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Impact of Polyphenols on Cardiomyocyte Function in Normal and Hyperglycemic Conditions: Experimental Study

Normal ve Hiperglisemi Durumlarında Polifenollerin Kardiyomiyosit Fonksiyonu Üzerindeki Etkisi: Deneysel Çalışma

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ABSTRACT Objective: Cardiovascular complications are the leading causes of morbidity and mortality in diabetic patients. Hyperglycemia plays a significant role in the pathogenesis of these complications, leading to detrimental cardiovascular effects, including hypertrophy and functional abnormalities. Conversely, dietary polyphenols are known to have preventive effects on the development of cardiac diseases. These polyphenols regulate blood glucose levels and offer protective effects in diabetes. Nevertheless, to our knowledge, their direct cardiac effects at the cellular level remain unknown. Thus, we aimed to investigate the effects of various commonly consumed polyphenolic substances from different classes (resveratrol, quercetin, apigenin, genistein) under normal and high glucose concentrations. **Material and Methods:** Isolated rat ventricular cardiomyocytes were incubated under normal (5.5 mM) or high (25.5 mM) glucose conditions in the presence or absence of polyphenols. Contractile function was evaluated using a video-based edge-detection system by measuring changes in cell length during shortening and relengthening. Protein expression levels of sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and Na^{+}/K^{+}-ATPase were determined by Western blot analysis. **Results:** High glucose impaired contractility, inducing a "diabetes-like" condition without affecting protein expression levels. Among the tested polyphenols, resveratrol most effectively preserved contractile function. The other polyphenols had partial or limited effects. **Conclusion:** Resveratrol showed superior cardioprotective properties against hyperglycemia-induced dysfunction at the cellular level, highlighting its potential as a therapeutic adjunct in diabetes.

Keywords: Polyphenol; hyperglycemia; cardiomyocyte; contractility; SERCA

ÖZET Amaç: Kardiyovasküler komplikasyonlar, diyabetik hastalarda morbidite ve mortalitenin önde gelen nedenleri arasındadır. Hiperglisemi, bu komplikasyonların patogenezinde önemli bir rol oynamaktadır. Hipertrofi ve fonksiyonel anormallikler dâhil olmak üzere çeşitli zararlı kardiyovasküler etkilere yol açmaktadır. Öte yandan diyetle alınan polifenollerin, kalp hastalıklarının gelişimi üzerinde önleyici etkileri olduğu bilinmektedir. Bu polifenoller, kan glukoz seviyelerini düzenlemekte ve diyabette koruyucu etkilere aracılık etmektedir. Ne var ki bu polifenollerin, hücresel düzeyde doğrudan kardiyak etkileri olup olmadığı bilinmemektedir. Bu nedenle çalışmamızda, normal ve yüksek glukoz konsantrasyonları varlığında farklı sınıflardan yaygın olarak tüketilen çeşitli polifenolik maddelerin (resveratrol, kuersetin, apigenin, genistein) etkilerinin araştırılması amaçlanmıştır. **Gereç ve Yöntemler:** İzole sıçan ventriküler kardiyomiyositleri, polifenollerin varlığında veya yokluğunda normal (5.5 mM) ve yüksek (25.5 mM) glukoz koşullarında inkübe edilmiştir. Kontraktil fonksiyon, hücre kısalması ve yeniden uzaması sırasında hücre uzunluğundaki değişimlerin video tabanlı kenar tespit sistemi kullanılarak ölçülmesiyle değerlendirilmiştir. Sarkoplazmik/endoplazmik retikulum Ca^{2+}-ATPaz (SERCA) ve Na^{+}/K^{+}-ATPaz protein ekspresyon düzeyleri Western blot analizi ile belirlenmiştir. **Bulgular:** Yüksek glukoz konsantrasyonları ile kısa süreli kültüre edilen hücrelerde, bozulan kontraktilite parametreleri "diyabet benzeri" bir duruma neden olmaktadır. Kontraktil fonksiyonun korunmasında, test edilen polifenoller arasında en belirgin etki resveratrol ile gözlenmiştir. Diğer polifenoller ise kısmi veya sınırlı etkiler göstermiştir. **Sonuç:** Resveratrol tedavisinin, hücreleri hiperglisemiye karşı korumada diğer polifenolik bileşiklere kıyasla üstünlük taşıdığı gözlenmiştir.

