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Role of F-4 Isoquinoline Alkaloid, Dihydroquercetin Flavonoid and Conjugate DKV-6 in Myocardial RyR2 and SERCA2a under Normal and Hypoxic Conditions

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Cardiovascular diseases are among the leading causes of death worldwide, according to the World Health Organization. A key pathogenic factor in ischemia and myocardial infarction is the disruption of $Ca^{2?}$ ion homeostasis and impaired function of the sarcoplasmic reticulum (SR) proteins RyR2 and SERCA2a. Therefore, identifying biologically active substances that modulate $Ca^{2?}$ transport via SERCA2a is of significant scientific and practical importance. In this study, the inotropic effects of the isoquinoline alkaloid F-4, the flavonoid dihydroquercetin (DHQ), and their conjugate DKV-6 were investigated using isolated rat heart papillary muscle preparations. Mechanographic results showed that F-4 (120 μM), DHQ (60 μM), and DKV-6 (50 μM) increased papillary muscle contractility by 32.9±3.1%, 51.4±3.4%, and 110.3±3.2%, respectively, compared to control. The post-rest potentiation (PRP) method was employed to assess changes in SR $Ca^{2?}$ levels. The effects of these biologically active compounds (BACs) on RyR2 were studied using tetracaine and ruthenium red, while the role of SERCA2a was evaluated with cyclopiazonic acid (CPA). The results indicated that the positive inotropic effect is closely associated with SERCA2a function. Furthermore, the DKV-6 conjugate exhibits distinct anti-hypoxic activity, effectively counteracting hypoxia-induced impairments in myocardial contractility. Its antiarrhythmic effect appears to be mediated through SERCA2a activation.

Keywords: Conjugate; Dihydroquercetin; Hypoxia; Isoquinoline alkaloid; Papillary muscle; SERCA2a.

Cardiovascular diseases (CVD) are among the leading causes of disability and mortality worldwide. In this context, cardiovascular disorders pose a significant threat to human health and daily functioning. Among cardiovascular ailments, ischemic heart disease and cardiac arrhythmias are particularly prevalent and contribute substantially to the risk of sudden cardiac death.[1,2] The progression of arrhythmias and ischemia leads to disturbances in key myocardial parameters, including heart rate and contractility.[3]

In the pathogenesis of these diseases, increased reactive oxygen species (ROS) production disrupts the functional activity of intracellular signaling systems and ATP-dependent processes, including Ca²z -ATPase, Naz /Kz -ATPase, membrane Kz ATP-channels, and Naz /Ca²z exchange.u { w Substantial evidence indicates that the effects of acute hypoxia on cardiomyocyte ion channels are associated with changes in channel phosphorylation states or cellular redox balance. The influence of hypoxia on channel regulation extends beyond direct effects, involving indirect pathways such as alterations in ROS levels.x { ¹p

While most cardioprotective drugs modulate these parameters, many are unsuitable for clinical use due to adverse effects. Therefore, developing novel, safe, and potent cardioprotective agents is critically important.¹t { ¹w Biologically active compounds derived from plants represent promising candidates for developing effective therapeutics with minimal side effects.¹x Among these, flavonoids¹y and alkaloids²p have been extensively studied.

In this study, we investigated the effects of the flavonoid dihydroquercetin and the isoquinoline alkaloid 1-(42 -methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (F-4), isolated by researchers at the Institute of Plant Chemistry, Academy of Sciences of the Republic of Uzbekistan, as well as their conjugate 2-(3,4-Dihydroxyphenyl)-6-{[6,7-dimethoxy-1-(4-methoxyphenyl)-3,4-dihydroisoquinolin-2(1H)-yl] methyl}-3,5,7-trihydroxychroman-4-one (DKV-6),²¹ on the contractile activity of cardiac papillary muscle under normal and hypoxic conditions (Figure 1).

MATERIALS AND METHODS

The experiments were conducted in the Cell Biophysics Laboratory of the Institute of Biophysics and Biochemistry at UzMU. All procedures involving animals were performed in accordance with the ethical principles of the Declaration of Helsinki and followed the guidelines established by the Council for International Organizations of Medical Sciences (CIOMS, 1985). The study strictly adhered to the institutional protocol titled "Bioethical Regulations for the Use of Laboratory Animals in Scientific Research" issued by the Institute of Biophysics and Biochemistry.

Myocardial contractile function was assessed in vitro using a mechanographic system. The contractile activity of isolated papillary muscles was recorded with a SI–BAM21–LC mechanographic setup (World Precision Instruments Inc., USA). The system included an

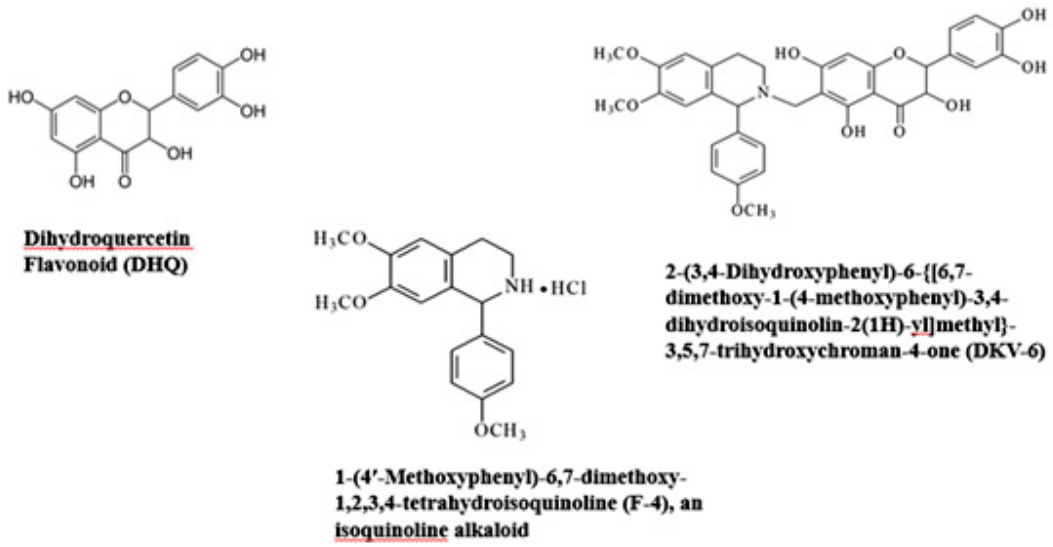

Fig. 1. Chemical structure of DHQ, the isoquinoline alkaloid F-4, and the conjugate DKV-6

SI–OHO2F force transducer. The mechanical signal from the muscle preparation, attached via an SI–KG20 piezoelectric sensor, was amplified by a SI–BAM21–LCB signal amplifier. Data were digitized using a Lab–Trax–4/16 converter (WPI, USA) and recorded in WLabScribe2 (*.iwxdata) format on a computer running the iWorx LabScribe2 software (iWorx Systems, Inc., USA) for subsequent primary mathematical and statistical analysis.

