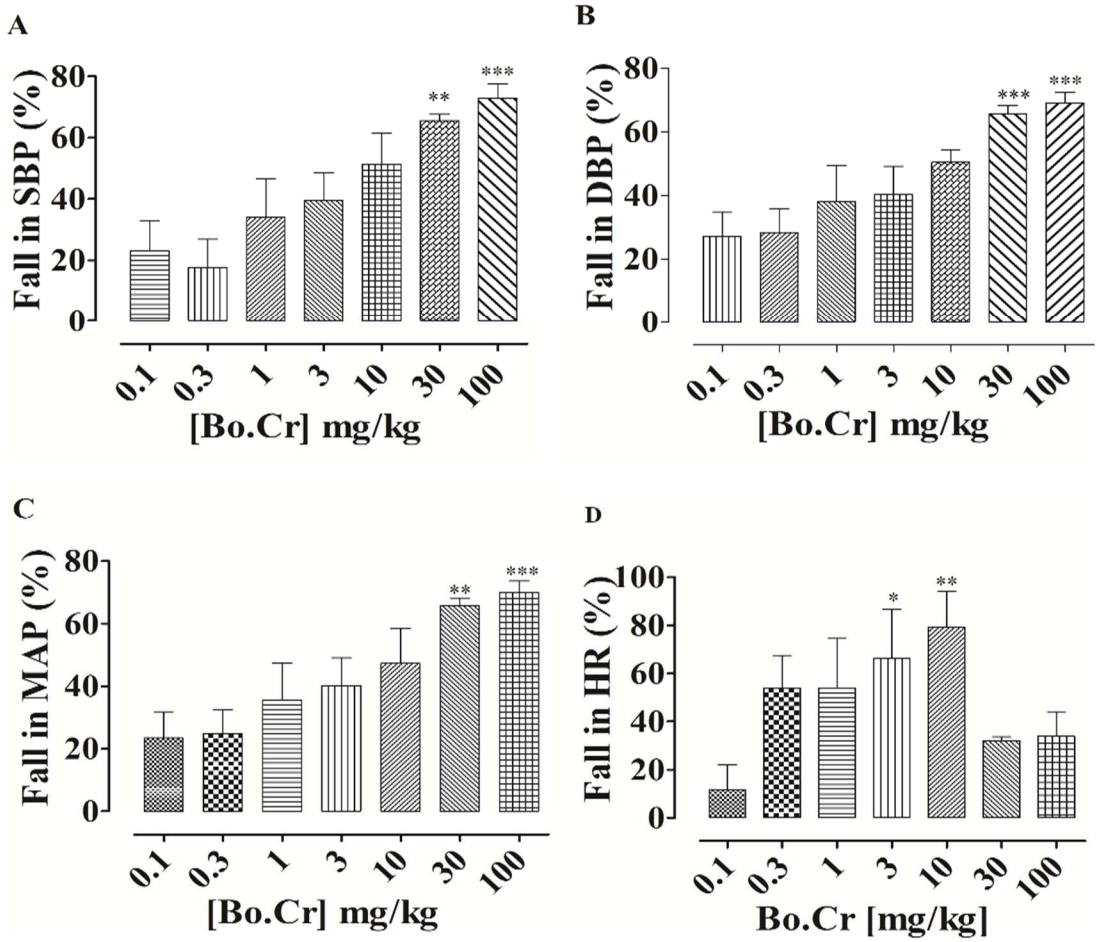

Fig. 2: Dose-dependent %age decrease in (a) systolic blood pressure (b) diastolic blood pressure (c) mean arterial pressure and (d) heart rate after intravenous administration of aqueous ethanolic extract of B. oleracea (Bo.Cr). Where significance $p<0.1$, $p<0.01$ and $p<0.001$.

