ORIGINAL ARTICLE

Effect of Quercetin and Glibenclamide Combination on PPAR-γ and Oxidative Stress: A Study on Cardiac Tissue of Diabetic Animal Model

Hendrawati A[a], Sulistyoningrum E[b]

[a]Departement of Biochemistry and Nutrition, Faculty of Medicine, Universitas Islam Indonesia, Indonesia
[b]Department of Histology and Biology, Faculty of Medicine, Universitas Islam Indonesia, Indonesia

ABSTRACT

INTRODUCTION: Type 2 diabetes mellitus (DM) contributes to cardiac failure through oxidative stress and reduced expression of peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ plays a protective role by enhancing metabolism and mitigating oxidative stress. Quercetin has been shown to activate PPAR-γ and reduce lipid peroxidation. This study aims to evaluate the effects of combining quercetin with glibenclamide on cardiac PPAR-γ expression and lipid peroxidation in diabetic rats. **MATERIALS AND METHODS:** This experimental study involved 25 paraffin-embedded cardiac tissue samples from three-month-old Wistar rats, divided into five groups: healthy control, diabetic control (placebo), diabetic with glibenclamide (5 mg/kg/day), diabetic with quercetin (20 mg/kg/day), and diabetic with both glibenclamide and quercetin. Treatments were administered orally for 4 weeks. Cardiac PPAR-γ expression was assessed via immunohistochemistry, and malondialdehyde levels were measured using the thiobarbituric acid reactive substances (TBARS) assay. **RESULTS:** Both quercetin and glibenclamide monotherapies significantly increased cardiac PPAR-γ expression. However, the combination therapy further enhanced PPAR-γ expression compared to either treatment alone ($p<0.05$). Malondialdehyde levels significantly decreased in all treated diabetic groups compared to the diabetic control, with no significant difference between monotherapy and combination groups. **CONCLUSION:** The combination of quercetin and glibenclamide enhances cardiac PPAR-γ expression more effectively than monotherapy, while reducing lipid peroxidation to a similar extent. This suggests potential synergistic benefits in managing oxidative stress-related cardiac complications in type 2 DM.

Keywords
quercetin, glibenclamide, type 2 diabetes mellitus, cardiac PPAR-γ, cardiac malondialdehyde

Corresponding Author
Dr. Asri Hendrawati
Departement of Biochemistry and Nutrition, Faculty of Medicine, Universitas Islam Indonesia, Indonesia
E-mail: 097110416@uii.ac.id

Received: 27th September 2024; Accepted: 11th April 2025

Doi: https://doi.org10.31436/imjm.v24i03/2723

INTRODUCTION

The global prevalence of diabetes mellitus (DM) among adults in 2021 reached 537 million.[1] This current prevalence of DM may not reflect the actual phenomenon in the population due to data variation among nations.[1] The prevalence of DM is predicted to reach 783 million in 2045, which may be caused by a higher prevalence of obesity, higher popularity of high-calorie food and beverages, and a higher prevalence of a sedentary lifestyle.[2–4] There are four types of DM, with the vast majority of patients suffering from type 2 DM, which reaches 95% of the total.[1]

Diabetes mellitus causes multiple organ damage, dysfunction, and failure, such as eyes, kidneys, heart, and blood vessel.[5] Type 2 diabetes mellitus is indicated by hyperglycemia, peripheral resistance to insulin, and damage on β pancreas cells.[6] Long-term hyperglycaemia in diabetes condition is the main cause of diabetes complications.[7] Various complications occurring in diabetes mellitus also may be caused by the dyslipidaemia condition related to diabetic milieu. Diabetes mellitus causes lipid metabolism disorders, which increase lipid peroxidation and increase malondialdehyde (MDA).

Increased MDA further increases the occurrence of insulin resistance and oxidative stress.[8] The increasing amount of glucose in the cell causes reactive oxygen species (ROS) formation, which activates the polyol pathway, advanced glycation end products (AGEs), protein kinase C (PKC), and hexosamine pathway. The increase in ROS is the result of imbalanced conditions of production and scavenging performed by antioxidant endogens, which directly or indirectly cause physiology function disorders on cellular macromolecules, such as DNA, protein, and lipids. Reactive oxygen species also activate sensitive signal pathways toward stress.[9] Moreover, excessive ROS production such as MDA causes diabetes complication such as neuropathy and cardiomyopathy.[10] Diabetes complication prevention can be done by decreasing ROS production. An example of ROS production alleviation through a scavenging mechanism performed by endogenous antioxidants is the superoxide dismutase enzyme (SOD) which alters the super-oxidant to be an unhazardous substance for cells.[11]