Experimental Protocols

Male white outbred rats (200–250 g) were used to anesthetize the experimental subject, using sodium pentobarbital (40 mg/kg). Under deep anesthesia, animals were euthanized by cervical dislocation and subsequent decapitation in accordance with international ethical guidelines. The rib cage was then opened, the heart was carefully removed, and immediately placed in a petri dish containing Krebs' solution. The left ventricle of the heart was opened and the papillary muscle was isolated. The prepared heart preparations were placed in a cell filled with Krebs solution with the following composition (mM): NaCl – 150; KCl – 4; $CaCl_2$ – 1.8; $MgCl_2$ – 1; NaHCO3 – 14; NaH_2PO_4 – 1.8; $C_6H_{12}O_6$ – 11.5; (pH=7.4).

The flavonoid dihydroquercetin, isoquinoline alkaloid F-4, and conjugates DKV-6 studied during the research were provided by the staff of the Institute of Chemistry of Plant Substances of the Academy of Sciences of the Republic of Uzbekistan. *In vitro*, the PRP value, the SR RyR2 agonists tetracaine and ruthenium red, and the SERCA2a inhibitor cyclopiazonic acid (CPA) (Sigma Ltd) were used to assess the contractile activity of rat cardiac papillary muscle under normal and hypoxic conditions.

Statistical analysis

In the experiments, the force of contraction of the papillary muscle at the excitation frequency of 0.1-1 Hz was calculated as a percentage (%) of the maximum, and the average arithmetic value of 5 experiments was calculated. Statistical significance for the observed differences between the experimental and control groups was established using the Student's t-test, with results considered significant if * –ð<0.05, ** –ð<0.01. The results of the study were analyzed using the statistical software OriginPro 2021 (OriginLab Corporation, USA).

***In vitro* Hypoxia model**

A hypoxia model was used to evaluate the cardioprotective activity of the flavonoid dihydroquercetin, the isoquinoline alkaloid F-4, and the conjugates DKV-6. The hypoxia model was created by aerating a 95% O2; 5% CO2 Krebs solution with a 95% N2/5% CO2 gas for 60 minutes.[22] The cardioprotective activity of the dihydroquercetin, the isoquinoline alkaloid [23] F-4, and the conjugates DKV-6 was studied under conditions where maximal changes in the parameters of rat papillary muscle contractile activity were observed after oxygen in Krebs solution was replaced with nitrogen for one hour. The heart muscle's contractility is significantly impaired when it becomes hypoxic. The main reason for this is the disruption of calcium (Ca^2z) transport systems and Ca^2z homeostasis in cardiomyocytes.[24,25] This condition is mainly associated with the loss of function of the sarcoplasmic reticulum Ca^2z -ATPase enzyme (SERCA2a), which plays a key role in maintaining Ca^2z homeostasis in cardiomyocytes.[26-28]

RESULTS

Initial studies investigated how the conjugate of DHQ affected outcomes at varying concentrations[29] (10-60 ìM), the isoquinoline alkaloid 25 F-4 (5-120 ìM), and DKV-6 (5-50 ìM) on the contractile activity of rat cardiac papillary muscle were studied. At all doses of the studied biologically active substances, a positive inotropic effect was observed, increasing the force of cardiac papillary muscle contraction by 51.4±3.4%, 32.9±3.1%, and 110.3±3.2%, respectively, compared to the control (control was taken as 100%) (Figure. 3 A and B).

The sarcoplasmic reticulum (SR) is an intracellular membrane-bound organelle that plays a key role in regulating Ca^{2+} concentration during contraction and relaxation. There are two important components of the SR involved in Ca^{2+} homeostasis: the SERCA2a and the RyR play a key role in regulating Ca^{2+} dynamics during myocardial contraction and relaxation. Ca^{2+} ions released from the SR is instrumental in the cardiac muscle's

contractile activity.[30,31] Taking this into account, in the next experiments, the effect of the studied compounds on the SR Ca^{2+} transport systems were carried out using the post-rest potentiation method. In this case, when stimulation is stopped for 30 seconds and then given, the force of the first contraction (B1) increases, which occurs as a result of an increase in the amount of Ca^{2+} released from the SR. Therefore, the effect of isometric force on resting muscle contraction after cessation of stimulation is considered an index of the amount of Ca^{2+} released from the SR.[32,33]

In these experiments, in the presence of F-4 alkaloid (120 ìM), DHQ (60 ìM), and DKV-6 (50 ìM) conjugate, the amplitude of papillary muscle contraction was observed to increase by 43.2±4.8%, 82.4±4.1%, and 93.1±3.8%, respectively, compared to the control after a rest period (30 sec). (Figure 4 A and B)

The studies indicate that the F-4 alkaloid, DHQ, and DKV-6 conjugate exerts its positive inotropic action by enhancing the uptake and subsequent release of Ca^{2+} ions by the SR. RyR2 is a predominantly Ca^{2+} channel that plays a key role in cardiac contractility. Alterations in RyR2 function result in an increase in the inward potential.[34-37] This process is associated with the release of Ca^{2+} ions from the SR.[38-41] The probability of RyR opening depends on the cytosolic Ca^{2+} concentration, and Ca^{2+} ions bind to the activating part of the RyR. The opening of L-type Ca^{2+} channels and the increased probability of RyR opening following dyadic Ca^{2+} entry are the main mechanisms for the activation of Ca^{2+}-induced Ca^{2+} release (CICR) during physiological activity. [42-44]

Thus, to investigate whether RyR2 is implicated in the positive inotropic response to the F-4 alkaloid, DHQ, and DKV-6 conjugate, the effect on PRP values under tetracaine and ruthenium red incubation conditions was examined. In this case, the PRP values of F-4 alkaloid, DHQ, and DKV-6 conjugate in the presence of ruthenium red (10 ìM) were 55,3±2,9%, 67.1±3.2%, and 72.1±4.1% (Figure 5 A).

