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Molecular docking analysis of flavonoid compounds from gandaria (*Bouea macrophlla* Griff) as potential alpha-glucosidase inhibitors

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Abstract: Diabetes mellitus represents a significant metabolic disorder with elevated global prevalence, necessitating development of effective antidiabetic therapies. This study investigates flavonoid compounds from gandaria (*Bouea macrophylla* Griff) as potential α-glucosidase inhibitors through molecular docking analysis. Eight flavonoid compounds were evaluated against human α-glucosidase enzyme (PDB ID: 2QMJ) using AutoDock Tools version 1.5.6. The methodology achieved validation with an RMSD value of 1.98 Å, confirming computational reliability. Lipinski's Rule of Five assessment identified four compounds meeting drug-likeness criteria for analysis. Quercetin demonstrated the strongest binding affinity among tested compounds with a binding energy of -4.72 kcal/mol, compared to the native ligand N-acetylglucosamine at -5.12 kcal/mol. Interaction analysis revealed quercetin formed significant hydrogen bonds with key active site residues including Lys389, Asn393, and Asn417, indicating potential competitive inhibition mechanisms. All flavonoid compounds exhibited consistent binding patterns with Lys389 serving as a critical interaction site. These computational findings establish quercetin as the most promising flavonoid candidate for α-glucosidase inhibition, supporting its potential as a natural antidiabetic agent.

Keywords: α-glucosidase inhibitor, antidiabetic agents, flavonoids, gandaria, molecular docking, quercetin

Introduction

Diabetes Mellitus (DM) represents a complex metabolic disorder that occurs when the body cannot produce sufficient insulin or utilize insulin effectively, resulting in elevated blood glucose levels [1]. According to the Riset Kesehatan Dasar 2013 database, DM prevalence in Indonesia reached 1.5%, with a subsequent increase of 0.5% documented in 2018 [2]. Indonesia currently ranks seventh among the ten countries with the highest global DM prevalence [3]. Without effective prevention and treatment strategies, the International Diabetes Federation projects that global DM cases will reach 700 million individuals by 2045 [4].

The pathophysiology of DM involves the body's inability to produce or utilize insulin in adequate quantities, leading to sustained hyperglycemia. Therapeutic interventions focus on reducing and maintaining stable blood glucose concentrations through inhibition of carbohydrate hydrolysis enzymes, particularly α-amylase and α-glucosidase, which effectively delays glucose absorption [5]. The digestive tract plays a crucial regulatory role in carbohydrate metabolism. Research by Khadayat et al. (2020) demonstrates that digestive tract α-amylase, secreted by pancreatic and salivary glands, facilitates the initial conversion of complex carbohydrates into oligosaccharides and simple sugars in the intestinal mucosa, which subsequently undergo conversion to glucose in the small intestine [6]. Competitive inhibition of α-glucosidase activity results in delayed carbohydrate digestion and absorption processes, thereby contributing to improved glycemic control [7,8].

The complex pathophysiology of DM and its high prevalence in Indonesia necessitate continued therapeutic development efforts. The exploration of natural compounds as DM therapeutics represents a promising avenue, given Indonesia's rich biodiversity. Flavonoid compounds have demonstrated significant potential as antidiabetic agents. Previous research has established that flavonoids possess the ability to inhibit α-glucosidase enzyme activity isolated from

Saccharomyces cerevisiae and rat intestines, as well as α-amylase isolated from flavonoid-containing plant sources [9].

Biodiversity presents substantial opportunities for discovering bioactive compounds, particularly flavonoids, which have attracted considerable attention for their therapeutic properties. The application of flavonoid compounds as antidiabetic agents represents a promising research direction. Given the global increase in diabetes prevalence, there exists an urgent need to explore novel approaches for modulating carbohydrate-metabolizing enzymes, including glucoamylase and maltase, which perform critical functions in postprandial glucose regulation. Therefore, this research aims to investigate the potential of flavonoid compounds and their derivatives through *in silico* approaches to evaluate their interactions with these enzymes.