The important gene related to glucose and lipid metabolism is peroxisome proliferator-activated receptor-γ (PPAR-γ). This gene is primarily expressed in adipose cells, the liver, and muscles. In glucose metabolism, PPAR-γ increases the activity of insulin receptor substrate (IRS-1) and glucose transporter (GLUT)-4, and thus, insulin sensitivity improves.[12] PPAR-γ increases lipid metabolism through inducing lipoprotein lipase, decreasing leptin, and increasing adipose cell differentiation.[13]

Nowadays, the administration of oral hypoglycemic agents is less effective in reducing oxidative stress in a diabetic patient. Therefore, giving antioxidants such as flavonoids plays an important role in DM therapy to protect cells from damage induced by free radicals. Quercetin is one of the flavonoid antioxidants. This compound is found in some plants, such as garlic, onion, green cabbage, apple, green tea leaf, and red grape. Quercetin and other antioxidants have the potential to prevent oxidative stress and thus prevent complications.[14,15]

Quercetin can increase the activity of antioxidant enzymes such as SOD, glutathione peroxidase, and catalase because they can increase the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and have a protection effect on the cardiac muscle and from damage caused by oxidative stress.[16,17] Hypoglycemic effect of quercetin can be done through increasing phosphorylation of tyrosine kinase, and thus, insulin activity increases.[18] Quercetin affects PPAR-γ expression. Activated PPAR-γ will bind to Liver X receptors (LXRs) and prevent lipogenic activity. Liver X receptors is a gene that triggers lipid metabolism, including decreased lipid peroxidation and MDA production, and the expression of lipogenic gene through the gene transcription of sterol regulatory element binding protein (SREBP)-1c.[19,20] PPAR-γ increases insulin sensitivity and glucose removal by cells. Quercetin increases PPAR-γ expression, thus increasing insulin sensitivity and glucose removal by cells. This mechanism decreases the blood sugar level of a diabetic patient.[21,22] Quercetin reduces malondialdehyde in various tissues such as the cardiac, kidneys, and liver.[23] Sulphonylureas such as glibenclamide and glimepiride have been studied to increase the hormone adiponectin. It is suspected that this effect is because sulphonylureas directly or indirectly affect the PPAR-γ expression pathway.[24] Glibenclamide also reduces oxidative stress by reducing malondialdehyde and increasing reduced glutathione (GSH) in various tissues.[25] Quercetin is often compared with diabetes mellitus drugs of choice, such as glibenclamide and metformin, in terms of its effect on reducing oxidative stress and improving condition in diabetes mellitus. According to previous research, quercetin can be combined with standard medicine for DM therapy and is thought to have better effects.[26] There has been no research combining quercetin and glibenclamide on the expression of PPAR-γ and malondialdehyde, including in cardiac tissue.

It is important to investigate the effects of the combination of quercetin and glibenclamide for DM treatment by reducing oxidative stress and increasing the expression of PPAR-γ. It is necessary to investigate whether combining quercetin with glibenclamide has a synergistic or antagonistic effect. This research aims

to investigate the effect of quercetin and glibenclamide combination on PPAR-γ and MDA in cardiac diabetic rats. The result of this research gives a crucial contribution to an elaborate comprehensive understanding of the usage of antioxidants in the treatment of diabetes mellitus.

MATERIALS AND METHODS

Research Design

This study used the post-test only with a control design. It was conducted at the Integrated Research Laboratory, Universitas Islam Indonesia, from May to August 2020.

Population and Sample

The protocol of this study was approved by the Ethical Comittee of Medical and Health Research Faculty of Medicine Universitas Islam Indonesia, number 04/Ka.Kom.Et/70/KE/XII/2015. This research used paraffin blocks of cardiac tissue of three-month-old male Wistar rats weighing 150-250 grams.

The number of samples was calculated based on the formula Federer:[27]

(n-1) (t-1) ≥15
n= the number of subjects in each group.
t= number of groups
(n-1) (5-1) ≥15 ➡ (n-1)X4≥15
(n - 1) ≥ 1 5 / 4 ➡ n≥3,75+1
n≥4,75 ~ 5

Thus, the number of rats per group was five rats in each group. This study used 25 rats randomly divided into 5 groups, each of which consisted of 5 rats (see Table I). Diabetic conditions were induced using intra-peritoneally streptozotocin (Sigma®) dosage 60 mg/kg, dissolved in citrate buffer with pH 4.5, and nicotinamide (Sigma®) dosage 120 mg/kg, dissolved in citrate buffer with pH 4.5. One week after the induction, the rat's fasting blood sugar was examined using spectrophotometry. Rats with fasting blood sugar of more than 126 mg/dL were considered diabetic rats and were involved in the study. Treatment was given orally for 4 weeks.[28,29]

