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Molecular docking studies FDA approved Quercetin inhibitory potential of ATP synthase F0F1 subunit beta from Streptococcus mutans

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ABSTRACT
Flavonoids primarily function as antioxidants because they modulate metabolism or because they block many pro-oxidant pathways associated with aging. Quercetin (3,3,4,5,7-pentahydroxyflavone) is one of the most well-studied flavonoids and is found in many plants.Because it inhibits the F1Fo ATP synthase (ATP synthase), a nanomachine involved in oxidative phosphorylation that produces ATP, quercetin molecules function as antioxidants. *Streptococcus mutans* ATP synthase subunit beta protein sequence was retrieved from Uniprot database and the subsequent structural Modeling was done using C-I-TASSER web server. The predicted Model was validated using PROCHECK Server. 3D ligand coordinates of Quercetin were downloaded from the PubChem database. Both Protein and Ligand were prepared using AutoDock Tools and LigPlot software tools were used for molecular visualization and analysis.
The present study includes the results of ATP Model Validation using PROCHECK
which shows Favoured regions more than 90% that indicates good quality model and Ribbon view of ATP-Quercetin complex was observed with a Binding Affinity -6.95 kcal/mol. The conclusion of our study suggest that the inhibition of mitochondrial F0F1-ATPase/ATP synthase may be a possible mechanism involved in the various effects of polyphenolics found in food and quercetin targets F1 in order to reduce the F0F1-ATPase activity.
Keywords: Disease, human, quercetin, F0F1-ATPase, health risk, Streptococcus mutans, chronic diseases

1. INTRODUCTION

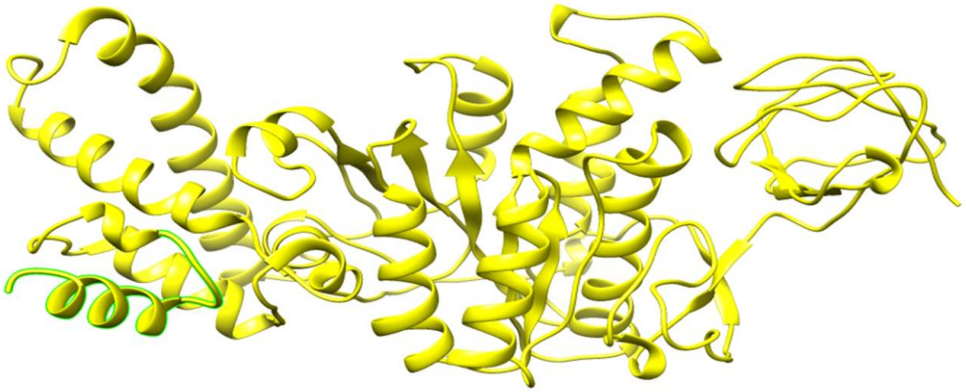
F0F1-ATPase/ATP synthase, also known as F-type ATPase, complex V, is found in the inner membrane of eukaryotic mitochondria and produces ATP, which powers the cell (1). Under some circumstances, it can also function in the other direction, hydrolyzing ATP and pumping protons. The two main complexes that the enzyme can be divided into are F0 and F1(2).The catalytic site of F1, a water-soluble catalytic complex with five subunits, is found on the b subunit. F0 is composed of the oligomycin sensitivity-conferring protein (OSCP), which contributes to the stalk region between F0 and F1, and a number of membrane proteins, including a, b, c, d, e, F6, and A6L (3). Additionally, when the F1 is de-energized, a natural peptide known as the F1 inhibitor protein, or IF1, is bound to the enzyme and functions to limit its ATPase activity (4).
Flavonoids, a subclass of polyphenols that have pleiotropic effects on many aspects of cell biology, are gaining special attention due to their potential as therapeutic agents (5),(6). When pro-oxidant assaults occur, plants produce flavonoids as a defensive mechanism (7),(8),(9). In terms of human health, flavonoid consumption from plants and fruits is crucial for the prevention and management of a variety of chronic diseases (10).Flavonoids primarily function as antioxidants because they modulate metabolism or because they block many pro-oxidant pathways associated with aging (11),(12). Quercetin (3,3,4,5,7-pentahydroxyflavone) is one of the most well-studied flavonoids and is found in many plants. It is also a regular component of human diets (13). Because quercetin can inhibit xanthine oxidase, remove reactive oxygen species, and donate hydrogen atoms, it has anti-aging and antioxidant qualities (14),(15). Certain chronic diseases, such cancer and cardiovascular disorders, can be prevented and treated in part by quercetin's high bioavailability and antioxidant properties (16,17).
Because it inhibits the F1Fo ATP synthase (ATP synthase), a nanomachine involved in oxidative phosphorylation that produces ATP, quercetin molecules function as antioxidants. Quercetin, in fact, binds to a common location on the inner surface of the N-terminal domains of the α and β subunits of the F1 moiety to prevent the rotation of the gamma subunit ATP synthase (18). As evidenced by the rod outer segments of the bovine retina, this inhibitory action causes the electron transport chain, which is linked to ATP synthase, to slow down and simultaneously produce reactive oxygen species (19). But flavonoids also function as broad-spectrum antibacterial agents; this action might possibly be attributed to a decrease in ATP synthase activity, since bacteria need energy generation continuously to maintain their high rate of proliferation through the regulation of protein synthesis and DNA replication (12),(20).Thus, the aim of the study is to analyze molecular docking studies FDA approved Quercetin inhibitory potential of ATP synthase F0F1 subunit beta from streptococcus mutans.