Methods

This computational docking study utilized AutoDock Tools version 1.5.6 and related software packages for molecular docking analysis. The α-glucosidase enzyme from *Homo sapiens* (PDB ID: 2QMJ, consisting of 870 amino acids) was obtained from the RCSB Protein Data Bank, featuring N-acetylglucosamine (NAG) as the co-crystallized ligand. The evaluated compounds included eight flavonoid derivatives: afzelin, kaempferol, mearnsitrin, mearnsetin, myricetin, naringenin, quercetin, and quercitrin, selected to assess their potential inhibitory interactions with the target enzyme.

Protein preparation

The initial step involved preparing the macromolecular structure for computational analysis. The α-glucosidase structure from *Homo sapiens* was retrieved from the Protein Data Bank (PDB ID: 2QMJ) through the RCSB website at https://www.rcsb.org/. The structure was downloaded in PDB format and subsequently processed using AutoDock Tools. During protein preparation, non-essential components including water molecules and ligands were removed, polar hydrogen atoms were added, and partial charges were assigned using standard protocols. The final prepared protein structure was saved in .pdbqt format to ensure compatibility with molecular docking procedures.

Validation procedure

Validation was performed to assess the repositioning accuracy of the native ligand (NAG) within the 2QMJ protein active site. The validation process employed AutoDock Tools software version 1.5.6, utilizing the Root Mean Square Deviation (RMSD) parameter to verify methodological appropriateness. The methodology was considered valid when the RMSD value remained below 2 Å, qualifying the approach for subsequent molecular docking procedures [10]. The validation process encompassed four distinct stages: protein and ligand preparation, grid box configuration, docking parameter establishment, and execution of the docking procedure.

Ligand preparation

The ligands employed in this study comprised flavonoid-derived compounds: afzelin, kaempferol, mearnsitrin, mearnsetin, myricetin, naringenin, quercitrin, and quercetin. Three-dimensional structural coordinates for these compounds were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and subsequently converted from .sdf to .pdb format using the SwissADME web-based tool (http://www.swissadme.ch/). Following format conversion, the ligand structures were prepared using AutoDock Tools to generate .pdbqt files compatible with the docking software.

Molecular docking

The 2QMJ protein structure was subjected to molecular docking analysis with the eight flavonoid-derived ligands using AutoDock Tools version 1.5.6 and the Lamarckian Genetic Algorithm method. Prior to docking execution, both protein and ligand structures were prepared in .pdbqt format according to standard protocols. The grid box dimensions were established based on validation results, utilizing coordinates of 28 × 16 × 22 Å to encompass the active site region. Following completion of docking procedures, the resulting protein-ligand interactions were analyzed and visualized using BIOVIA Discovery Studio 2021 software to assess binding poses and characterize molecular interactions within the enzyme active site.

Results

The Lipinski Rule of Five analysis was conducted to evaluate the drug-likeness properties of all ligand

Table 1. Ligand parameters for Lipinski's rule

Compounds	Molar mass (g/mol)	Log P	Number of hydrogen bond donors	Number of hydrogen bond acceptors
Afzelin	432.4	1.2	6	10
Kampferol	286.24	1.9	4	6
Mearnsitrin	478.4	0.8	7	12
Mearnsetin	332.26	1.5	5	8
Myricitin	318.23	1.2	6	8
Naringenin	580.5	-0.5	8	14
Quercitrin	448.4	0.9	7	11
Quercetin	302.23	1.5	5	7

compounds utilized in this study, providing essential pharmacokinetic assessment for potential therapeutic development. Lipinski's rule establishes that a molecule demonstrates acceptable drug-like characteristics when it satisfies four criteria: molecular weight ≤500 Da, log P value ≤5, number of hydrogen bond donors ≤5, and number of hydrogen bond acceptors ≤10 [11]. The analysis presented in Table 1 reveals that afzelin, mearnsitrin, naringenin, and quercitrin compounds violated Lipinski's criteria, while kaempferol, mearnsetin, myricetin, and quercetin satisfied all specified conditions.

Despite these violations, all eight compounds were included in the molecular docking analysis for several scientific justifications. First, this investigation represents an exploratory computational screening aimed at understanding structure-activity relationships among available flavonoid derivatives from gandaria, regardless of their initial drug-likeness profiles. Second, compounds that violate Lipinski's criteria may still provide valuable insights into binding mechanisms and serve as lead compounds for structural optimization through medicinal chemistry approaches. Third, the violations observed were primarily related to molecular weight and hydrogen bonding capacity, which can potentially be addressed through structural modifications such as glycoside cleavage or functional group optimization.