In subsequent experiments, when tested in the presence of tetracaine (15 ìM) in the medium, it was found that the effect of the F-4 alkaloid, DHQ, and DKV-6 conjugate on the post-rest

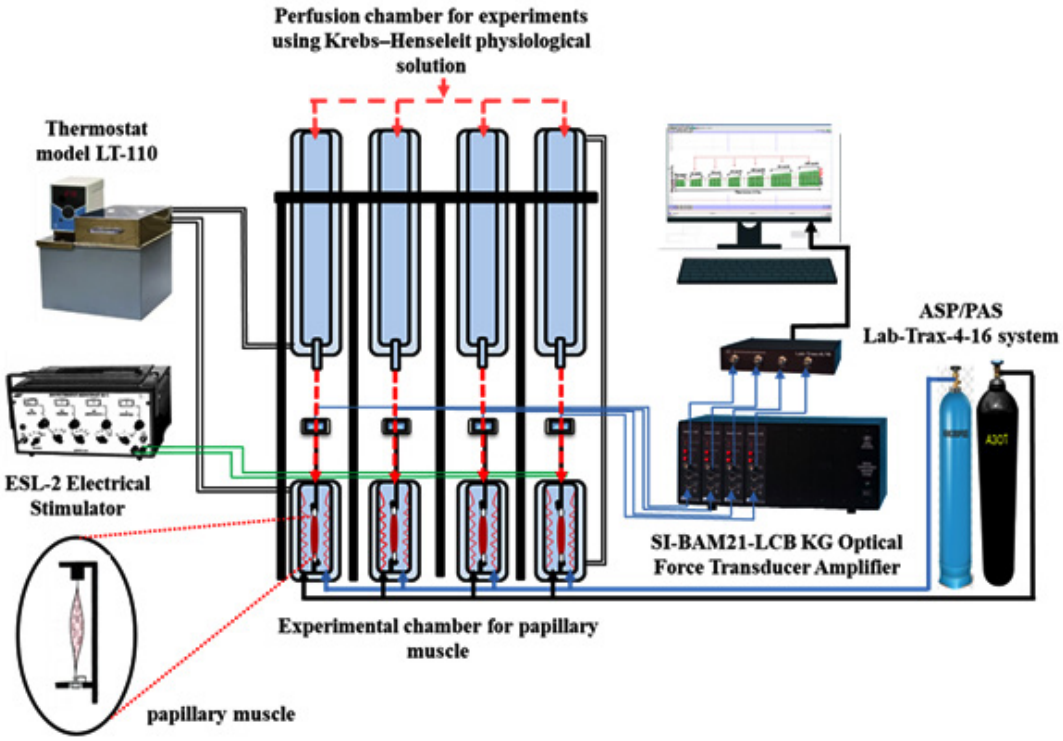

Fig. 2. Schematic of a device for recording rat heart papillary muscle activity in vitro.