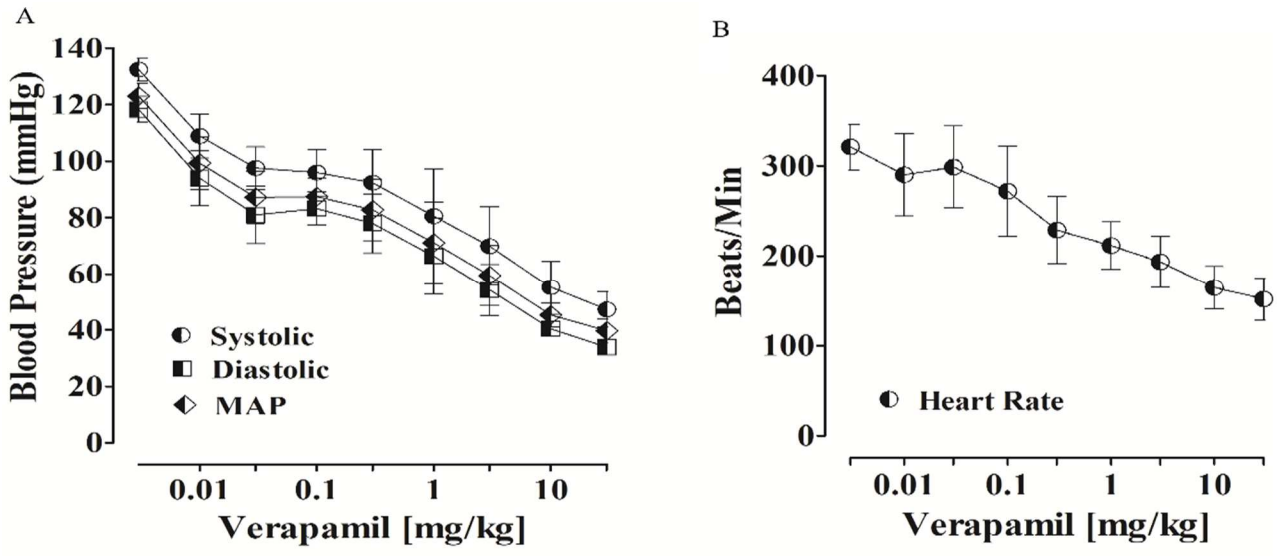

Fig. 3: Dose-dependent effects of verapamil on (A) blood pressure and (B) heart rate in normotensive anesthetized rats.