Table 2 presents a comparative analysis of binding affinity values among the tested ligands. The native ligand N-acetylglucosamine demonstrated the lowest binding energy at -5.12 kcal/mol, indicating stronger binding affinity compared to all flavonoid derivatives. This finding suggests that the evaluated flavonoid compounds possess lower binding affinity than the native ligand. The strength of molecular interactions depends on bond distances, with hydrogen bonds forming due to high electronegativity differences between atoms covalently bonded to hydrogen.

Tabel 2. Molecular docking results of ligands against 2QMJ protein

Compounds	Binding energy (kcal/mol)
Native Ligand (NAG)	-5.12
Afzelin	-3.24
Kampferol	-3.88
Mearnsitrin	-2.19
Mearnsetin	-3.24
Myricitin	-3.01
Naringenin	-3.65
Quercitrin	-2.6
Quercetin	-4.72

The molecular docking results demonstrate that quercetin achieved the most favorable binding energy among the tested flavonoid compounds at -4.72 kcal/mol. The ligand conformation with the lowest energy was selected for each compound based on binding affinity calculations. Binding affinity represents a drug's capacity to interact with its target receptor, with lower energy values indicating stronger receptor-ligand interactions.

The protein-ligand interaction analysis was visualized using BIOVIA Discovery Studio 2024 software to generate two-dimensional interaction maps.

