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VASORELAXANT EFFECT OF THE KC-4 POLYPHENOL ON VASCULAR SMOOTH MUSCLE: ANALYSIS OF CALCIUM TRANSPORT AND POTENTIAL PHARMACOLOGICAL MECHANISMS

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Annotatsion. The contraction and relaxation of vascular smooth muscle depend on the coordinated activity of intracellular Ca^{2+} concentration, membrane ion channels, calcium stores in the sarcoplasmic reticulum, and enzymes responsible for Ca^{2+} transport. Therefore, the vasorelaxant properties of new biologically active compounds should be evaluated not only through the overall contractile response but also at several levels of Ca^{2+} regulation. In this study, the effects of the plant-derived polyphenol KC-4 on rat aortic smooth muscle were examined using an isolated-organ preparation and molecular docking approaches. The effects of KC-4 at concentrations of 5–60 μM were assessed against KCl- and phenylephrine-induced contractions.

KC-4 progressively reduced KCl-induced contraction as its concentration increased, with a calculated IC_{50} of 23.15 μM. In the phenylephrine model, the IC_{50} was 18.21 μM, which was 4.94 μM, or 21.34%, lower than that in the KCl model. This finding suggests that KC-4 may affect not only Ca^{2+} influx associated with membrane depolarization but also receptor-mediated Ca^{2+} mobilization. Molecular docking predicted the most favorable binding energies for KC-4 with Ca^{2+} -ATPase (−11.7 kcal/mol) and L-type Ca^{2+} channels (−10.8 kcal/mol). Values of −10.2 kcal/mol were obtained for SERCA and R-type channels, −9.6 kcal/mol for NCX1, and −7.7 kcal/mol for RyR.

Comparative experiments with verapamil supported the possible involvement of L-type Ca^{2+} channels in the action of KC-4. However, the combined response indicated that its mechanism cannot be explained solely by classical Ca^{2+}-channel blockade. Overall, the findings suggest that the vasorelaxant activity of KC-4 may be associated with reduced Ca^{2+} influx, changes in intracellular Ca^{2+} homeostasis, and modulation of receptor-operated calcium-signaling pathways.

Keywords: KC-4, polyphenol, vascular smooth muscle, vasorelaxation, Ca^{2+} homeostasis, L-type Ca^{2+} channel, SERCA, Ca^{2+} -ATPase, phenylephrine, KCl, verapamil, molecular docking.

Introduction. The functional state of vascular smooth muscle is an important determinant of vascular resistance and arterial blood pressure. Contraction and relaxation of these cells depend primarily on cytoplasmic Ca^{2+} levels and on the balance among calcium entry across the plasma membrane, release from intracellular stores, and subsequent sequestration. Accordingly, systems that regulate calcium fluxes are central to explaining vasomotor responses.

During membrane depolarization, L-type voltage-dependent Ca^{2+} channels open and increase calcium entry into the cytoplasm. The incoming Ca^{2+} binds to calmodulin, activates myosin light-chain kinase (MLCK), and initiates the contractile machinery. However, the role of L-type channels is not limited to providing an entry route for extracellular calcium; these channels are also functionally linked to intracellular calcium signaling.

Intracellular Ca^{2+} balance is regulated not only by influx from outside the cell but also by exchange with the sarcoplasmic reticulum. SERCA pumps return Ca^{2+} from the cytoplasm to the reticulum, whereas ryanodine receptors (RyR) participate in the release of stored calcium. Compounds that affect one or more of these mechanisms may alter smooth-muscle tone at different stages.

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Plant-derived polyphenols are a group of natural compounds that may affect the cardiovascular system. Their biological activity cannot be explained by a single mechanism: in some cases, the endothelial nitric oxide pathway is involved, while in others, ion channels, Ca^{2+} exchange, or intracellular signaling processes may contribute.

The scientific literature reports that some flavonoids reduce contractile responses in isolated aortic preparations. For example, studies of prunetin have discussed concentration-dependent reductions in contractions induced by KCl and phenylephrine, as well as mechanisms involving calcium flux.

The potential relationship between polyphenols and the SERCA system is also noteworthy. SERCA supports relaxation by returning cytoplasmic Ca^{2+} to the sarcoplasmic reticulum; compounds affecting its activity may therefore alter intracellular calcium homeostasis.

In this context, describing the effects of KC-4 solely as general vasorelaxation is insufficient. Comparing KCl and phenylephrine models can help assess differences between extracellular Ca^{2+} influx and receptor-associated calcium mobilization, while docking results should be interpreted as indicating potential molecular targets.

The aim of this study was to characterize the vasorelaxant activity of KC-4 in rat aortic rings using concentration-dependent responses, compare its effects on KCl- and phenylephrine-induced contractions, and assess potential targets involved in Ca^{2+} regulation through molecular docking.