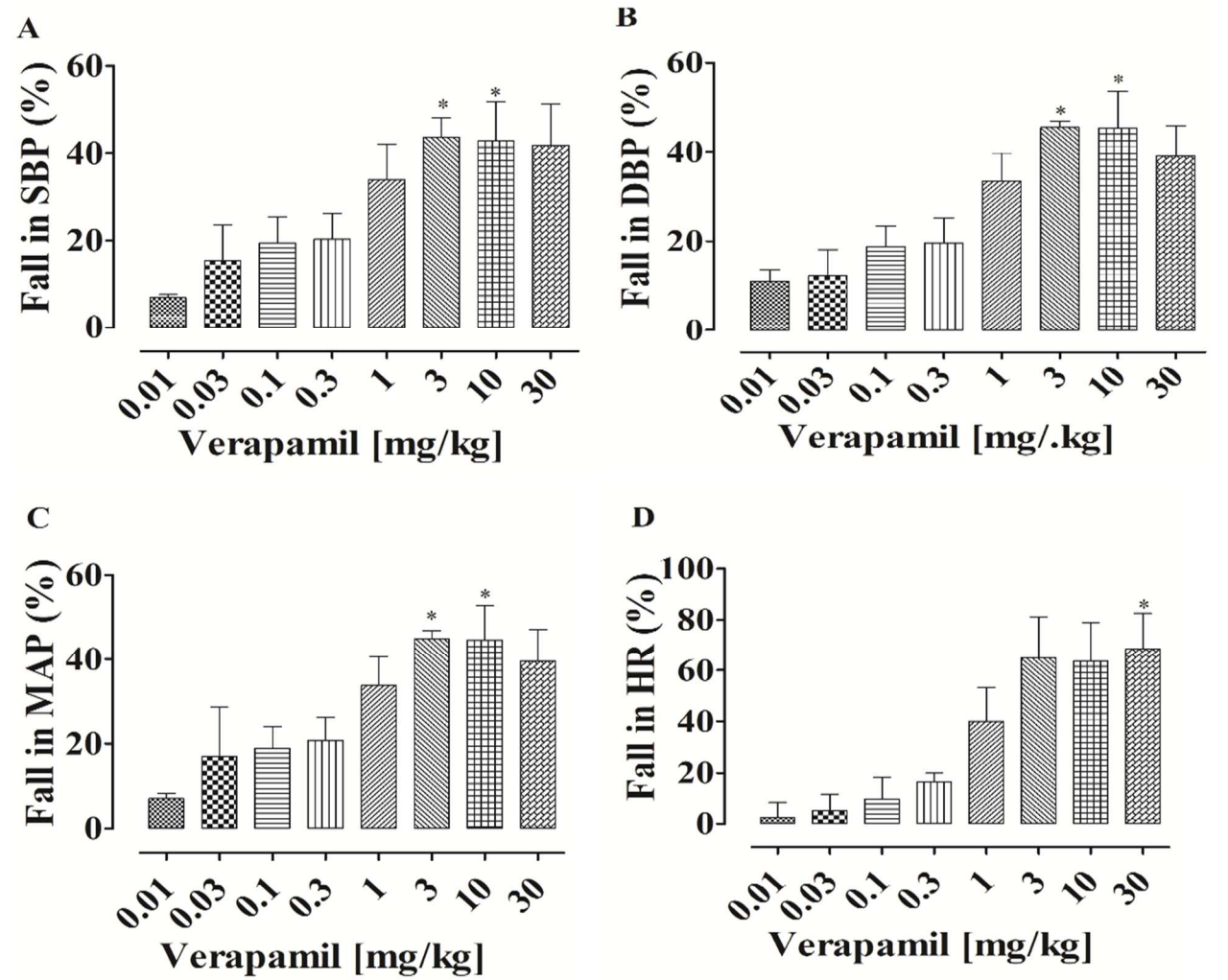

Fig. 4: Dose-dependent %age decrease in (a) systolic blood pressure (b) diastolic blood pressure (c) mean arterial pressure and (d) heart rate after intravenous administration of verapamil. Where significance $p<0.1$, $p<0.01$ and $p<0.001$.