Table I: The group description

Groups	Description
K1	Group of healthy rats without treatment
K2	Group of diabetic rats given placebo/day
K3	Group of diabetic rats given glibenclamide 5 mg/kg/day[29]
K4	Group of diabetic rats given quercetin 20 mg/kg/day
K5	Group of diabetic rats given quercetin 20 mg/kg/day and glibenclamide 5 mg/kg/day

Histological analysis

After treatment, the rats were anesthetized using ketamine 1 mg/kg intramuscular and underwent euthanasia. A surgical incision was performed at the thoracal area and cardiac tissue was taken and then fixed in formalin 10% for 3x 24 h. The tissue specimen was then dehydrated with a serial alcohol solution, and then the tissue was embedded in a paraffin block. The paraffin block was sectioned off 5 mm thick and then processed in 3% hydrogen peroxide for 20 minutes at 24-25°C. The slides were then treated with 0.01 M citrate buffer with a pH of 6.0 in boiling water. The slides were then incubated with primary antibody anti-PPAR-Ɣ (Sigma®, catalog No. SAB4502262) and then left overnight at room temperature. After that, the slides were washed in PBS (phosphate-buffered saline) and treated with streptavidin complex and chromogen (diaminobenzidine). After the slides were counterstained with hematoxylin, the slides were ready to be measured for the expression level of PPAR-ɣ. Cells that positively expressed PPAR-ɣ showed brown nuclei while cells with negative expression showed blue nuclei. The PPAR-ɣ expression level was measured as percentage of positive cells divided by all cells. PPAR-ɣ percentage was examined from 5 fields of view on each slide.[28] The calculations were performed independently by two individuals using a blinded method, and the results were subsequently averaged.

MDA analysis

The cardiac wall was dissected and then rinsed with cold saline. The tissue was then weighed and pushed between filter papers. The tissue was homogenized in a cold solution made from PBS and potassium phosphate 50 mM at pH 7.4. The homogenate was then centrifugated at 3,000 rpm at 4°C for 20 minutes, and then the supernatant was taken to analysis. A 200 µl of 20% TCA

(trichloroacetic acid) and 400µl 0.67% thiobarbituric acid were added into 400µL supernatant. The mixture was then mixed with a vortex, heated for 50 minutes, and cooled at room temperature. The absorbance of the sample was measured at 532 nm, as a result was expressed in nmol/g.[30]

Statistics

We ran statistical analyses using IBM SPSS Statistics version 20.0 (SPSS Inc., Chicago, IL, USA). The normality of the data was tested with Shapiro-Wilk. Normally distributed data were presented as mean ± standard deviation. The differences in PPAR-ɣ expression levels were analyzed using one-way ANOVA and post hoc LSD. The differences in MDA levels were analyzed using one-way ANOVA and post hoc LSD.

RESULTS

The weight and fasting blood glucose in this study were eligible, so all rats were given complete treatment. The MDA levels and PPAR-ɣ expression level data were normally distributed and had same variance, so the data was tested using One-Way ANOVA. Figure 1 shows the cardiac muscles that express PPAR-γ in the nucleus of each group. Figure 2 shows the comparison of PPAR-ɣ expression percentage each group.

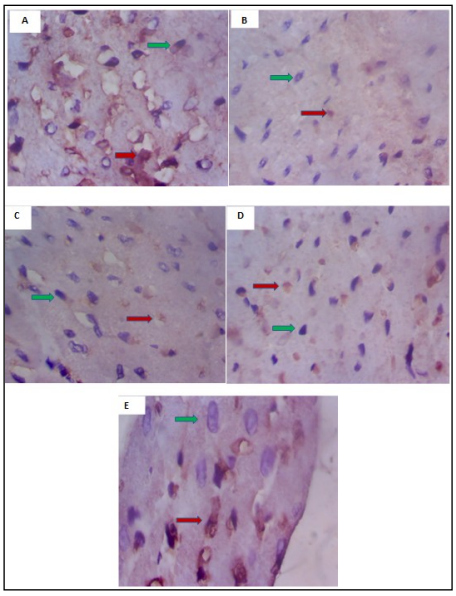

Figure 1. Representative photomicrograph of cardiac muscles each group. Cardiac muscle cells' nuclei that express PPAR-ɣ were stained brown (red arrow) while cardiac muscle cells' nuclei that did not express PPAR-ɣ were stained blue (green arrow). K1 (A): healthy rats, K2 (B): diabetic rats, K3 (C): diabetic rats given glibenclamide 5 mg/kg/day, K4 (D): diabetic rats given quercetin 20 mg/kg/day (D), and K5 (E): diabetic rats given quercetin 20 mg/kg/day and glibenclamide 5 mg/kg/day, 400X magnification.