Materials and Methods

2.1. Experimental model

The study describes experiments using ring preparations, 3–4 mm in length, obtained from the thoracic aortas of male albino rats weighing 200–250 g. The preparations were maintained in Krebs–Henseleit solution at 37°C and continuously aerated with a mixture of 95% O_2 and 5% CO_2. The protocol was reported to have followed the relevant animal-ethics requirements.

According to the article, KC-4 was described as a polyphenolic compound isolated from the plant Caralina caspia. The compound was obtained from the Plant Cytoprotectors Laboratory of the Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan.

2.2. Recording isometric contractile responses

Aortic rings were attached to an isometric force transducer and equilibrated for 60 minutes under an initial tension of 1 g. Contractions were induced using 50 mM KCl or 1 μM phenylephrine. Once a stable contraction had developed, KC-4 was added cumulatively over a concentration range of 5–60 μM.

2.3. Pharmacological controls

Verapamil at 0.1 μM was used to compare the possible involvement of L-type Ca^{2+} channels, while phentolamine at 10 μM was used to assess the α-adrenergic receptor pathway. The article states that the antagonists were added 15 minutes before the agonist.

2.4. Molecular docking

The potential binding of KC-4 to proteins involved in Ca^{2+} transport was computationally assessed using AutoDock Vina. The targets considered were Cav1.2, NCX1, RyR2, and SERCA. The results were compared according to the most favorable ligand conformation and the calculated minimum binding energy.

2.5. Statistical and mathematical analysis

Results were expressed as mean ± SEM. Concentration–response relationships were assessed using nonlinear regression, and IC_{50} values were calculated. The article reports n = 3 experimental points.

The supplementary analysis calculated the following measures: percentage inhibition; the difference between IC_{50} values for KCl and phenylephrine; the IC_{50} ratio; relative differences among

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molecular-docking values; and regions showing steep changes in the concentration–response profile. These supplementary measures do not replace original measurements; they are secondary mathematical calculations based on the results presented in the article.

Results

3.1. Effect of KC-4 on KCl-induced contraction

The effect of KC-4 on KCl-induced contraction was limited at lower concentrations and became stronger at higher concentrations. At 5 μM, the remaining contraction was 96% of the control value; at 10, 15, 20, and 25 μM, it decreased to 82%, 70%, 60%, and 45%, respectively. Between 30 and 40 μM, the response fell from 35% to 20%, while at 45–60 μM approximately 12–15% of the initial response remained.

KC-4 concentration (μM)	Remaining contraction (%)	Inhibition (%)
5	96	4
10	82	18
15	70	30
20	60	40
25	45	55
30	35	65
35	25	75
40	20	80
45–60	12–15	85–88

Inhibition did not change at a constant rate as the concentration increased. The reduction in contraction was moderate between 5 and 15 μM, whereas a substantially steeper decline occurred between 20 and 40 μM. This profile indicates a nonlinear concentration–effect relationship for KC-4.

The calculated IC_{50} for the KCl model was 23.15 μM. This value quantitatively characterizes the ability of KC-4 to attenuate a contractile response associated with membrane depolarization.

3.2. Response in the phenylephrine model

The effect of KC-4 in aortic rings contracted with phenylephrine was also concentration-dependent. The remaining contraction was 95% at 5 μM, 85% at 10 μM, and 75% at 15 μM. At 20 μM, the response decreased to 35%; at 25 μM it reached 15%, and at 30–35 μM it was approximately 13–14%.

KC-4 concentration (μM)	Remaining contraction (%)	Inhibition (%)
5	95	5
10	85	15
15	75	25
20	35	65
25	15	85
30	13–14	86–87
35	13–14	86–87

The IC_{50} in the phenylephrine model was calculated as 18.21 μM. This was 4.94 μM lower than the value obtained in the KCl model, indicating that sensitivity to KC-4 differed between the two contractile conditions.

Calculation:

$23.15 - 18.21 = 4.94$ μM

$(4.94 / 23.15) \times 100 = 21.34\%$

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Based on these calculated values, the IC_{50} in the phenylephrine model was 21.34% lower than in the KCl model. This may be associated with a possible effect on receptor-regulated Ca^{2+} signaling, but it does not directly prove the mechanism.

Thus, the difference between the two models means that the effects of KC-4 should not automatically be attributed solely to blockade of voltage-dependent Ca^{2+} channels.

3.3. Comparison of the KCl and phenylephrine models

The two models initiate contraction through different pathways. KCl depolarizes the membrane and activates voltage-dependent Ca^{2+} channels. Phenylephrine activates α_1-adrenergic receptors, eliciting a response associated with the PLC/IP_{50} system and mobilization of calcium from intracellular stores.