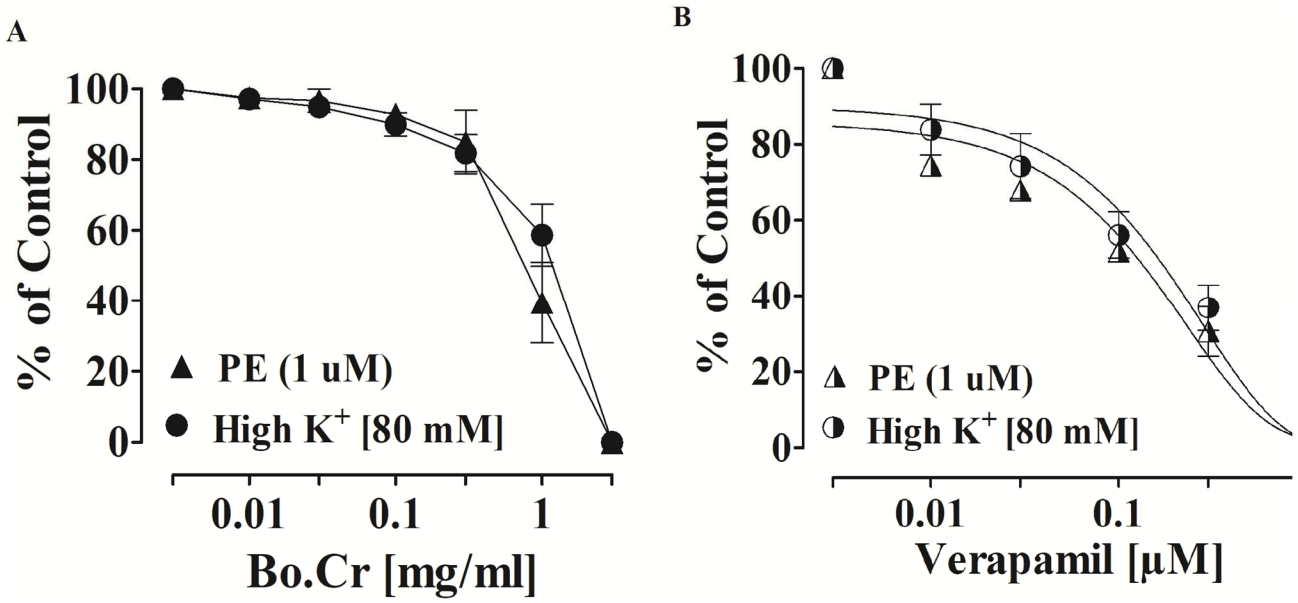

Fig. 5: Concentration-dependent decreasing effects exhibited by (A) aqueous ethanolic extract of B. oleracea (Bo.Cr) and (B) verapamil on high K+ [80 mM] and phenylephrine (1 µM) mediated contractions.

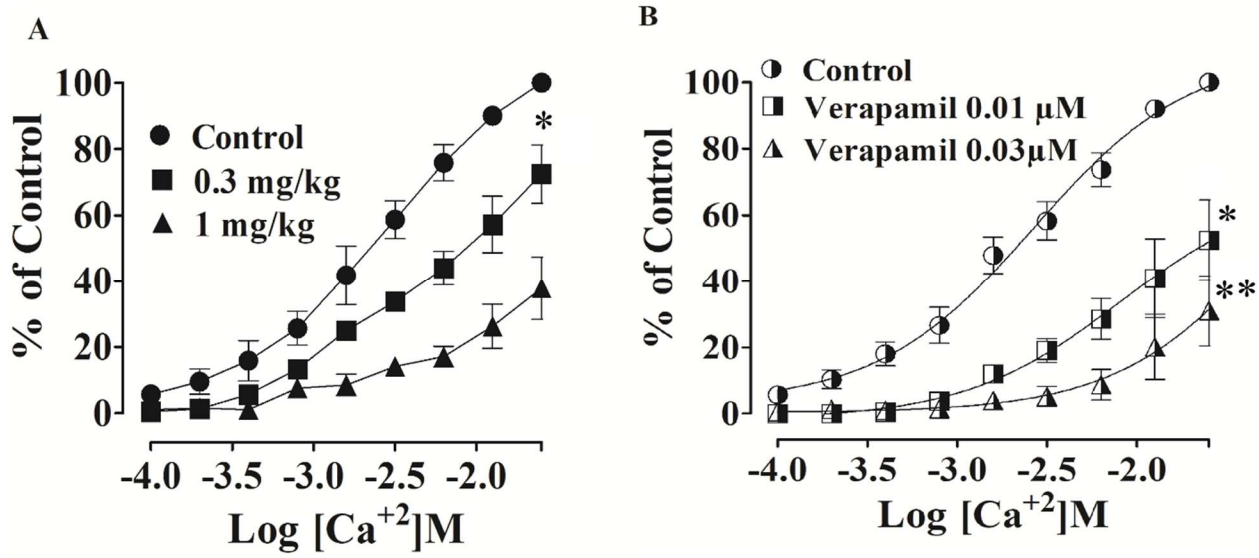

Fig. 6: Concentration-dependent inhibitory effects of (A) aqueous ethanolic extract of B. oleracea (Bo.Cr) and (B) verapamil on Ca2+ concentration-response curves. Where significance * = p<0.1 and ** = p<0.01.

Calcium blocking activity

Bo.Cr triggered a concentration-dependent (0.3 and 1 mg/ml) shift towards right side in the Ca^{2+} concentration-response curves, with the reduction of maximum response (Emax) as (mean + SEM) 72.44±8.82% and 37.86±9.54% on 0.3 and 1 mg/ml respectively (n=5) (Fig. 6A), comparable to verapamil with the reduction of maximum response 52.47± 12.12% and 31.02± 10.58% at 0.01 and 0.03 µM (n=5) (Fig. 6B).

DISCUSSION

Results of present study revealed that administering the aqueous ethanolic extract of *Brassica oleracea* L. (Bo.Cr) intravenously, gave a dose-dependent (0.1-100 mg/kg) fall in diastolic, systolic and, mean arterial pressure in normotensive rats, comparable to verapamil (0.01-30 mg/kg): a known calcium channel blocker (Akhtar and Humaira, 2022), indicate the hypotensive potential of *B. oleracea* (Duke and Beckstrom-Sternberg, 2022). A significant response (p<0.01 and p<0.001) was observed at later doses (30 and 100 mg/kg) across all parameters; however, the level of significance was observed at earlier doses (3 and 10 mg/kg) for heart rate.