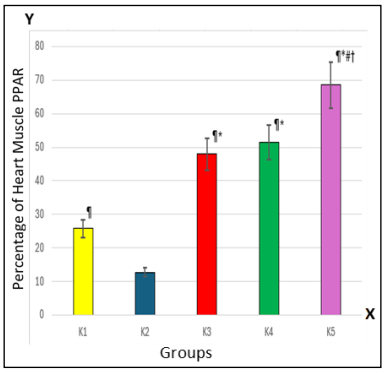

Figure 2: Comparison of PPAR-ɣ expression percentage among groups. The X-axis represents the groups, and the Y-axis represents the percentage of PPAR-ɣ in heart muscle. K5 expresses the highest PPAR-ɣ, and K2 expresses the lowest PPAR-ɣ. K3 and K4 express PPAR-ɣ higher than K1. ¶p < 0.05 compared with K2, *p<0.05 compared with K1, # p<0.05 compared with K3, †# p<0.05 compared with K4, ANOVA followed with LSD analyses. K1: healthy rats, K2: diabetic rats, K3: diabetic rats given glibenclamide 5 mg/kg/day, K4: diabetic rats given quercetin 20 mg/kg/day, and K5: diabetic rats given quercetin 20 mg/kg/day and glibenclamide 5 mg/kg/day.

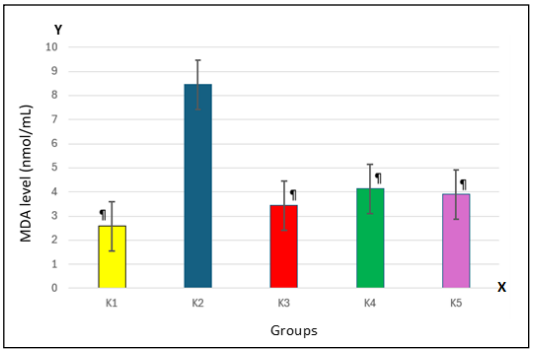

Figure 3: Comparison of MDA level among groups. The X-axis represents the groups, and the Y-axis represents the MDA level (nmol/ml). ¶p < 0.05 compared with K2, ANOVA followed with LSD analyses. K1: healthy rats, K2: diabetic rats, K3: diabetic rats given glibenclamide 5 mg/kg/day, K4: diabetic rats given quercetin 20 mg/kg/day, and K5: diabetic rats given quercetin 20 mg/kg/day and glibenclamide 5 mg/kg/day.

Based on Figure 2, group K5 expresses the highest PPAR-ɣ, and group K2 expresses the lowest PPAR-ɣ. Group K3 and K4 express PPAR-ɣ higher than K1.

Figure 3 shows a comparison of MDA levels among groups, where group K2 shows the highest MDA level and groups K3, K4, and K5 show higher MDA levels than K1. Post hoc test reveals significant difference between K2 and all other groups.

DISCUSSION

From the results, the untreated diabetic group showed the highest cardiac tissue MDA level, representing a high status of oxidative stress. This result is concomitant with other research that reported elevated cardiac myocytes' MDA levels.[31,32] Previous research reported that diabetes mellitus induces lipid metabolism dysfunction, and increases lipid peroxidation and malondialdehyde.[33] Oxidative stress plays a substantial role

in the organ-targeted complications of diabetes. The imbalance of redox status may be caused by the robust production of free radicals and reduction of the antioxidant system, which is detrimental to the cells and may lead to cellular dysfunction and further cellular injury.[34,35]

From this perspective, oxidative stress, chronic inflammatory reaction, defects in glucolipid metabolism, and reactive oxygen species (ROS) generation are considered as the potential pathophysiological condition underlying diabetic cardiomyopathy.[36] Therefore, the administration of antioxidants, which bring back the balance between reactive oxygen species (ROS) accumulation and scavenging, can be a promising candidate for cardiac myopathy treatment.[37]

Our current research also reported that the administration of glibenclamide reduces cardiac muscle cells MDA level. This result is consistent with a previous study, which reported that sulfonylurea, such as glibenclamide, were shown to have antioxidant effects and reduce MDA levels.[38] Conversely, a previous study reported that glibenclamide produced no significant effects on TBARS and antioxidant enzymes except GPx in diabetic rats.[39] Another study reported that despite glibenclamide reducing oxidative stress biomarkers in diabetic patients, the level of antioxidant properties is still less than metformin.[25]

We reported that administering quercetin reduces cardiac muscle cells MDA level. In previous studies, quercetin was able to reduce oxidative stress, including reducing MDA levels.[17] We previously also reported that quercetin improves cardiac cell damage and attenuates diabetes-induced cardiac muscle cell fibrosis via promoting the nuclear translocation of Nrf2 in cardiac cells of diabetic rats.[40,41]