Anahtar Kelimeler: Polifenol; hiperglisemi; kardiyomiyosit; kontraktilite; SERCA

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Diabetes mellitus is a syndrome characterized by chronic hyperglycemia, leading to organ damage and various complications. Among these complications, cardiac issues are the primary cause of morbidity and mortality in diabetic patients. Cardiac complications occur 2 to 4 times more frequently in diabetic patients compared to those without diabetes.[1]

In addition to present pharmacotherapies focusing on the pathogenesis of diabetes, alternative therapies using nutraceuticals are also preferred by the diabetic patients. Epidemiological studies have demonstrated that the consumption of polyphenol-rich foods has been associated with a reduced risk of cardiovascular diseases and potentially diabetes due to their antioxidant properties.[2] Furthermore, certain phytotherapeutics containing polyphenols have shown positive effects on blood glucose control, glucose utilization, and insulin secretion.[3] They have also been demonstrated to possess anti-inflammatory properties and to regulate calcium homeostasis.[4-6] Additionally, they improve intracellular signaling and enhance cardiac energy metabolism.[7-9] Numerous studies have highlighted the significance of polyphenols in safeguarding cellular components against oxidation.[10]

Despite these known effects obtained by the studies focusing on systemic effects or indirect models, the direct impact of polyphenols on cardiomyocyte function under hyperglycemic (HG) conditions remain to be clarified.

In our study, we aimed to evaluate and compare the effects of selected polyphenols on cardiomyocyte function under HG conditions using "diabetes-like" rat cardiomyocyte culture model.[11] We have selected four widely studied and structurally distinct flavonoids- resveratrol (stilbene group), quercetin (flavonol group), apigenin (flavone group), and genistein (isoflavone group) to represent major polyphenol subclasses.[12] These compounds were chosen based on their previously reported cardioprotective properties and their differential mechanisms of action, allowing us to explore potential subtype-specific effects.

The hypothesis of this study is that selected polyphenols exert differential protective effects on cardiomyocyte function under HG conditions, potentially through distinct mechanisms such as calcium handling, energy metabolism, or oxidative stress regulation. By using an in vitro system, this study examines the direct cellular effects of polyphenols on cardiomyocytes, thereby identifying potential therapeutic adjunct candidates.

MATERIAL AND METHODS

CHEMICALS

Resveratrol (R5010, MW: 228.24, purity ≥99%, dissolved in dimethylsulfoxide), genistein (G6649, MW: 270.24, purity ≥98%, dissolved in dimethylsulfoxide), apigenin (10798, MW: 270.24, purity ≥95%, dissolved in sodium hydroxide) and quercetin (Q4951, MW: 302.24, purity ≥95%, dissolved in dimethylsulfoxide) were all purchased from Sigma Aldrich (St. Louis, Missouri, USA). Cardiomyocyte isolation was done with collagenase Type 2 from Wortington Biochemical Corporation (Lakewood, NJ, USA).

CARDIOMYOCYTE ISOLATION

We used 8-10-week-old male Sprague Dawley rats weighing 300-400 g. These rats were procured from Bilkent University (Ankara) and housed at Ankara University Faculty of Pharmacy Experimental Animal Unit until the day of the experiment. Ethical approval for this study was obtained from the Ankara University Local Ethics Committee for Experimental Animals (date: March 1, 2017; no: 2017-5-34) in accordance with the guidelines of Directive 2010/63/EU and the Guide for the Care and Use of Laboratory Animals of National Research Council. On the day of the experiment, the rats were anesthetized with isoflurane. The depth of anesthesia was monitored by assessing reflexes to ensure complete unconsciousness and the absence of pain perception before proceeding. Once fully anesthetized, the animals were humanely euthanized, and their chests were opened, the hearts were excised, and then placed in containers filled with cold Tyrode's solution containing heparin. The hearts were then suspended by their aortas onto the Langendorff system. Initially, the hearts were perfused with calcium-free Tyrode's

solution followed by Tyrode's solution containing collagenase. After enzymatic perfusion, the hearts were mechanically disrupted, and the resulting cell suspension was filtered and kept at 37 °C. Following calcium adaptation, the cells were subjected to different culture conditions.