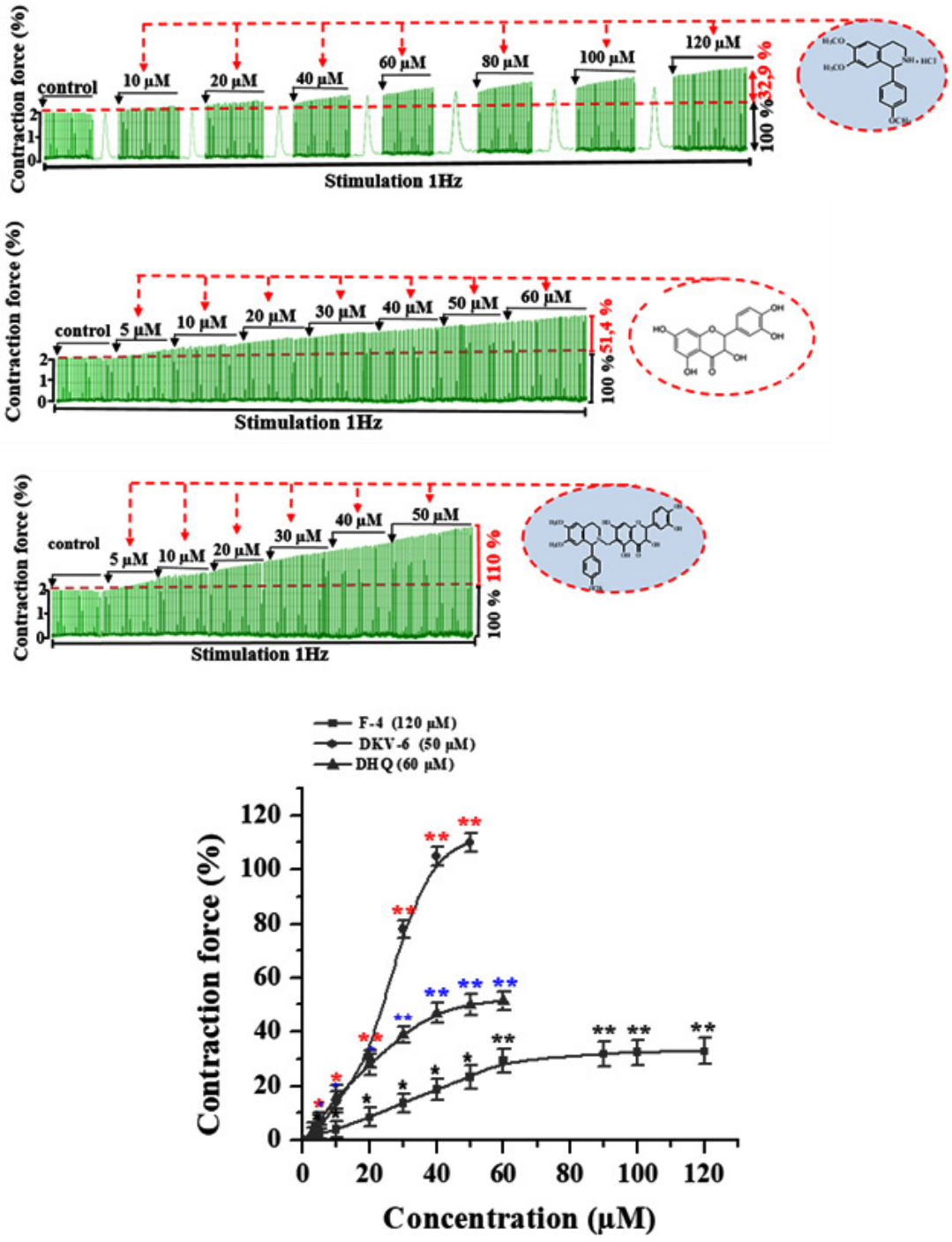

Fig. 3. A. Positive inotropic effect of biologically active compounds on papillary muscle contractile activity (Representative trace of isometric contraction). B. Dose-dependent positive inotropic effect of the isoquinoline alkaloid F-4, DHQ, and DKV-6 conjugate on papillary muscle contractile activity. The ordinate axis represents the force of contraction of the papillary muscle, expressed as a percentage of the maximum value, which is taken as 100%. The abscissa axis represents the concentration of conjugates. Stimulation frequency is 1 Hz (t=+36±0.5ºC maintained by a thermostatic bath); * –ð<0.05, ** –ð<0.01 n=5.

potentiation value had a similar effect to the results of experiments conducted with ruthenium red (Figure 5B).

The findings of this research suggest that the DKV-6 conjugate exhibits a beneficial impact on cardiac contractility, which is based on the F-4 alkaloid and the DHQ flavonoid, is due to the low involvement of RyR2.

The study showed that the F-4 alkaloid increased the force of heart muscle contraction (positive inotropic effect). Furthermore, the DHQ and DKV-6 conjugate appears to influence how Ca^{2+} are stored within the SR. In order to validate this premise, we assessed the impact of the investigated BFB on SERCA2a. Experiments were conducted in the presence of the SERCA2a inhibitor cyclopiazonic acid (CPA).[45-47]

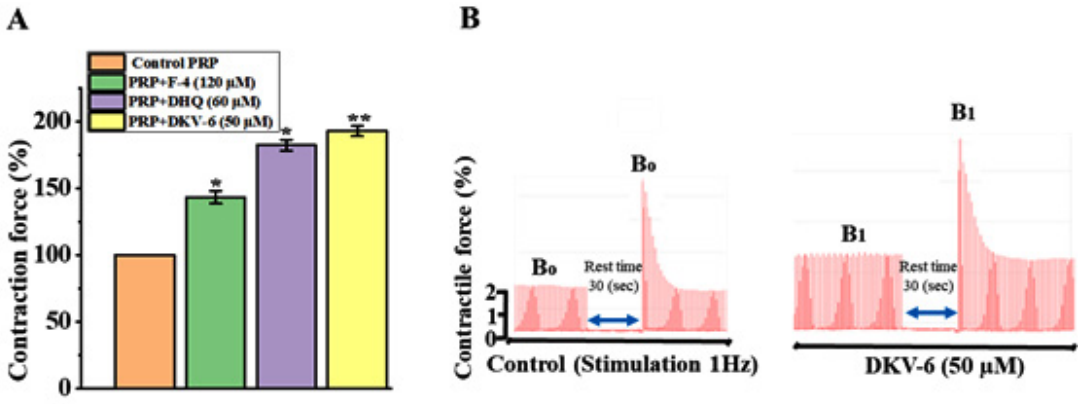

Fig. 4. Effect of alkaloid A, F-4, and conjugates DHQ, DKV-6 on the post-rest potentiation value of rat cardiac papillary muscle. B- Representative trace of isometric contraction. The stimulation cessation time was 30 sec. B - the force of controlled contraction of the muscle after rest (post-rest potentiation) was taken as 100%. Increase in the value of post-rest potentiation under the influence of F-4, F-36 and DKV-6, DKV-8 conjugates. The frequency of drug stimulation was 1 Hz. In all cases (t=+36±0.5ºC maintained by a thermostatic bath); *-p<0.05; **-p<0.01; n =5.

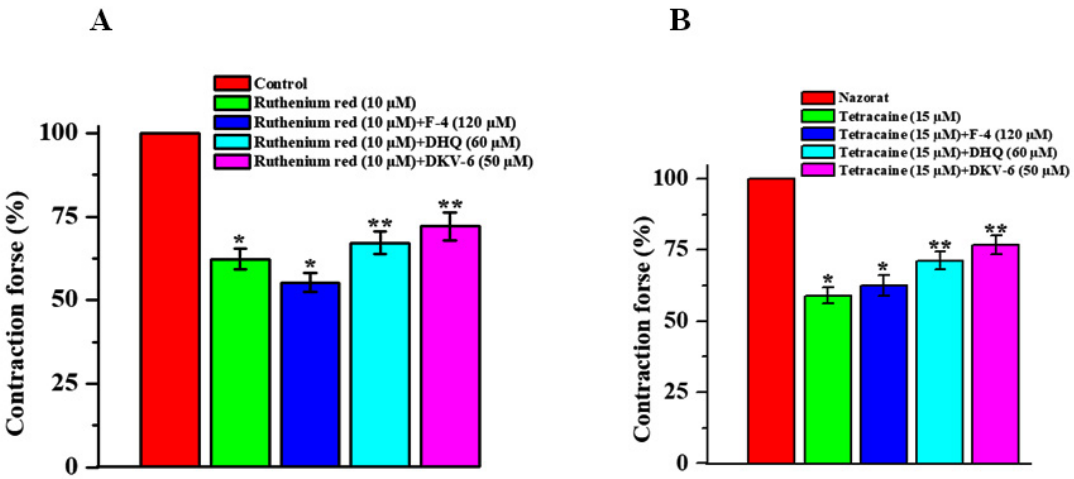

Fig. 5. A, B. Effect of F-4 isoquinoline alkaloids and DHQ, DKV-6 conjugates on the value of papillary muscle post-rest potentiation in the presence of ruthenium red and tetracaine. The stimulation cessation time was 30 sec. On the ordinate axis, the muscle's post-rest potentiation was taken as 100%. The stimulation frequency was 1 Hz (t=+36±0.5ºC maintained by a thermostatic bath); * - p<0.05, ** - p<0.01, n=5.