In this study, the combination of quercetin and glibenclamide showed no difference in reduced MDA levels capability as with each administration. However, the authors have not found any research that measures the effect of quercetin and glibenclamide combinations on the MDA level. A previous study showed that combining quercetin and gliclazide (another sulphonylurea agent) reduces oxidative stress by increasing superoxide dismutase enzymes and GSH better than without a combination, but no difference in MDA levels. Both probably do not have agonistic or antagonistic properties on MDA levels.[42]

On PPAR-*γ* expression level percentage measurement of cardiac muscle cells, the lowest percentage of PPAR-*γ* is found in a group of diabetic rats given a placebo (K2), and the highest percentage of PPAR-*γ* is found in a group of diabetic rats given quercetin 20 mg/kg/day (K4) and glibenclamide dose 5 mg/kg/day combination. In the diabetic rats group given a glibenclamide dose of 5 mg/kg/day, the PPAR-*γ* percentage was significantly increased. Gene PPAR-*γ* bound to its ligands will translocate from the cytoplasm to the nucleus and become active. Those transcription factors have a role in adipose cell differentiation and can trigger gene expression, which involves fat metabolism. Previous research showed that diabetes mellitus agents are ligands for PPAR-*γ* and can increase expression and activity of PPAR-*γ,* thus being profitable for patients of type 2 DM because PPAR-*γ* will improve fatty acid storage in adipose tissues, thus improving muscle sensitivity toward insulin.[43] This condition is in line with the previous research that sulphonylureas, such as glimepiride and glibenclamide, can increase the transcription activity of PPAR-*γ* because they become the ligands.[44] Another research also reports that sulphonylureas are an agonist for PPAR-*γ* and increase the transcriptional activity of PPARγ.[45]

In the group of diabetic rats given quercetin 20 mg/kg/day, the PPAR-*γ* percentage significantly increased. This finding aligns with the previous research that quercetin can increase PPAR-*γ* gene expression because quercetin is a ligand for the PPAR-*γ* receptor. Therefore, quercetin can activate PPAR-*γ*. Liu et al. reported that quercetin improved cardiac damage induced by ischemia and reperfusion injury by activating PPARγ and probably inhibiting the NF-κB (Nuclear factor kappa B) pathway.[46] Another study showed that quercetin can increase the activity of Nrf2, which can form a complex heterodimer and DNA along with PPAR-γ. Therefore, quercetin can

indirectly activate PPAR-γ.[19] Previous research reported that quercetin influences signal transduction and intensifies the utilization of glucose by intervening in the transportation of glucose and insulin-receptor signaling. This function is similar to the effect of a PPAR-γ agonist.[47]

In the group of diabetic rats given a combination of quercetin 20 mg/kg/day and glibenclamide 5 mg/kg/day, PPAR-*γ* percentage in the nucleus of cardiac muscle cells significantly increased higher than both single administrations of quercetin and glibenclamide. The authors have not found any research that measures the effect of quercetin and glibenclamide combinations on PPAR-γ expression. However, a previous study reported that a combination of quercetin and pioglitazone (thiazolidinedione, also known as PPAR-ϒ agonist) had shown beneficial in inhibiting aortic tissue contraction modulated by angiotensin-II in type-2 diabetic animals induced by fructose and streptozotocin.[48] Previous research also showed that giving a combination of two agonists of PPAR-γ, such as fenofibrate combined with pioglitazone, tends to give effects to three types of PPAR-α,γ,δ.[49] The limitation of this study is that no dose variation was used.

CONCLUSION

Combining quercetin 20 mg/kg/day and glibenclamide 5 mg/kg/day increases cardiac muscle PPAR-γ expression better than no combination. The combination also decreases cardiac tissue MDA levels compared to no combination. From the conclusion, combining quercetin and glibenclamide can be considered as DM therapy to prevent cardiac damage. Further research involving a longer duration and dose variation of treatment is needed to establish the effect of quercetin and glibenclamide combination therapy in preventing myocardial complications from DM.

CONFLICT OF INTEREST

The authors do not have any conflicts of interest.

ACKNOWLEDGEMENT

The author's sincere gratitude to the Faculty of Medicine, Universitas Islam Indonesia for funding this research.

AUTHORS CONTRIBUTION

AH: Concept and designed the experiments, wrote and revised the manuscript; ES: Wrote and revised the manuscript