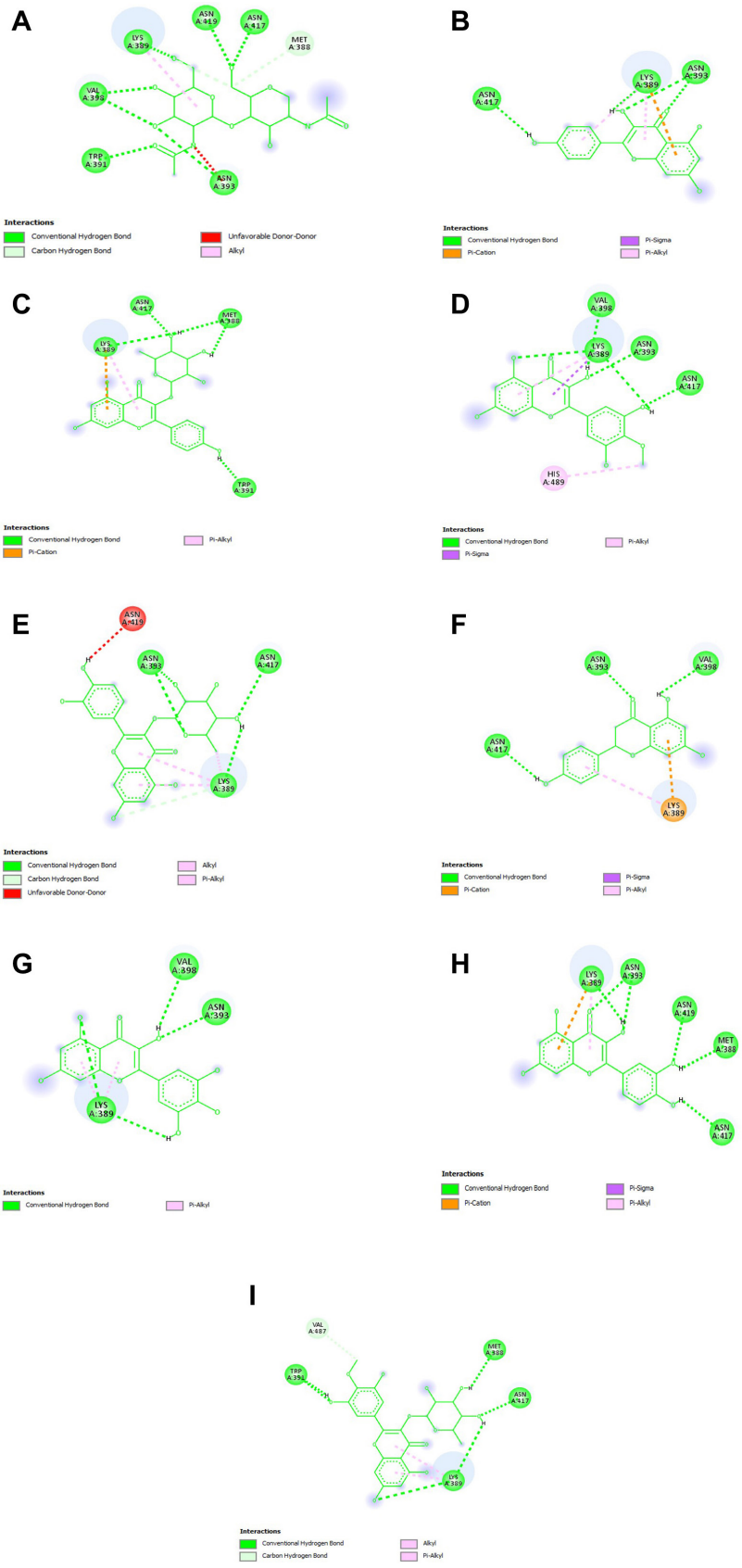

Figure 1. Two-dimensional visualization of protein-ligand interactions between 2QMJ receptor and various ligands. (A) 2-acetamido-2-deoxy-beta-D-glucopyranose (native ligand), (B) Kaempferol, (C) Afzelin, (D) Mearnsetin, (E) Quercitrin, (F) Naringenin, (G) Myricetin, (H) Quercetin, and (I) Mearnsitrin

The two-dimensional visualization analysis revealed diverse binding patterns between the 2QMJ receptor and the nine evaluated ligands. The native ligand 2-acetamido-2-deoxy-beta-D-glucopyranose established multiple interactions including unfavorable donor binding to Asn393, carbon-hydrogen bonds with Met388, and conventional hydrogen bonds with Trp391, Asn393, Val398, Lys389, Asn419, and Asn417. All flavonoid compounds demonstrated strong binding through conventional hydrogen bonds with key residues Lys389, Asn393, and Asn417, accompanied by pi-interactions including pi-sigma, pi-cation, and pi-alkyl bonds primarily involving Lys389. The consistent involvement of Lys389 across all ligands indicates its critical role in ligand recognition within the 2QMJ receptor active site.

Discussion

Physicochemical properties can be assessed using Lipinski's Rule of Five to evaluate drug-like characteristics. Molecular weight, measured in atomic mass units, should not exceed 500 Da for optimal cell membrane permeability. Molecules exceeding 500 Da encounter difficulties penetrating cellular membranes. The partition coefficient reflects substance solubility in lipid and aqueous environments, with optimal log P values ranging from -0.4 to 5. Extremely negative partition coefficients indicate poor lipid bilayer penetration capability. Increasing log P values correspond to enhanced molecular hydrophobicity. Highly water-insoluble molecules demonstrate increased toxicity potential due to their tendency to accumulate within cellular lipid bilayers and distribute extensively throughout the body, thereby reducing selective binding capacity to target enzymes. Greater numbers of hydrogen bond donors and acceptors increase hydrogen bonding capacity, requiring additional energy for molecular absorption.

This investigation employed eight flavonoid compounds for molecular docking analysis under flexible ligand conditions. Flexible ligand docking enables identification of compounds capable of establishing optimal receptor binding configurations. The primary parameter evaluated was Gibbs free energy (ΔG), where more negative values indicate enhanced stability of ligand-receptor complexes, resulting in stronger molecular interactions [12]. The AutoDock program determines Gibbs binding energy through multiple factors including van der Waals, hydrogen bonding, electrostatic, and desolvation energies. Van der Waals energy represents attractive forces between carbon atoms, while hydrogen bonding energy results from interactions between hydrogen and oxygen atoms. Electrostatic energy develops from opposite charge interactions between molecules, and desolvation energy emerges from macromolecule-ligand binding in solution.