The extract showed a depressant effect on the heart, characterized by decreased heart rate and cardiac contraction, as both diastolic and systolic blood pressure

decreased (Hall and Hall, 2020). Heart rate was initially decreased (188.53±56.95), then decreased further, followed by an increase in (273.57±15.26 and 269.72±18.15) as at higher doses (30mg/kg and 100mg/kg) in normotensive anesthetized rats, is possibly mediated by vasodilation-induced reflex tachycardia, indicating the presence of strong vasodilator mechanism behind the hypotensive effect of Bo.Cr (Vatner *et al*., 1974).

Since the blood pressure is the product of cardiac output and peripheral resistance (Saugel and Sessler, 2021). A number of drugs used to decrease the blood pressure having different mechanism of action(s), ultimately end up with either a decrease in peripheral resistance or cardiac output. So, calcium channel blockers bind to L-type calcium channels in vascular smooth muscles and cardiac muscles, leading to a fall in blood pressure by decreasing cardiac output and peripheral resistance (Katzung *et al*., 2004).

A similar pattern was observed with verapamil administration, indicating the efficiency of Bo.Cr in the regulation of blood pressure but also creates a perception about the possible occurrence of calcium channel-blocking components in crude extract. To make the perception clearer, the study was followed by in vitro experiments, which showed that the vasorelaxant activity of B. oleracea provided additional evidence of its hypotensive activity. The vasorelaxant effect of the crude extract was tested on high K+ (80 mM)- and PE (1 µM)-triggered aortic contraction. It is conventional that K^+ with the dose of 80 mM depolarizes the cell membrane of smooth muscles, results in increased cytosolic Ca^{2+} by activation of voltage-dependent Ca^{2+} channels, causes constriction of vascular smooth muscles (Chaudhry *et al*., 2021b). Whereas aortic contraction induced by PE also involves an increased level of Ca^{2+}. It happens when PE converts phosphatidylinositol to inositol-1,4,5-trisphosphate by activating α1-adrenergic receptors; in turn, this increases Ca2+ release from intracellular stores and, in the last step of this mechanism, L-type voltage-dependent Ca^{2+} channels increase the influx of Ca^{2+} (Aslam *et al*., 2016). *B. oleracea* exhibit complete relaxation on high K^+ and PE (1 µM) mediated aortic contraction at same concentration (3 mg/kg) evoke the possibility for the existence of Ca^{2+} channel blocking activity. Now, the perception of calcium-blocking activity has become stronger when Bo.Cr concentrations (0.3 and 1 mg/kg) shifted Ca2+ concentration-response curves to the right, analogous to verapamil (0.01 and 0.03 µM) (Malik *et al*., 2017).

CONCLUSION

To conclude the above discussion, it can be stated that the crude extract of *B. oleracea* L. exhibited blood pressure-lowering activity in normotensive anesthetized rats and this was supported by *in vitro* vasorelaxant effects of Bo.Cr, possibly arbitrated by Ca^{2+} channel blocking activity. The present study disclosed pharmacologic validation to the traditional use of B. *oleracea* in hypertension. However, more work is required on the mechanism and on its effects on the heart.

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Authors' contributions
MAC: Conceived and designed the study; MSH and MAC: Planned the study layout, analyzed the data and supervised the study; MA: Carried out the experimental work and prepared the initial draft; MH: Conducted literature survey, helped in experimental work and result compilation. All authors critically reviewed and approved the final draft.

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Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
All experiments were conducted according to the guidelines of the Laboratory Animal Resources of the National Research Council, after getting approval from the institutional animal ethical committee, Deprtment of pharmacy, The University of Lahore (IAEC-2015- 02). This study was performed in adherence with the ARRIVE guidelines. See supplementary file for the ARRIVE checklist.

Conflict of interest
The authors declare no conflict of interest.

Supplementary data
https://www.pjps.pk/uploads/2026/07/SUP1784209615.pdf

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