REFERENCES

1. Webber S. International Diabetes Federation. 10th ed. Vol. 102, Diabetes Research and Clinical Practice. 2021. 147–148 p.
2. Cho NH, Shaw JE, Karuranga S, et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract [Internet]. 2018;138:271–81. Available from: https://doi.org/10.1016/j.diabres.2018.02.023. Accessed April 20, 2023.
3. Ong KL, Stafford LK, McLaughlin SA, et al. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the global burden of disease study 2021. Lancet. 2023;402(10397):203–34. DOI: 10.1016/S0140-6736(23)01301-6. Accessed April 20, 2023.
4. Galaviz KI, Narayan KMV, Lobelo F, Weber MB. Lifestyle and the prevention of type 2 diabetes: a status report. Am J Lifestyle Med. 2018;12(1):4–20. DOI: 10.1177/1559827615619159. Accessed April 20, 2023.
5. Galicia-garcia U, Benito-vicente A, Jebari S, Larrea-sebal A. Costus ignus: insulin plant and it's preparations as remedial approach for diabetes mellitus. Int J Mol Sci. 2020;1–34. Available from: http://dx.doi.org/10.3390/ijms21176275. Accessed April 22, 2023.
6. Dludla P V, Mabhida SE, Ziqubu K, et al. Pancreatic β-cell dysfunction in type 2 diabetes: implications of inflammation and oxidative stress. World J Diabetes. 2023;14(3):130–46. Available from: http://dx.doi.org/10.3390/ijms21176275. Accessed April 22, 2023.

7. Mengstie MA, Chekol Abebe E, Behaile Teklemariam A, et al. Endogenous advanced glycation end products in the pathogenesis of chronic diabetic complications. Front Mol Biosci. 2022;9(September):1–11. DOI: 10.3389/fmolb.2022.1002710. Accessed April 20, 2023.
8. Goycheva P, Petkova-Parlapanska K, Georgieva E, Karamalakova Y, Nikolova G. Biomarkers of oxidative stress in diabetes mellitus with diabetic nephropathy complications. Int J Mol Sci. 2023;24 (17). DOI: 10.3390/ijms241713541. Accessed May 15, 2024.
9. Caturano A, D'Angelo M, Mormone A, et al. Oxidative stress in type 2 diabetes: impacts from pathogenesis to lifestyle modifications. Curr Issues Mol Biol. 2023;45(8):6651–66. Available from: https://doi.org/10.3390/cimb45080420. Accessed May 15, 2024.
10. Sudo SZ, Montagnoli TL, Rocha B de S, et al. Diabetes-induced cardiac autonomic neuropathy: impact on heart function and prognosis. Biomedicines. 2022;10(12). Available from: https://doi.org/10.3390/biomedicines10123258. Accessed April 20, 2023. Accessed May 15, 2023.
11. Liu J, Han X, Zhang T, et al. Reactive oxygen species (ROS) scavenging biomaterials for anti-inflammatory diseases: from mechanism to therapy. J Hematol Oncol [Internet]. 2023;16(1):1–34. Available from: https://doi.org/10.1186/s13045-023-01512-7. Accessed May 15, 2024.
12. Sharma V, Patial V. Peroxisome proliferator-activated receptor gamma and its natural agonists in the treatment of kidney diseases. Front Pharmacol. 2022;13(October):1–18. DOI: 10.3389/fphar.2022.991059. Accessed June 21, 2023.
13. Sun C, Mao S, Chen S, Zhang W, Liu C. Ppars-orchestrated metabolic homeostasis in the adipose tissue. Int J Mol Sci. 2021;22(16). Available from: https://doi.org/10.3390/ijms22168974. Accessed June 21, 2023.
14. Anand David AV, Arulmoli R, Parasuraman S. Overviews of biological importance of quercetin: a bioactive flavonoid. Pharmacogn Rev. 2016;10 (20):84–9. DOI: 10.4103/0973-7847.194044. Accessed January 11, 2020.
15. Ansari P, Choudhury ST, Seidel V, et al. Therapeutic potential of quercetin in the management of type-2 diabetes mellitus. Life. 2022;12(8):1–18. Available from: https://doi.org/10.3390/life12081146. Accessed June 21, 2023.
16. Zhang L, Xu LY, Tang F, et al. New perspectives on the therapeutic potential of quercetin in non-communicable diseases: targeting Nrf2 to counteract oxidative stress and inflammation. J Pharm Anal [Internet]. 2024;14(6):100930. Available from: https://doi.org/10.1016/j.jpha.2023.12.020. Accessed August 31, 2024.
17. Qi W, Qi W, Xiong D, Long M. Quercetin: its antioxidant mechanism, antibacterial properties and potential application in prevention and control of toxipathy. Molecules. 2022;27(19). Available from: https://doi.org/10.3390/molecules27196545. Accessed June 21, 2023.
18. Sok YF, Shu QC, Tan SSS, et al. Hypoglycemic effects of plant flavonoids: a review. Evidence-based Complement Altern Med. 2021;2021. Available from: https://doi.org/10.1155/2021/2057333. Accessed June 21, 2023.;2021.
19. Ballav S, Biswas B, Sahu VK, Ranjan A, Basu S. PPAR-γ partial agonists in disease-fate decision with special reference to cancer. Cells. 2022;11(20). Available from: https://doi.org/10.3390/cells11203215. Accessed June 21, 2023.
20. Aghababaei F, Hadidi M. Recent advances in potential health benefits of quercetin. Pharmaceuticals. 2023;16(7):1–31. Available from: https://doi.org/10.3390/ph16071020. Accessed March 12, 2024.
21. Kim NY, Lim CM, Park HM, et al. MMPP promotes adipogenesis and glucose uptake via binding to the PPARγ ligand binding domain in 3T3-L1 MBX cells. Front Pharmacol. 2022;13(October):1–12. DOI: 10.3389/fphar.2022.994584. Accessed March 12, 2024.
22. Wang JY, Nie YX, Dong BZ, et al. Quercetin protects islet β-cells from oxidation-induced apoptosis via Sirt3 in T2DM. Iran J Basic Med Sci. 2021;24(5):629–35. DOI: 10.22038/ijbms.2021.52005.11792 . Accessed March 23, 2023.