The α-glucosidase enzyme utilized in this study was obtained from the RCSB Protein Data Bank using specific parameters for *Homo sapiens* species selection. The chosen protein (PDB ID: 2QMJ) comprises 870 amino acids. The docking procedure employed oriented docking methodology based on grid box determination as the docking target. This approach utilized flexible ligands with rigid receptor configurations, employing N-acetylglucosamine as the native ligand. N-acetylglucosamine contributes to improved insulin sensitivity, addressing a fundamental problem in type 2 diabetes. Enhanced insulin sensitivity enables more efficient cellular glucose utilization from blood circulation, facilitating blood glucose level reduction. The 2QMJ protein demonstrates known capacity for improving insulin sensitivity, allowing effective insulin utilization by body cells for glucose uptake from bloodstream. Variations in torsional flexibility affect ligand docking duration. The validation process enabled comparison of binding energy differences between the native ligand and tested flavonoid derivatives.

Grid box determination involved validation procedures using the 2QMJ protein with its native ligand. The optimal grid box configuration was established at dimensions of 28 × 16 × 22 Å (coordinates: X=4.817; Y=8.779; Z=-20.737) with a binding energy value of -5.12 kcal/mol and an RMSD reference value of 1.98 Å. The selection of flavonoids and their derivatives as antidiabetic compounds for glucoamylase maltase enzyme analysis was based on biodiversity considerations and the documented therapeutic benefits of flavonoid compounds, particularly their antidiabetic properties. Flavonoid compounds function as antidiabetics while providing dual benefits through free radical scavenging activity, preventing diabetes development by interrupting free radical reaction chains [13]. Flavonoids inhibit α-glucosidase enzyme activity through hydroxylation mechanisms and β-ring displacement [14].

The method validation results demonstrated that N-acetylglucosamine binding to 2QMJ protein yielded a binding energy of -5.12 kcal/mol. Molecular docking

analysis of target compounds produced binding energies of -3.24, -3.88, -2.19, -3.24, -3.01, -3.65, -2.6, and -4.72 kcal/mol for afzelin, kaempferol, mearnsitrin, mearnsetin, myricetin, naringenin, quercitrin, and quercetin, respectively. Quercetin demonstrated the lowest binding energy at -4.72 kcal/mol, while mearnsitrin exhibited the highest value at -2.19 kcal/mol. Quercetin was identified as possessing the most potent binding characteristics among all tested ligands.

Although quercetin demonstrated the strongest binding affinity among flavonoid compounds, its binding energy remained higher than the native ligand N-acetylglucosamine. This comparison indicates that N-acetylglucosamine maintains superior binding potential compared to quercetin. The study results suggest that quercetin possesses antihyperglycemic activity potential due to its demonstrated affinity for the 2QMJ protein. The interaction between quercetin and the 2QMJ protein may facilitate enzyme inhibition, as these interactions occur at the target protein's active site, resulting in inhibitory activity. Binding affinity between ligands and target proteins correlates with the number of amino acid residues participating in molecular interactions. Increased amino acid residue involvement strengthens ligand-protein binding relationships, and these binding interactions can lead to effective enzyme inhibition.

Conclusion

This molecular docking investigation successfully demonstrates the potential of flavonoid derivatives as α-glucosidase inhibitors for antidiabetic therapy development, with quercetin emerging as the most promising candidate among the evaluated compounds. The analysis utilizing AutoDock Tools and the *Homo sapiens* α-glucosidase enzyme (PDB ID: 2QMJ) revealed that quercetin achieved the strongest binding affinity at -4.72 kcal/mol, establishing significant interactions with critical active site residues including Lys389, Asn393, and Asn417 that indicate potential competitive inhibition mechanisms.

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Declaration of interest

The authors declare that none of them has any conflict of interest with any private, public or academic party related to the information contained in this manuscript.

Author contributions

Conceptualization, AHS, LN, WNA; Methodology, QAA, NAFR, GPS, ARA, PMS, PU, WNA; Investigation, WNA, AHS; Writing – Original Draft, LN, QAA, NAFR, GPS, ARA, PMS, PU, AHS; Writing – Review & Editing, AHS.