ESTABLISHMENT OF THE HYPERGLYCEMIC MODEL AND CELL INCUBATION

Following calcium adaptation, the cells were placed in M199 medium containing 2 mM carnitine, 5 mM creatine, 5 mM taurine and 100 U/mL penicillin-100 µL/mL streptomycin. Cells incubated in this medium with 5.5 mM glucose were considered normoglycemic (NG). To create high glucose conditions, an additional 20 mM glucose was added to the culture medium, resulting in a total of 25.5 mM glucose. Cells incubated in this high glucose concentration were considered HG. Cardiomyocytes in the culture medium were kept in a 5% CO_2 incubator at 37 °C for 3 hours. The concentrations of the polyphenolic substances used in the experiments, shown in Table 1, were determined based on a literature review and selected for their relevance and effectiveness in similar experimental models reported in previous studies.

CONTRACTILITY MEASUREMENT IN CARDIOMYOCYTES

The mechanical properties of cardiomyocytes were evaluated using the SoftEdge Myocam [IonOptix® (IonOptix LLC, Westwood, MA, USA)] system. Cardiomyocytes were subjected to frequencies of 0.5, 1, and 2 Hz, and the lengthening and shortening of the cell were recorded. Parameters such as cell length at rest, maximum shortening size, shortening-elongation rates (±dL/dt), and time required for elongation to decrease to 90% (TR90) were calculated from the obtained responses.

TABLE 1: Polyphenolic substances and their concentrations used in the study

Polyphenolic substance	Concentration	Reference
Resveratrol	30 µM	20
Quercetin	20 µM	21
Apigenin	25 µM	22
Genistein	20 µM	23

WESTERN BLOTTING

Cell pellets obtained by centrifugation at 500 rpm for 3 minutes were placed in radioimmunoprecipitation assay buffer including Na_2VO_3 (sodium orthovanadate, 200 mM) and protein inhibitor cocktail (100X). They were homogenized with an ultrasonic homogenizer, followed by centrifugation for 15 minutes at 10,700 rpm at +4 °C. The protein concentrations of the supernatant were calculated by bicinchoninic acid protein analysis. Equal amounts of protein were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The proteins were then transferred onto polyvinylidene fluoride membrane for 2 hours at 100 V. Membranes were then incubated with phosphate buffered saline buffer containing 0.05% Tween-20 (Sigma-Aldrich, St. Louis, Missouri, USA) and 2% bovine serum albumin for 1 h at room temperature. Membranes were then incubated overnight at +4 °C with primary antibodies. The following day, they were washed for 1 h with phosphate buffered saline buffer containing 0.05% Tween 20, and incubated for 2 h at +4 °C with horseradish peroxidase (HRP)-conjugated secondary antibodies.

STATISTICAL ANALYSIS

Experimental results are presented as mean±standard error of the mean. Statistical significance was determined using analysis of variance, followed by the Bonferroni "post hoc" test for multiple comparisons between groups. GraphPad Prism (GraphPad Software, San Diego, CA, USA) software was used for statistical analysis, with significance accepted at $p<0.05$.

RESULTS

Figure 1, which includes sample records from two different environments, shows that the resting lengths, shortening-lengthening lengths, and sarcomere lengths of HG cells have changed, resulting in a "diabetes-like" appearance. Based on these results, we determined the incubation period for the experiments to be 3 hours and the glucose concentration to be 25.5 mM.

As seen in Figure 2, the contraction parameters of cardiomyocytes, including resting length, peak shortening and maximal contraction velocity (dep v)