23. Arslan A. S., Seven I. MSI. Potential ameliorative effect of dietary quercetin against lead-induced oxidative stress, biochemical changes, and apoptosis in laying Japanese quails. Ecotoxicol Environ Saf. 2022;231. DOI: 10.1016/j.ecoenv.2022.113200. Accessed December 1, 2024.
24. Emini-Sadiku M, Car N, Begolli L, et al. The differential influence of glimepiride and glibenclamide on insulin resistance and adiponectin levels in patients with type 2 diabetes. Endocr J. 2019;66(10):915–21. DOI: 10.1507/endocrj.EJ18-0493. Accessed December 1, 2024.
25. Almulathanon AAY, Mohammad JA, Fathi FH. Comparative effects of metformin and glibenclamide on the redox balance in type 2 diabetic patients. Pharmacia. 2021;68(2):327–32. DOI:10.3897/pharmacia.68.e63365. Accessed December 2, 2024.
26. Bashiri M, Ahangarpour A. A comparison between the effectiveness of quercetin and glibenclamide on β -cells of male mice under oxidative stress. Rom J Diabetes, Nutr Metab Dis. 2024;31(2):126–32. DOI: 10.46389/rjd-2024-1411. Accessed December 2, 2024.
27. Lusiantari R, Pramaningtyas MD, Nurmasitoh T, Pattimura RH, Dewanti A. Shortening tends to increase aortic foam cell count and wall thickness in male Wistar rats. Universa Med. 2018;37(1):13–8. Available from: http://dx.doi.org/10.18051/UnivMed.2018.v37.13-18. Accessed January 14, 2020.
28. Hendrawati A, Winardi M. Effects of quercetin and omega-3 combination on nuclear factor kappa B (NFkB) expression level in pancreatic tissue of rats with type-2 diabetes mellitus. J Pharm Nutr Sci. 2017;7(1):1–5. Available from: https://doi.org/10.18051/UnivMed.2014.v33.185-191. Accessed January 14, 2020.
29. Bayani M, Ahmadi-Hamedani M, Javan AJ. Study of hypoglycemic, hypocholesterolemic and antioxidant activities of Iranian Mentha spicata leaves aqueous extract in diabetic rats. Iran J Pharm Res. 2017;16 (August 2015):75–82. Accessed January 14, 2020.
30. Alamoudi AA, Alharbi AS, Abdel-Naim AB, et al. Novel nanoconjugate of apamin and ceftriaxone for management of diabetic wounds. Life. 2022;12(7). DOI: 10.3390/life12071096. Accessed January 14, 2024.
31. Farrag EAE, Hammad MO, Safwat SM, Hamed S, Hellal D. Artemisinin attenuates type 2 diabetic cardiomyopathy in rats through modulation of AGE -RAGE/HMGB-1 signaling pathway. Sci Rep [Internet]. 2023;13(1):1–13. Available from: https://doi.org/10.1038/s41598-023-37678-w. Accessed January 21, 2024.
32. Shabab S, Mahmoudabady M, Gholamnezhad Z, Fouladi M, Asghari AA. Diabetic cardiomyopathy in rats was attenuated by endurance exercise through the inhibition of inflammation and apoptosis. Heliyon [Internet]. 2024;10(1):e23427. Available from: https://doi.org/10.1016/j.heliyon.2023.e23427. Accessed August 31, 2024.
33. Shalash M, Badra M, Imbaby S, ElBanna E. Malondialdehyde in type 2 diabetics and association with cardiovascular risk factors. J Med Res Inst. 2020;41(2):21–30. DOI:10.21608/jmalexu.2020.147116. Accessed August 31, 2023.
34. De Geest B, Mishra M. Role of oxidative stress in diabetic cardiomyopathy. Antioxidants. 2022;11(4). DOI: 10.3390/antiox11040784. Accessed August 31, 2023.
35. Byrne NJ, Rajasekaran NS, Abel ED, Bugger H. Therapeutic potential of targeting oxidative stress in diabetic cardiomyopathy. Free Radic Biol Med [Internet]. 2021;169(April):317–42. Available from: https://doi.org/10.1016/j.freeradbiomed.2021.03.046. Accessed August 21, 2023.
36. Tang Z, Wang P, Dong C, et al. Oxidative Stress Signaling Mediated Pathogenesis of Diabetic Cardiomyopathy. Oxid Med Cell Longev. 2022;2022 (1). DOI: 10.1155/2022/5913374. Accessed August 21, 2023.
37. Xu N, Liu S, Zhang Y, et al. Oxidative stress signaling in the pathogenesis of diabetic cardiomyopathy and the potential therapeutic role of antioxidant naringenin. Redox Rep. 2023;28(1). DOI: 10.1080/13510002.2023.2246720. Accessed July 31, 2024.
38. Nunes PR, Bueno Pereira TO, Bertozzi Matheus M, et al. Glibenclamide Increases Nitric Oxide Levels