2. MATERIALS AND METHOD.

2.1 Protein Modelling and Docking Studies

Streptococcus mutans ATP synthase subunit beta protein sequence was retrieved from Uniprot database (Uniprot ID: P95789; UniProt, 2023) (21) and the subsequent structural Modeling was done using C-I-TASSER web server (22). The predicted Model with highest confidence score (C-Score: 1.08) was further validated using PROCHECK Server and subsequently used for Protein-Ligand docking studies. 3D ligand coordinates of Quercetin were downloaded from PubChem database (PubChem CID: 5280343;). Both Protein and Ligand were prepared using AutoDock Tools (Morris *et al.,* 2009)(23) by removing water molecules, protonation and addition of Gasteiger charges prior to docking. Protein-Ligand docking studies performed using AutoDock 4.2 (Morris *et al.,* 2009). PyMOL (Schrödinger, LLC) and LigPlot+ (Laskowski & Swindells, 2011) software tools were used for molecular visualization and analysis(24).

3. RESULTS



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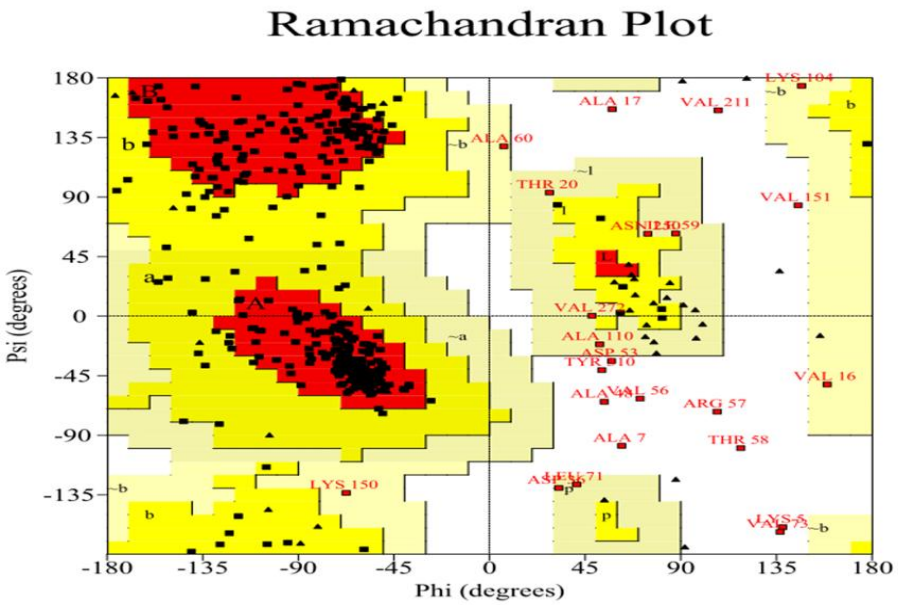
3.1 ATP Model Validation using PROCHECK