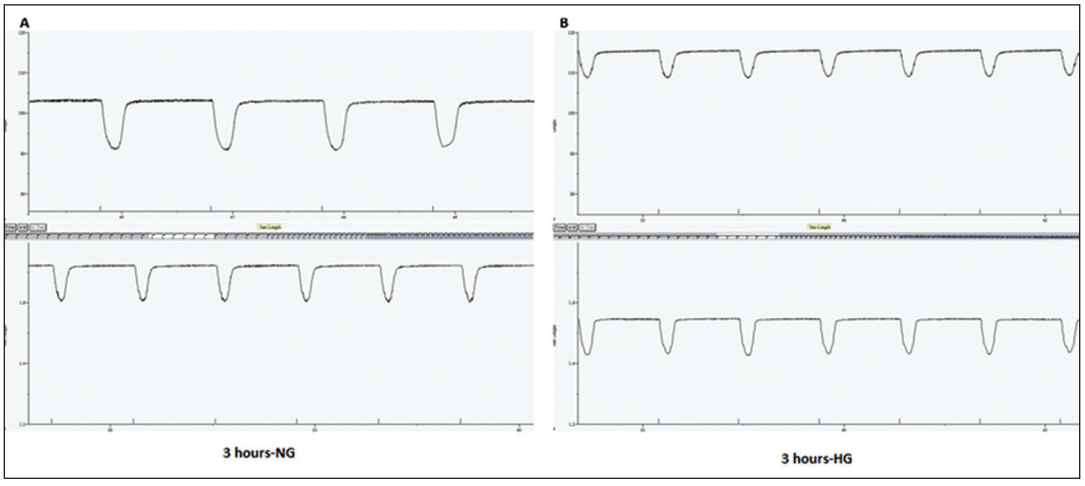


FIGURE 1: Comparison of sample recordings from cardiomyocytes maintained in normoglycemic (NG) (A) and hyperglycemic (HG) (B) conditions for 3 hours.
NG: Normoglycemic; HG: Hyperglycemic; Res: Resveratrol; Quer: Quercetin; Api: Apigenin; Gen: Genistein

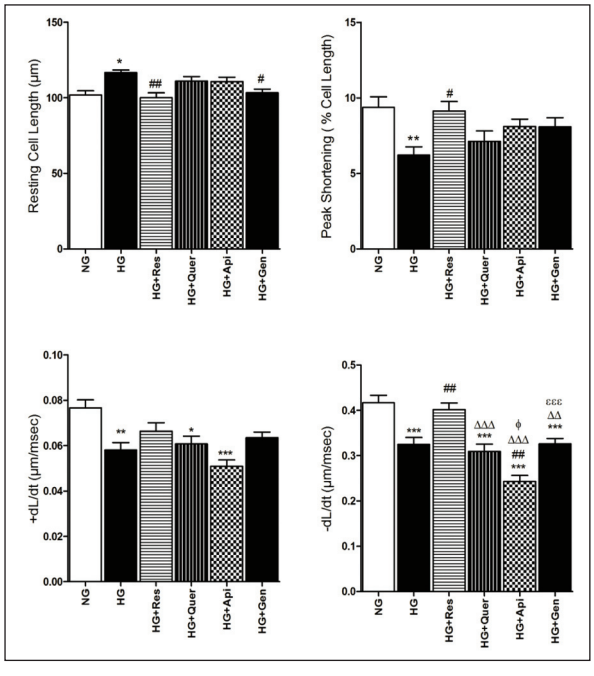


FIGURE 2: Bar graphs of resting cell length **(A)**, maximum shortening dimension **(B)**, shortening **(C)** and lengthening velocities **(D)** of cells stimulated with 0.5 Hz frequency

*p<0.05 significance according to NG; **p<0.01 significance according to NG; ***p<0.001 significance according to NG; #p<0.05, significance according to HG; ##p<0.01, significance according to HG; ΔΔp<0.01 significance according to resveratrol receiving group; ΔΔΔp<0.001 significance according to resveratrol receiving group; Φp<0.05 significance according to quercetin receiving group; εεεp<0.001 significance according to apigenin receiving group; NG: Normoglycemic (5.5 mmol/L); HG: Hyperglycemic (25.5 mmol/L); Res: Resveratrol; Quer: Quercetin; Api: Apigenin; Gen: Denistein; (n=3-5 different hearts for each group, 8-12 different cells from each heart)

and maximal relaxation velocity (vet v) all indeed exhibited a "diabetes-like" profile.

When examining resting cell lengths, an increase in the size of the cells incubated in HG conditions was observed, indicating the onset of a hypertrophic process. Resveratrol and genistein treatments protected the cells against this increase. However, cells incubated with quercetin and apigenin showed only partial, non-significant improvement (Figure 2). Electrical stimulation was then applied to these cells at a frequency of 0.5 Hz and the contraction size of the HG cells decreased significantly. Resveratrol improved this decrease, while other active substances applied had no significant effect on this parameter (Figure 2). The shortening and lengthening speeds of the cells per unit time were also compared. It was observed that the shortening-lengthening speed was significantly reduced in HG cells. All treatments applied showed varying degrees of protection against the decrease in shortening and lengthening speeds observed in hyperglycemia (Figure 2).