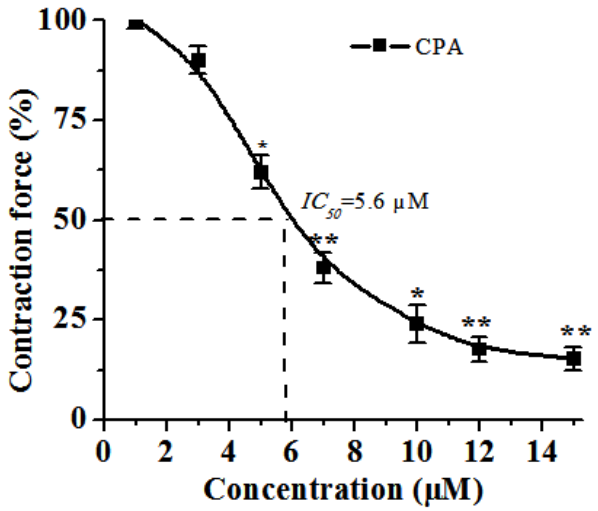

Fig. 6. Dose-dependent effect of CPA on papillary muscle contraction force. The ordinate axis shows the amplitude value of the contraction force expressed as a percentage (%) of the maximum, and the abscissa axis shows the concentration of CPA expressed in logarithms (iM) (*-p<0.05; **-p<0.01). Stimulation frequency 0.5 Hz, t=+36±0.5ºC maintained by a thermostatic bath; n=5.

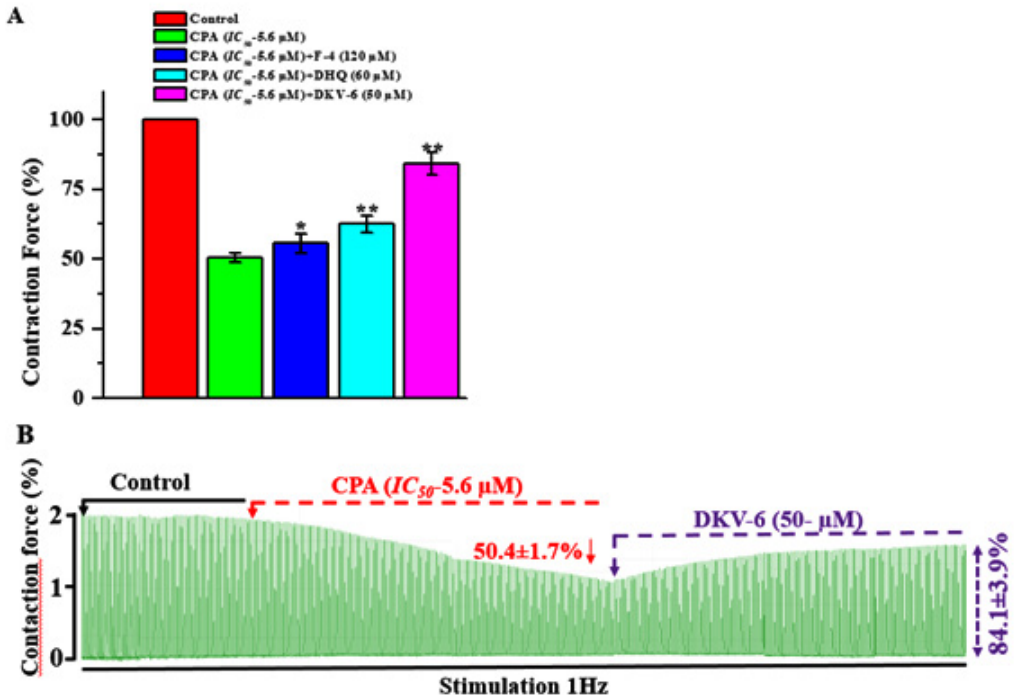

Fig. 7. A. Effect of the isoquinoline alkaloid F-4, DHQ, and DKV-6 conjugate on papillary muscle contraction force in the presence of the SERCA2a inhibitor CPA (IC_{50}-5.6 iM) in the incubation medium. On the ordinate axis, the force of papillary muscle contraction is expressed as a percentage (%). The stimulation frequency is 1 Hz (t=+36±0.5ºC maintained by a thermostatic bath) * - p<0.05, ** - p<0.01; n=5. B. Effect of DKV-6 conjugate on papillary muscle contraction force in the presence of cyclopiazonic acid (IC_{50}-5.6 iM) (*Representative trace of isometric contraction*).

Research suggests that the isoquinoline alkaloid F-4, a compound formed by linking DHQ and DKV-6, enhances the contractile strength of rat heart papillary muscle by influencing how Ca^{2+} ions are stored within the sarcoplasmic reticulum.

To clarify this assumption, we investigated the effect of the studied isoquinoline alkaloid F-4, a conjugate of DHQ and DKV-6, on SERCA2a. Experiments were conducted in the presence of the SERCA2a inhibitor cyclopiazonic acid (CPA).[48,49] To investigate how varying concentrations of CPA (from 1 to 15 ìM) influenced papillary muscle contraction, control experiments were conducted. It was found that CPA at a concentration of 15 ìM reduced the force of papillary muscle contraction by 80.7±4.8%. The half-maximal inhibitory concentration of CPA was IC_{50}-5.6 ìM (Figure 6).

In the next experiments, the effects of F-4 alkaloid (120 ìM), DHQ (60 ìM), and DKV-6 conjugate (50 ìM) were examined in the presence of the half-maximal inhibitory concentration (IC_{50}-5.6 ìM) of the SERCA2a inhibitor CPA. Under these conditions, the amplitude of the contraction force of the papillary muscle of the rat heart was 57.6±3.5%, 60.2±5.3%, and 84.1±3.9%, respectively, compared to the control (Figure. 7 A and B).