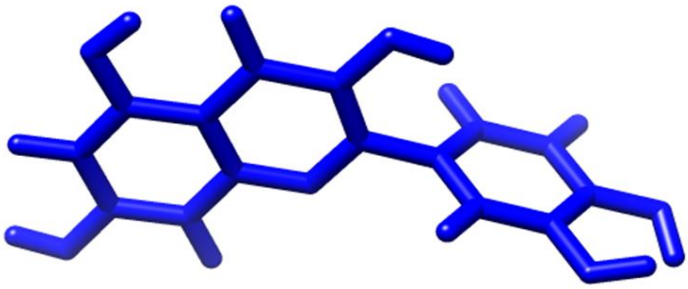
Favoured regions 97%
Favoured regions > 90% shows good quality model

Plot statistics

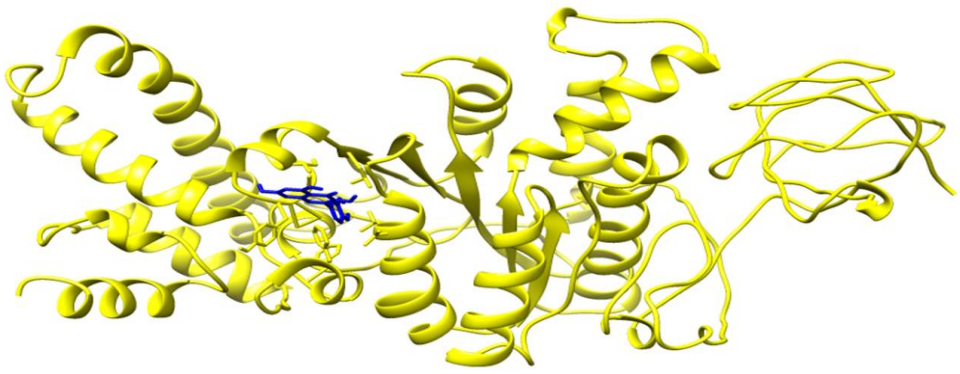
Residues in most favoured regions [A,B,L]	320	79.6%
Residues in additional allowed regions [a,b,l,p]	59	14.7%
Residues in generously allowed regions [~a,~b,~l,~p]	11	2.7%
Residues in disallowed regions	12	3.0%
Number of non-glycine and non-proline residues	402	100.0%
Number of end-residues (excl. Gly and Pro)	3	
Number of glycine residues (shown as triangles)	44	
Number of proline residues	20	
Total number of residues	469	

Based on an analysis of 118 structures of resolution of at least 2.0 Angstroms and R-factor no greater than 20%, a good quality model would be expected to have over 90% in the most favoured regions.