On the other hand, we compared the maximum shortening time (TPS) and TR90 of cardiomyocytes as indicators of shortening and lengthening performance. TPS was significantly reduced in HG cells, and this reduction was reversed only by resveratrol.

The other active substances applied were ineffective. When comparing TR90 values, no significant differences were observed between the groups (Figure 3).

Initially, the cells were recorded at a frequency of 0.5 Hz. Subsequently, they were subjected to frequencies of 0.5 Hz, 1 Hz, and 2 Hz, and their shortening-lengthening graphs were recorded. As shown in Figure 4, the peak points in NG cells remain unchanged despite the increase in frequency. This indicates that the cells can return to their original size after contraction, meaning they can relax at the same rate. However, in HG cells, the peak points were decreased as the frequency increased, suggesting that the cardiomyocytes cannot fully relax and remain contracted. Among the treatments applied and resveratrol partially improved this condition, while other treatments did not correct the response to frequency changes in HG cells.

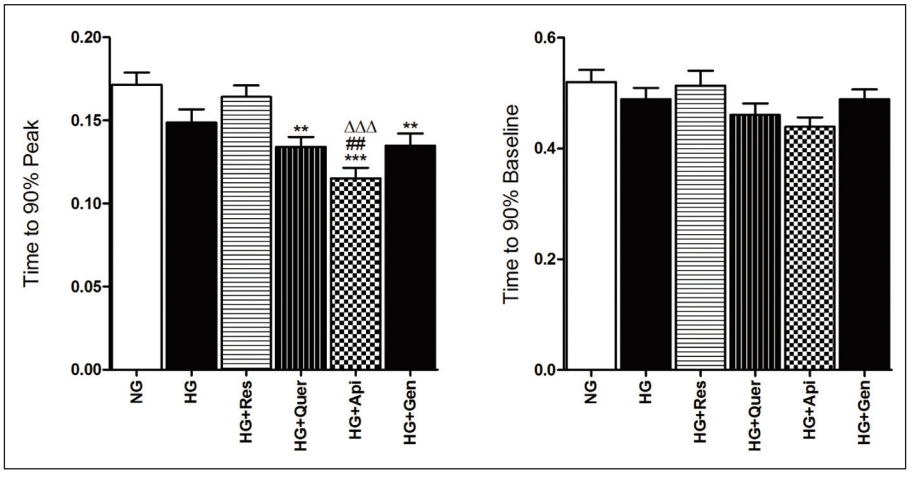


FIGURE 3: Bar graphs of maximum shortening time **(A)** and time required for 90% elongation **(B)**
**p<0.01 significance according to NG; ***p<0.001 significance according to NG; ##p<0.01, significance according to HG; ΔΔΔp<0.001 significance according to resveratrol receiving group; NG: Normoglycemic (5.5 mmol/L); HG: hyperglycemic (25.5 mmol/L); Res: Resveratrol; Quer: Quercetin; Api: Apigenin; Gen: Genistein; (n=3-5 different hearts for each group, 8-12 different cells from each heart)