and Decreases Oxidative Stress in an In Vitro Model of Preeclampsia. Antioxidants. 2022;11(8). DOI: 10.3390/antiox11081620. Accessed December 12, 2023.

39. Erejuwa OO, Sulaiman SA, Wahab MSA, et al. Antioxidant protective effect of glibenclamide and metformin in combination with honey in pancreas of streptozotocin- induced diabetic rats. Int J Mol Sci. 2010;11(5):2056–66. Available from: https://doi.org/10.3390/ijms11052056. Accessed August 31, 2023.
40. Hendrawati A, Nadhir N. Quercetin reduce cardiomyocytes damage in type 2 diabetic rats. Univ Med 2014;33(3):185–91. Available from: https://doi.org/10.18051/UnivMed.2014.v33.185-191. Accessed August 11, 2024.
41. Wei Z, Jing Z, Pinfang K, Chao S, Shaohuan Q. Quercetin inhibits pyroptosis in diabetic cardiomyopathy through the Nrf2 pathway. Genet Res (Camb). 2022;2022. DOI: 10.1155/2022/9723632. Accessed August 31, 2023.
42. Abdelkader NF, Eitah HE, Maklad YA et al. New combination therapy of gliclazide and quercetin for protection against STZ-induced diabetic rats. Life Sci [Internet]. 2020 [cited 2023 Dec 3];247. Available from: https://doi.org/10.1016/j.lfs.2020.117458.
43. Cai W, Yang T. Peroxisome proliferator-activated receptor γ (PPARγ): a master gatekeeper in CNS injury and repair. Physiol Behav [Internet]. 2019;176 (3):139–48. Available from: file:///C:/Users/Carla Carolina/Desktop/Artigos para acrescentar na qualificação/The impact of birth weight on cardiovascular disease risk in the.pdf. Accessed April 21, 2024.
44. Haas B, Hass MDS, Voltz A, et al. Sulfonylureas exert antidiabetic action on adipocytes by inhibition of PPARγ serine 273 phosphorylation. Mol Metab [Internet]. 2024;85(May):101956. Available from: https://doi.org/10.1016/j.molmet.2024.101956. Accessed August 31, 2024.
45. Xi Y, Zhang Y, Zhu S, et al. PPAR-mediated toxicology and applied pharmacology. Cells. 2020;9 (2). DOI:10.3390/cells9020352. Accessed January 31, 2024.
46. Liu X, Yu Z, Huang X, et al. Peroxisome proliferator-activated receptor γ (PPARγ) mediates the protective effect of quercetin against myocardial ischemia-reperfusion injury via suppressing the NF-ϰB pathway. Am J Transl Res. 2016;8(12):5169–86. Accessed January 31, 2024.
47. Dhanya R, Arya AD, Nisha P, Jayamurthy P. Quercetin, a lead compound against type 2 diabetes ameliorates glucose uptake via AMPK pathway in skeletal muscle cell line. Front Pharmacol. 2017;8 (JUN):1–9. DOI: 10.3389/fphar.2017.00336. Accessed April 11, 2024.
48. Kunasegaran, T., Mustafa, M. R., Murugan, D. D. & Achike FI. The bioflavonoid quercetin synergises with PPAR-γ agonist pioglitazone in reducing angiotensin-II contractile effect in fructose-streptozotocin induced diabetic rats. Biochimie. 2017;125:131–9. DOI: 10.1016/j.biochi.2016.03.008. Accessed April 11, 2024.
49. Honda A, Kamata S, Akahane M, et al. Functional and structural insights into human pparα/δ/subtype selectivity of bezafibrate, fenofibric acid, and pemafibrate. Int J Mol Sci. 2022;23(9). Available from: https://doi.org/10.3390/ijms23094726. Accessed April 11, 2024.