The lower IC_{50} under phenylephrine stimulation supports the hypothesis that KC-4 may affect one or more components of receptor-associated Ca^{2+} signaling.

Similar differences have been observed with other natural compounds. Some substances have been reported to relax aortic rings contracted by KCl and phenylephrine in a concentration-dependent manner, with reduced Ca^{2+} flux potentially contributing to the response.

The effects of KC-4 may therefore be considered in relation to two parallel pathways:
KCl → membrane depolarization → L-type Ca^{2+} channel → Ca^{2+} influx → contraction
Phenylephrine → α_1 receptor → PLC/IP_3 → Ca^{2+} mobilization + Ca^{2+} influx → contraction.

Because KC-4 attenuated contraction in both models, its action may involve several stages of Ca^{2+} regulation. However, separate functional experiments are needed to determine which molecular component is decisive.

3.4. Molecular docking results

The most favorable calculated binding energy was −11.7 kcal/mol for Ca^{2+}-ATPase and −10.8 kcal/mol for the L-type Ca^{2+} channel. Values of −10.2 kcal/mol were reported for SERCA and the R-type channel, −9.6 kcal/mol for NCX1, and −7.7 kcal/mol for RyR.

Potential target	Docking energy (kcal/mol)	Main role in Ca^{2+} physiology
Ca^{2+} -ATPase	−11.7	Ca^{2+} transport
L-type Ca^{2+} channel	−10.8	Extracellular Ca^{2+} influx
R-type Ca^{2+} channel	−10.2	Ca^{2+} flux across the membrane
SERCA	−10.2	Return of Ca^{2+} to the sarcoplasmic reticulum
NCX1	−9.6	Na^{+}/ Ca^{2+} exchange
RyR	−7.7	Ca^{2+} release from the sarcoplasmic reticulum

The docking energy for Ca^{2+} -ATPase was 0.9 kcal/mol lower than that for the L-type channel, indicating a more favorable predicted interaction within the computational model. This difference should not be interpreted as a percentage measure of biological efficacy.

Docking predicts potential protein–ligand interactions computationally. Therefore, the energy values do not prove that KC-4 actually activates or inhibits the function of a protein; they should be interpreted alongside experimental findings and used to identify potential targets for further investigation.

3.5. Comparison of KC-4 and verapamil

In the KCl model, the remaining contraction was approximately 54% at a KC-4 concentration close to its IC_{50}. With verapamil at 0.1 μM, this value was approximately 40%; when KC-4 and verapamil were applied together, it decreased to about 35%.

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These observations permit three cautious interpretations. First, the stronger response to verapamil is consistent with the central role of L-type Ca^{2+} channels in KCl-induced contraction. Second, although weaker than verapamil, the substantial effect of KC-4 raises the possibility that it also affects Ca^{2+} -regulatory systems other than L-type channels. Third, the additional inhibition in the combination may reflect partly overlapping effects as well as the involvement of independent mechanisms.

The importance of L-type channels in vascular smooth-muscle contraction has been established in other studies. Nevertheless, natural polyphenols do not affect these channels uniformly; some flavonoids may even increase L-type channel activity. It is therefore necessary to avoid the generalization that all polyphenols are Ca^{2+} -channel blockers and to evaluate each compound experimentally.

3.6. Comparison of KC-4 and phentolamine

In the phenylephrine model, KC-4 alone reduced the contractile response to approximately 35%; with phentolamine, the residual response was approximately 20%. When the two compounds were administered together, contraction was reported to be around 40%.

This observation is insufficient to classify KC-4 as a direct α-adrenergic receptor antagonist. The response observed with phentolamine does not fit a simple additive antagonism pattern, so the result requires cautious interpretation.

The potential site of KC-4 action may lie downstream of the receptor, within signaling steps such as PLC/IP_{50}-mediated Ca^{2+} mobilization, membrane ion transport, or the Ca^{2+} sensitivity of the contractile apparatus.

Discussion

The main observation is that KC-4 attenuated aortic contraction induced by both KCl and phenylephrine in a concentration-dependent manner. The IC_{50} values of 23.15 µM in the KCl model and 18.21 µM in the phenylephrine model suggest that the compound may affect more than one contractile signaling pathway.

Membrane depolarization and voltage-dependent Ca^{2+} channels play important roles in KCl-induced contraction. Accordingly, the docking value calculated for the L-type channel may be consistent with the functional observation. Nevertheless, docking does not confirm direct channel blockade; this should be investigated using patch-clamp recording or intracellular Ca^{2+} imaging.

The relatively greater sensitivity observed in the phenylephrine model requires separate consideration. Activation of α-adrenergic receptors affects Ca^{2+} release from the sarcoplasmic reticulum and calcium entry into the cell through the PLC/IP_3 pathway.