According to the experimental results, F-4 alkaloid's ability to increase heart muscle contractility, DHQ, and DKV-6 conjugate on

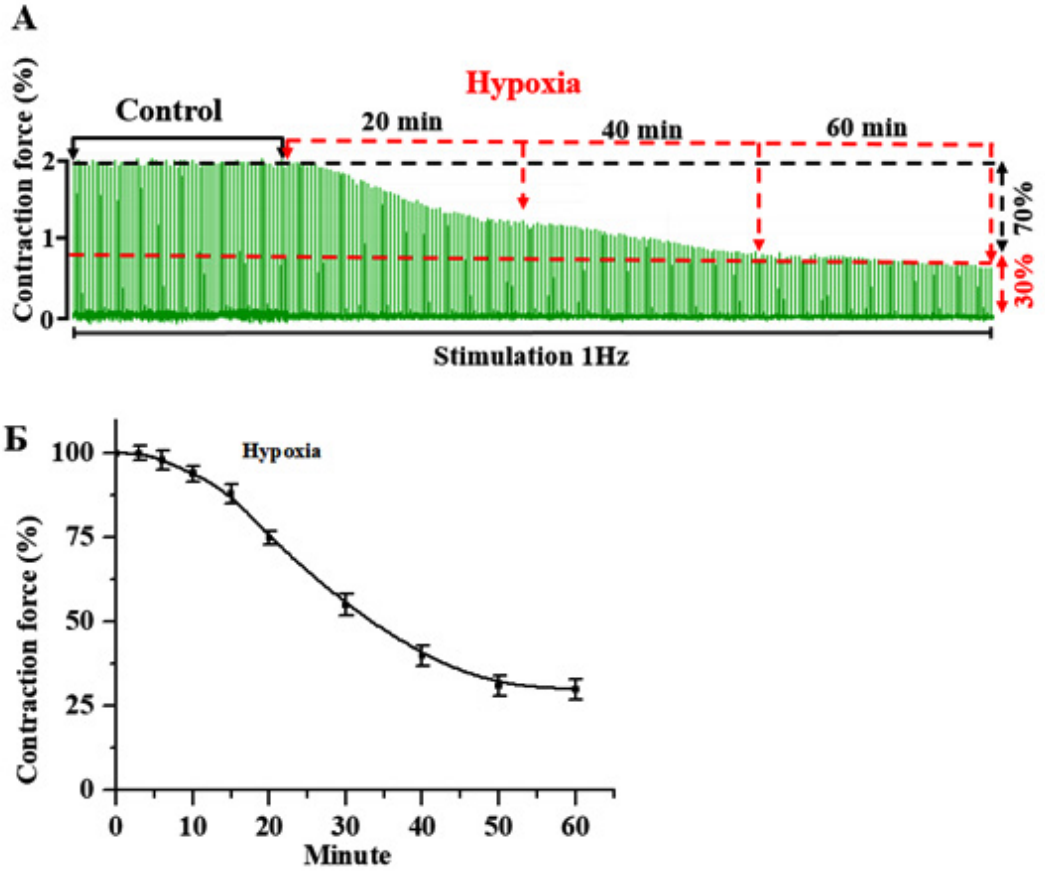

Fig. 8. A. Effect of hypoxia on rat heart papillary muscle contractile activity (Representative trace of isometric contraction). B. On the ordinate axis - muscle contraction force, the control obtained under normal oxygenation of physiological solution is expressed as a percentage and is taken as 100%. The abscissa axis shows the deoxygenation time of the solution aerated with nitrogen. The drug was stimulated with a frequency of 1 Hz. In all cases, (t=+36±0.5ºC maintained by a thermostatic bath) * - $p<0.05$, ** - $p<0.01$; n=5.

papillary muscle contractile activity is explained by the fact that SR Ca^{2+} transport systems play an important role, with a small participation of RyR2 and a predominantly important role played by SERCA2a. Hypoxia causes a significant decrease in the force of heart muscle contraction. The main role in this is played by the disruption of Ca^{2+} homeostasis in cardiomyocytes, the function of Ca^{2+} transport systems, and the production of ATP and creatine phosphate, the main energy sources in cardiomyocytes.[50-51]

In this regard, an experimental model of hypoxia was used to study the effects of the F-4 alkaloid, DHQ, and DKV-6 conjugate on hypoxia-induced impairments in rat heart papillary muscle contractility. This model was performed by perfusion of rat heart papillary muscle preparations with modified Krebs saline (N_2 95%/O_2 5%). When rat heart papillary muscle preparation was perfused with modified Krebs solution for 60 minutes, it was found that the contractile force decreased to 30.4±3.1% compared to the control (Figure 8 A and B).

Further investigations examined how the F-4 alkaloid, DHQ, and the DKV-6 conjugate influenced papillary muscle contraction strength during hypoxic conditions, it was found that they restored the impairment of papillary muscle contraction activity caused by hypoxia to 47.3±3.1%, 52.2±3.8%, and 80.9±3.6% (Figure 9 A and B).

Based on the results of the above experiments, it can be said that the F-4 alkaloid, DHQ, and DKV-6 conjugate effectively eliminates disorders in the contractile activity of the heart muscle as a result of hypoxia, demonstrating strong cardioprotective properties.

Ischemic heart disease leads to impaired ATP synthesis, including impaired SR Ca^{2+}-ATPase (SERCA2a) activity. In this regard, the effect of the indole alkaloids under study on SERCA2a in myocardial cells under hypoxic conditions was examined. When the effects of F-4 alkaloid (120 ìM), DHQ (60 ìM), and DKV-6 conjugate (50 ìM) in the presence of the SERCA2a inhibitor