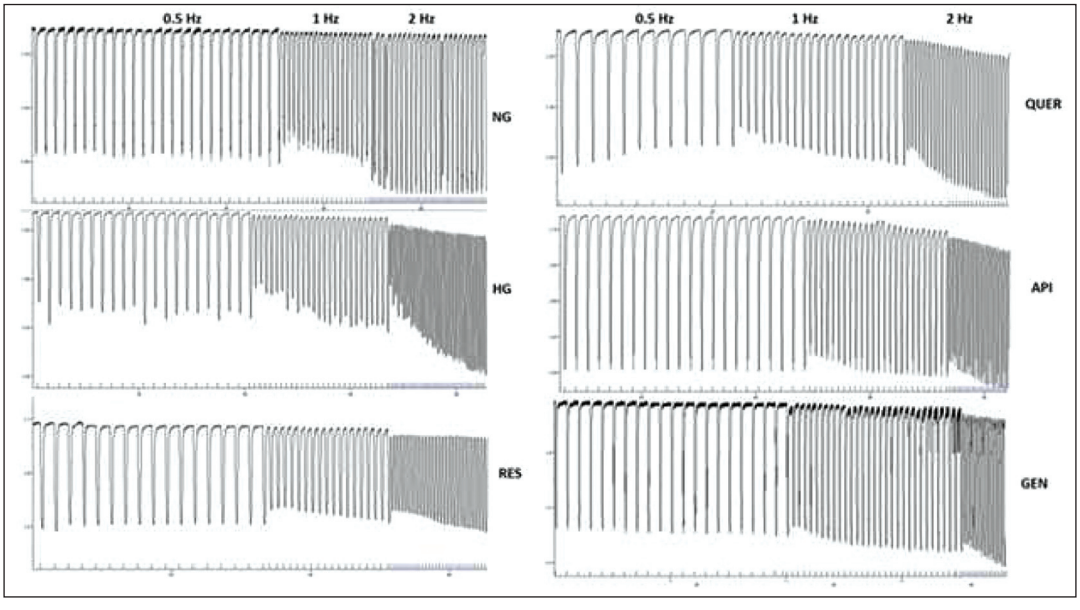


FIGURE 4: Representative shortening-lengthening graphs for each group of cardiomyocytes subjected to frequencies of 0.5 Hz, 1 Hz, and 2 Hz
NG: Normoglycemic (5.5 mmol/L); HG: Hyperglycemic (25.5 mmol/L); Res: Resveratrol; Quer: Quercetin; Api: Apigenin; Gen: Genistein

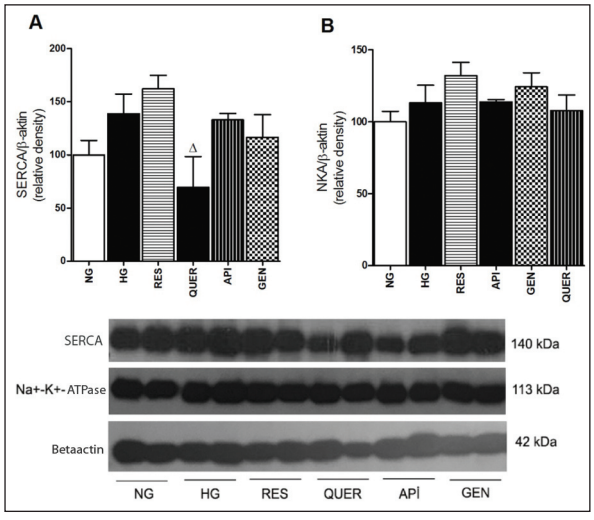


FIGURE 5: Protein expressions and representative signals for the groups **A)** SERCA, **B)** NKA (n=4-6)
^p<0.05 significance according to resveratrol receiving group;
SERCA: Sarcoplasmic/endoplasmic reticulum Ca2+ ATPase; NKA: Na+/K+ ATPase;
NG: Normoglycemic; HG: Hyperglycemic; Res: Resveratrol;
Quer: Quercetin; Api: Apigenin; Gen: Genistein

Sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA) and Na^{+}/K^{+} ATPase (NKA) expressions were then evaluated. SERCA expression was found to be increased in HG cells. A similar increase with a higher rate was observed in cells incubated with resveratrol, apigenin, and genistein. Conversely, quercetin had a reducing effect on SERCA expression (Figure 5). There was no significant difference in NKA expression between the groups, except a significant increase was observed in cells incubated with resveratrol (Figure 5).

DISCUSSION

Hyperglycemia is a significant health concern with many adverse effects, leading patients to seek additional solutions alongside their treatments. One of these options is the use of polyphenols. Therefore, understanding the potential effects of polyphenols is crucial. In this study, we assessed the direct effects of various polyphenolic compounds on cardiomyocyte contractility by examining their impact on shortening and lengthening at the cellular level. The effectiveness of each polyphenolic substance varied. Among the compounds investigated, resveratrol emerged as the most effective preventive treatment against hyperglycemia, as evidenced by its significant improvement in shortening and lengthening parameters. In contrast, quercetin showed reduced effectiveness, while apigenin and genistein had moderate effects on peak shortening. Only resveratrol improved rate of relaxation, whereas the others did not have a preventive effect on this parameter.