The lower IC_{50} in this model strengthens the hypothesis that KC-4 may also participate in intracellular Ca^{2+} regulation. This interpretation is compatible with the docking values calculated for Ca^{2+} -ATPase and SERCA, although those values do not establish a causal relationship.

The potential interaction with SERCA deserves specific investigation because this pump promotes muscle relaxation by returning cytoplasmic Ca^{2+} to the sarcoplasmic reticulum. The docking result identifies this pathway as a candidate mechanism for future experiments.

On this basis, the following mechanistic hypothesis is proposed:

KC-4 → modulation of L- Ca^{2+} channels → reduced extracellular Ca^{2+} influx

KC-4 → Ca^{2+} -ATPase/SERCA systems → alteration of intracellular Ca^{2+} homeostasis

KC-4 → receptor-operated Ca^{2+} signaling → attenuation of the phenylephrine response

Final outcome → reduced cytoplasmic Ca^{2+} → reduced contractile-apparatus activity → vasorelaxation.

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Overall, a multi-target model may serve as a working hypothesis to explain the observed responses. The present results are insufficient to establish it as the definitive mechanism; direct functional and molecular evidence is required.

Quantitative comparison

Considering the IC_{50} values for both models together helps identify the conditions under which KC-4 appears more potent.

Measure	KCl model	Phenylephrine model
IC_{50} (μM)	23.15	18.21
IC_{50} difference	—	−4.94 μM
Relative difference	—	−21.34%
IC_{50} ratio	1.00	0.787
Region of steepest response	20–40 μM	15–25 μM
Maximum inhibition at high concentrations	≈85–88%	≈86–87%

The table suggests that maximum inhibition may be broadly similar in both models, although the phenylephrine model approached this level at a lower concentration. Future analyses should therefore distinguish maximum effect (efficacy) from the concentration required to produce an effect (potency). This approach can support more meaningful comparisons between KC-4 and other vasorelaxant compounds.

Scientific significance

The following points emerge from the results presented:

1. Evidence suggesting that the effects of KC-4 in the KCl and phenylephrine models are not limited to a single pharmacological mechanism has been organized and evaluated.
2. The 21.34% lower IC_{50} for phenylephrine than for KCl was identified as an analytical indicator of potentially greater sensitivity in pathways associated with receptor-operated Ca^{2+} signaling.
3. Ca^{2+} -ATPase, the L-type Ca^{2+} channel, and SERCA were highlighted as potential principal molecular targets of KC-4.
4. The functional organ model and molecular-docking findings were integrated into a single mechanistic scheme.
5. The concept of KC-4 as a multi-target modulator of Ca^{2+} homeostasis, rather than simply a classical Ca^{2+} -channel blocker, was proposed as a scientifically plausible interpretation.

Study limitations and future directions

The reported number of experimental points, n = 3, means that the findings should be treated as preliminary observations. Larger samples and complete statistical reporting are needed to improve reliability and assess differences between groups.

In addition, endothelium-dependent mechanisms were not investigated independently. Some polyphenols may affect vascular tone through endothelial pathways such as nitric oxide (NO), prostacyclin, or endothelium-derived hyperpolarizing factor (EDHF). Future experiments comparing aortic rings with intact endothelium and rings from which the endothelium has been mechanically removed would help establish the contribution of the endothelium.

Ca^{2+} imaging could directly track changes in intracellular calcium concentration over time after KC-4 administration. Patch-clamp recording would be suitable for testing the direct effect of KC-4 on currents through L-type Ca^{2+} channels. Molecular-dynamics simulations could further assess the time-dependent stability of the ligand–protein complexes proposed by docking.

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Conclusion

The calculated IC_{50} was 23.15 μM for KCl-induced contraction and 18.21 μM for the phenylephrine model. The 21.34% lower value in the latter model suggests that KC-4 may also affect receptor-associated Ca^{2+}- signaling.

In docking calculations, Ca^{2+}-ATPase (−11.7 kcal/mol), the L-type Ca^{2+} channel (−10.8 kcal/mol), and SERCA (−10.2 kcal/mol) emerged as potential targets with relatively favorable predicted binding energies for KC-4.

Comparison with verapamil is consistent with possible involvement of L-type Ca^{2+} channels, but the overall pharmacological response cannot be explained by this channel alone. Accordingly, the action of KC-4 is best regarded as a hypothesis that may involve extracellular Ca^{2+} influx, intracellular calcium homeostasis, and receptor-mediated contractile signaling pathways.

Further studies using larger biological samples, Ca^{2+} imaging, patch-clamp recording, Western blotting/qPCR, and molecular-dynamics analyses are required to confirm the mechanism.

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