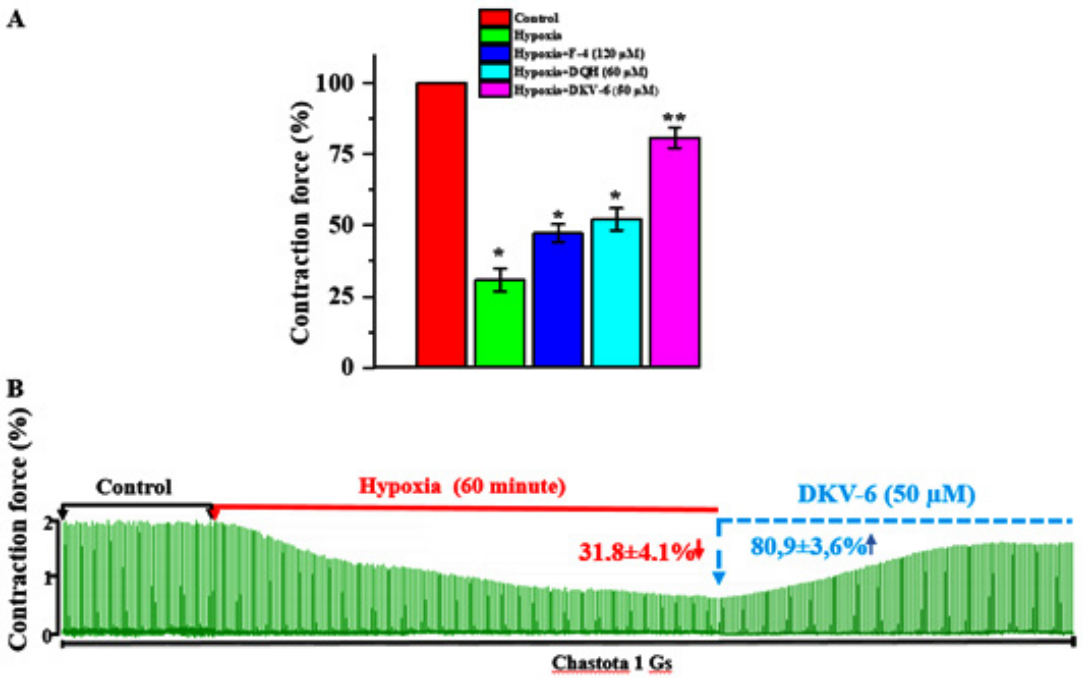

Fig. 9. A. In vitro effects of F-4 isoquinoline alkaloids and DHQ, DKV-6 conjugates on the contractile activity of rat heart papillary muscles under hypoxic conditions. B. Representative trace of isometric contraction. On the ordinate axis, the post-rest potentiation of the muscle was taken as 100%. The stimulation frequency was 1 Hz (t=+36±0.5ºC maintained by a thermostatic bath); * - $p<0.05$, ** - $p<0.01$, n=5.

CPA (IC_{50}-5.6 ìM) under hypoxic conditions were tested, the papillary muscle contraction force was 19.6±3.5%, 25.2±5.3%, and 35.6±3.4%, respectively, compared to the control (Figure. 10 A and B).

The results of these experiments showed that the F-4 alkaloid, DHQ, and DKV-6 conjugate can eliminate hypoxia-induced dysfunction of SERCA2a and normalize changes in rat heart papillary muscle contractile activity.

DISCUSSION

Our results demonstrate that the isoquinoline alkaloid F-4, dihydroquercetin (DHQ), and the DKV-6 conjugate synthesized from these compounds exert a positive inotropic effect on the contractile activity of rat heart papillary muscles. Analysis revealed that the DKV-6 conjugate had the most pronounced effect among the tested substances, significantly increasing papillary muscle contraction force. This enhanced effect may be attributed to a synergistic interaction between the flavonoid and alkaloid components within the conjugate.

The sarcoplasmic reticulum proteins RyR2 and SERCA2a play crucial roles in maintaining $Ca^{2}z$ homeostasis and regulating intracellular $Ca^{2}z$ dynamics in cardiomyocytes. In experiments examining the effects of F-4, DHQ, and DKV-6 on RyR2 function, we found that the positive inotropic effects of these compounds in the presence of tetracaine and ruthenium red were not primarily mediated by RyR2. Conversely, experiments using cyclopiazonic acid (CPA) indicated that the positive inotropic effects of F-4, DHQ, and DKV-