These results align with previous studies highlighting the cardioprotective effects of resveratrol.[7,13-15] Resveratrol is an extensively investigated polyphenol known for its beneficial effects. Our study further supports its protective role at the level of individual cardiomyocytes, likely due to its enhancement of SERCA and NKA activity, which improves Ca^{2+} signaling.

Conversely, quercetin, has been shown to have cardioprotective effects, including antioxidant, anti-inflammatory, lipid and blood pressure lowering properties.[16] Similarly, genistein has shown improvements in ischemia and reperfusion injury, cardiac toxicity, lipid and blood pressure profile.[17] Apigenin is also recognized for its beneficial effect on atherosclerosis, stroke, hypertension, and ischemia/reperfusion injury.[18] However, our findings suggest that these compounds do not significantly impact single cardiomyocytes at the tested time and concentrations.

Our study indicates that resveratrol improves cardiac function in conditions associated with impaired contractility, such as diabetes. The differential effects of various polyphenols highlight the importance of tailoring therapeutic strategies to target specific pathways.

While resveratrol's positive effects on cardiomyocytes align with previous literature, the lack of significant impact observed with quercetin, apigenin and genistein warrants further investigation. One possible explanation is that these polyphenols may influence different molecular pathways that are not directly involved in the regulation of cardiomyocyte contractility, compared to resveratrol that is known for improving calcium signaling and activating protective pathways.[19] Besides, although the doses selected were based on the literature, using

only a single concentration in the current study is a limitation which may be limiting the effectiveness of the tested drugs. Another limitation of our study is the use of isolated cardiac myocytes, which may not fully represent the complex environment of the intact heart. Thus, these results should be interpreted carefully before applying to clinical settings. Additionally, the acute HG conditions and short duration of polyphenol exposure may not capture the long-term effects on cardiac function. Future *in vivo* studies should investigate the long-term effects of polyphenol treatment on cardiac health.

Future studies should focus on exploring the long term effects of polyphenol treatment in more clinically relevant models, such as *in vivo* experiments using chronic exposure and different dosages. Addressing the limitations of the current study will help to provide a more comprehensive understanding of the potential therapeutic roles of polyphenols in hyperglycemia-induced cardiac dysfunction.

CONCLUSION

In conclusion, our study demonstrates that polyphenols differ in their direct effects on cardiac contractility, with resveratrol showing the most pronounced cardioprotective effect. The lack of effect from quercetin, apigenin and genistein may relate to differences in molecular targets or tested doses. The novelty of our study lies in its direct comparison of multiple polyphenols on single cell contractility in a diabetes-like model. These results underscore the potential of polyphenols as adjuncts therapies and pave the way for further research into their mechanisms of action and clinical applications. Importantly, while our results offer valuable insights into the cardioprotective potential of polyphenols, future studies are needed to investigate their translational relevance in human models.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gizem Kayki Mutlu, Ebru Arıoğlu İnan, Nuray Arı;* ***Design:*** *Gizem Kayki Mutlu, Ebru Arıoğlu İnan, Betül Rabia Erdoğan Vadacca, Zeynep Elif Yeşilyurt Dirican, Nuray Arı;* ***Control/Supervision:*** *Gizem Kayki Mutlu;* ***Data Collection and/or Processing:*** *Gizem Kayki Mutlu, Ebru Arıoğlu İnan, Betül Rabia Erdoğan Vadacca, Zeynep Elif Yeşilyurt Dirican;* ***Analysis and/or Interpretation:*** *Gizem Kayki Mutlu, Ebru Arıoğlu İnan, Betül Rabia Erdoğan Vadacca, Zeynep Elif Yeşilyurt Dirican, Nuray Arı;* ***Literature Review:*** *Gizem Kayki Mutlu, Ebru Arıoğlu İnan, Betül Rabia Erdoğan Vadacca, Zeynep Elif Yeşilyurt Dirican, Nuray Arı;* ***Writing the Article:*** *Gizem Kayki Mutlu, Betül Rabia Erdoğan Vadacca, Zeynep Elif Yeşilyurt Dirican;* ***Critical Review:*** *Ebru Arıoğlu İnan, Nuray Arı;* ***References and Fundings:*** *Gizem Kayki Mutlu, Ebru Arıoğlu İnan, Betül Rabia Erdoğan Vadacca, Zeynep Elif Yeşilyurt Dirican, Nuray Arı.*

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