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References

1. Bulu A, Wahyuni TD, Sutriningsih A, Program M, Ilmu S, Fakultas K, et al. Hubungan Antara Tingkat Kepatuhan Minum Obat Dengan Kadar Gula Darah pada Pasien Diabetes Melitus Tipe II. Nursing News: Jurnal Ilmiah Keperawatan. 2019;4. https://doi.org/10.33366/nn.v4i1.1501
2. Badan Penelitian dan Pengembangan Kesehatan. Laporan Nasional Riskesdas 2018. Lembaga Penerbit Balitbangkes. Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan; 2018.
3. Situmeang A, Sinaga M, Simamora H. Efektivitas Aktivitas Fisik dan Pola Makan Terhadap Kecepatan Pengendalian Kadar Gula Darah Pada Penderita DM. Jurnal Keperawatan dan Fisioterapi (JKF). 2019;2: 47–51. https://doi.org/10.35451/jkf.v2i1.259
4. Magliano DJ, Boyko EJ. IDF Diabetes Atlas [Internet]. 10th edition Brussels: International Diabetes Federation. 2021; 1–141. Available: https://pubmed.ncbi.nlm.nih.gov/35914061/
5. Hossain U, Das AK, Ghosh S, Sil PC. An overview on the role of bioactive α-glucosidase inhibitors in ameliorating diabetic complications. Food and Chemical Toxicology. 2020;145: 111738. https://doi.org/10.1016/j.fct.2020.111738
6. Khadayat K, Marasini BP, Gautam H, Ghaju S, Parajuli N. Evaluation of the alpha-amylase inhibitory activity of Nepalese medicinal plants used in the treatment of diabetes mellitus. Clinical Phytoscience. 2020;6. https://doi.org/10.1186/s40816-020-00179-8
7. Oyedemi SO, Oyedemi BO, Ijeh II, Ohanyerem PE, Coopoosamy RM, Aiyegoro OA. Alpha-Amylase Inhibition and Antioxidative Capacity of Some Antidiabetic Plants Used by the Traditional Healers in Southeastern Nigeria. Scientific World Journal. 2017;2017. https://doi.org/10.1155/2017/3592491

8. Van Quan N, Xuan TD, Tran HD, Thuy NTD, Trang LT, Huong CT, et al. Antioxidant, α-Amylase and α-Glucosidase Inhibitory Activities and Potential Constituents of Canarium tramdenum Bark. Molecules. 2019;24. https://doi.org/10.3390/molecules24030605
9. D. Yuliana N, Budijanto S, Hanny Wijaya C, Khatib A. Senyawa Inhibitor α-Glukosidase dan Antioksidan dari Kumis Kucing Dengan Pendekatan Metabolomik Berbasis FTIR. Jurnal Teknologi dan Industri Pangan. 2016;27: 17–30. https://doi.org/10.6066/jtip.2016.27.1.17
10. López-Camacho E, García-Godoy MJ, García-Nieto J, Nebro AJ, Aldana-Montes JF. A new multi-objective approach for molecular docking based on rmsd and binding energy. Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics). 2016;9702: 65–77. https://doi.org/10.1007/978-3-319-38827-4_6
11. Lipinski CA. Lead- and drug-like compounds: The rule-of-five revolution. Drug Discovery Today: Technologies. 2004. pp. 337–341. https://doi.org/10.1016/j.ddtec.2004.11.007
12. Khan AR, Lawrence AJ, Azad I, Raza S, Khan T. Molecular Docking Simulation with Special Reference to Flexible Docking Approach. JSM Chemistry,;6(1):1-5. 2018;6: 1–5. https://doi.org/10.47739/1053
13. Ridwan A, Astrian RT, Barlian A. Pengukuran Efek Antidiabetes Polifenol (Polyphenon 60) Berdasarkan Kadar Glukosa Darah dan Histologi Pankreas Mencit (Mus musculus L.) S.W. Jantan yang Dikondisikan Diabetes Mellitus. Jurnal Matematika & Sains. 2012;17.
14. Ho E, Bray TM. Antioxidants, NFκB activation, and diabetogenesis. Proceedings of the Society for Experimental Biology and Medicine. 1999;222: 205–213. https://doi.org/10.1046/j.1525-1373.1999.d01-137.x