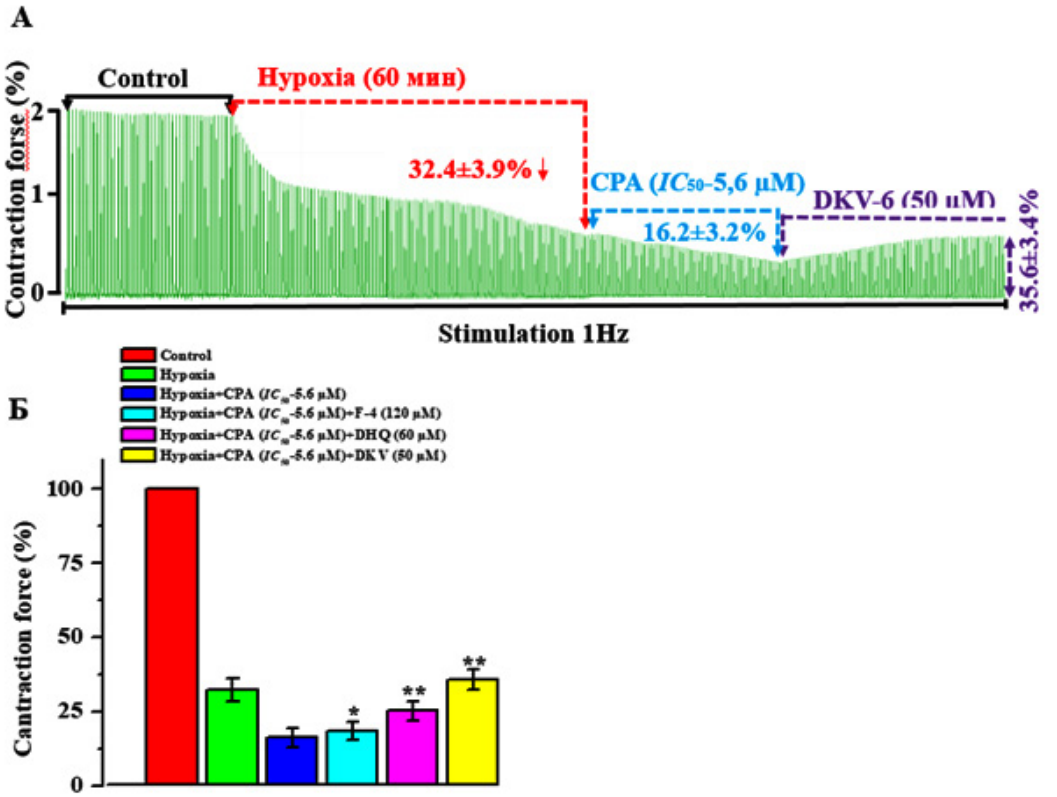

Fig. 10. A. Effect of DKV-6 conjugate on papillary muscle contraction force in the presence of CPA (IC_{50}-5.6 ìM) under hypoxic conditions. (representative trace of isometric contraction) B. Effect of F-4 alkaloid, DHK and DKV-6 conjugate on papillary muscle contraction force in the presence of CPA (IC_{50}-5.6 ìM) under hypoxic conditions. On the ordinate axis - the force of contraction of the papillary muscle expressed as a percentage (%). Stimulation frequency is 1 Hz. (t=+36±0.5ºC maintained by a thermostatic bath), * - $p<0.05$, ** - $p<0.01$; n = 5.

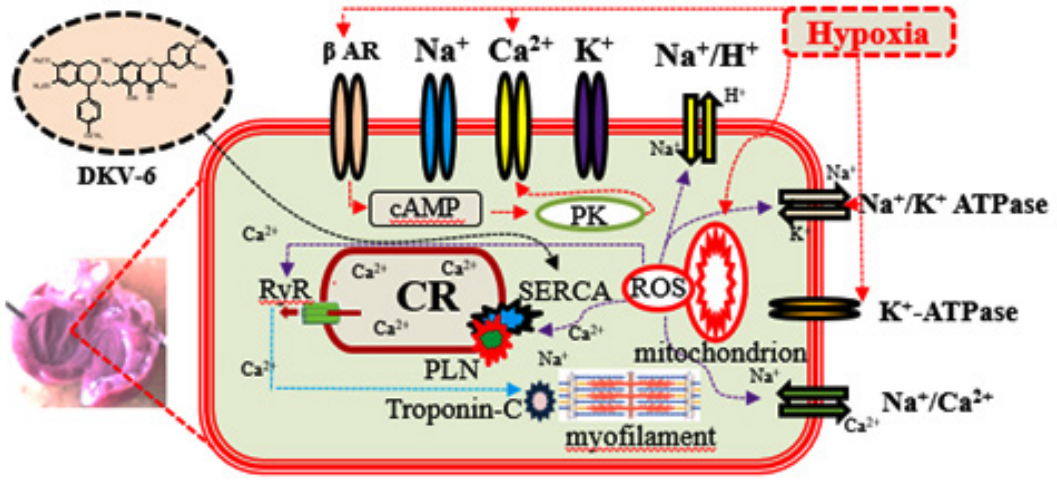

Fig. 11. Inotropic and antihypoxant effects of F-4 alkaloid, DGK and DKV-6 conjugate.

6 on papillary muscle contractility are mediated through modulation of SERCA2a function.

Under hypoxic conditions, the force of cardiac papillary muscle contraction decreased by up to 70%. This reduction is primarily due to disruption of the Ca²z transport system and impairment of ATP-dependent processes. However, treatment with F-4, DHQ, and particularly the DKV-6 conjugate partially restored contractile force during hypoxia, suggesting their potential role in restoring SERCA2a activity and normalizing Ca²z homeostasis.

These data further indicate that the DKV-6 conjugate exhibits superior cardioprotective properties under hypoxic conditions compared with F-4 and DHQ alone. The findings suggest that these compounds, especially the DKV-6 conjugate, hold therapeutic potential for the treatment of ischemic heart disease.

CONCLUSION

Compared to the F-4 isoquinoline alkaloid, DHQ flavonoid, the DKV-6 conjugate is recognized to increase the force of contraction in the papillary muscle of a rat heart to a greater extent. Under conditions of hypoxia, changes occur in the function of ion channels, which are mainly associated with ATP. Considering this, the F-4 isoquinoline alkaloid, DHQ and DKV-6 conjugate studied above was induced by hypoxia. SR effectively eliminates disorders in the function of the Ca^{2+}-ATPase system and normalizes changes in the contractile activity of rat cardiac papillary muscles. This can restore the activity of special signaling systems that provide communication between the SR, regulate the concentration of intracellular Ca^{2+} ions, and the function of the SR.

ACKNOWLEDGMENT

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Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

The experimental protocols complied with the standards and requirements for the humane treatment of animals and the provisions

of the Ethical Commission of the IBB at the National University of Uzbekistan. (Protocol No. 7 BEC/IBB-NUU of 04/07/2022) on the use of laboratory animals. Isolated cardiac papillary muscle preparations were obtained using a specific method.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required

Clinical Trial Registration

This research does not involve any clinical trials

Permission to reproduce material from other sources

Not Applicable

Author Contributions

Boboev Sadriddin Nurillo Ugli: Conceptualization, Methodology, Writing – review & editing, Writing – Original Draft, Supervision; Zhumaev Inoyat Zulfiqorovich: Methodology, Writing – review & editing, Writing – original draft, Validation, Formal analysis, Project Administration; Usmanov Pulat Bekmuratovich: Conceptualization, Methodology, Writing – review & editing, Supervision, Resources, Funding acquisition; Zaripov Abdisalim Abdikarimovich: Writing – review & editing, Writing – Original Draft; Rustamov Shavkat Yusubovich: Visualization, Resources; Qurbonova Shakhnoza Bakhtiyorovna: Visualization, Resources; Eldor Bakhtiyor ugli Ibragimov: Visualization, Resources; Sardor Bakhtiyor ugli Sobirov: Visualization, Resources; Zhurakulov Sherzod Niyatkobulovich: isoquinoline alkaloid 1-(4¢-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (F-4) isolated by the staff of the Institute of Chemistry of Plant Substances of the Academy of Sciences of the Republic of Uzbekistan, as well as the conjugate 2-(3,4-Dihydroxyphenyl)-6-{[6,7-dimethoxy-1-(4-methoxyphenyl-3,4-dihydroisoquinolin-2(1H)-yl] methyl}-3,5,7-trihydroxychroman-4-one (DKV-6)

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