3.2 Quercetin 3D Structure



3.3 Ribbon view of ATP-Quercetin complex with a Binding Affinity -6.95 kcal/mol



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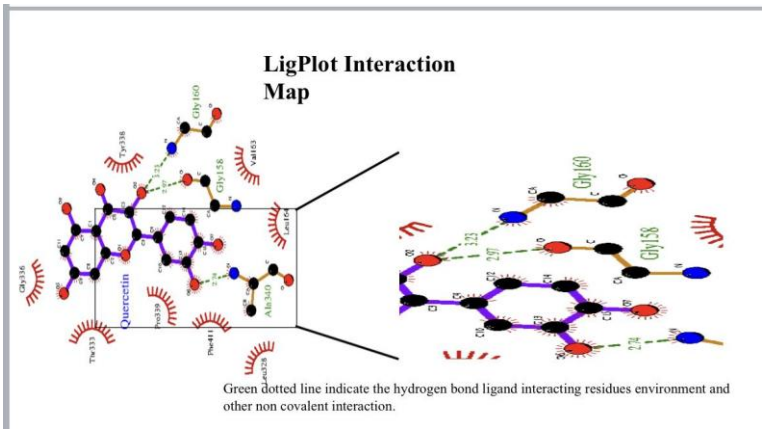
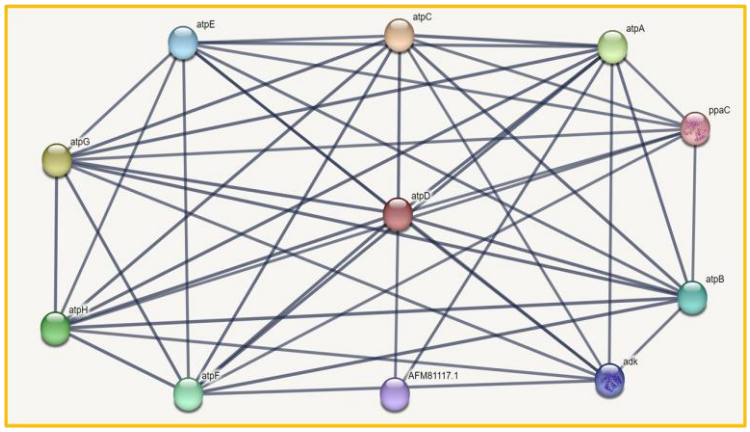


Green dotted line indicate the hydrogen bond ligand interacting residues environment and other non covalent interaction.

3.4 Predicted atpD protein-protein interactions



4. DISCUSSION

Numerous diseases with no cure and bacteria with several resistances are worldwide concerns. Thus, it is imperative to take advantage of novel molecular targets in order to broaden the range of treatments available for these ailments. A multitude of clinical disorders are linked to the dysfunction of FOF1-ATP synthase(25). Nevertheless, despite numerous attempts, no pharmaceutical modulator of this intriguing target has been given clinical approval for the treatment of illnesses other than infectious ones(26).The concept of treating human diseases with exogenous FOF1-ATP synthase inhibitors is not new. Positive outcomes have been documented in the inhibition of this enzyme by polyphenols, aurovertins, and glyco macrolides, which stops the growth of many tumor cell lines(27). Though further study is still required, it is theoretically possible to target exogenous inhibitor binding sites to treat various disorders involving FOF1-ATP synthase.

In vitro and in silico, Shastri et al. (2025) showed that quercetin (QC) exhibits broad-spectrum antibiofilm and anti-quorum sensing activities against Gram-negative bacteria. They reported minimum inhibitory concentration (MIC) values of 125 µg/mL against Chromobacterium violaceum, 250 µg/mL against Pseudomonas aeruginosa, and 500 µg/mL against Serratia marcescens(28). Similarly, a 2024 investigation on broad-spectrum antibacterial activity by Mandal et al. established ATP synthase inhibition as a key mechanism of antibacterial action by confirming that quercetin's hydroxyl groups act on bacterial membranes and energy transduction systems (29).Additionally, quercetin and similar flavonoids harm the bacterial respiratory chain and disturb the bioenergetic status, including inhibition of ATP synthase and membrane depolarization, according to a 2023 study published in Molecules, highlighting the crucial significance of this target(30).

In a previous study, they investigated the impact of combining resveratrol with other active inhibitors at suboptimal quantities to see if resveratrol and other phytochemicals additively contribute to the inhibitory effect of dietary phytochemicals on F0F1-ATPase. Red wine contains inadequate levels of kaempferol, quercetin, and resveratrol(31). These combinations have a cumulative inhibitory effect that results in 56% inhibition as compared to the separate components alone.Thus, even at much lower quantities of individual substances, the combination of these and other active chemicals in the diet may be able to modify the enzymatic activity of the F0F1-ATPase in vivo(32). Experiments continue to support this synergistic principle. Quercetin and cirsiliol, two structurally related flavones, inhibit ATP synthesis and dramatically lower the intracellular energy balance in methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant Staphylococcus epidermidis (MRSE) isolated from patients, according to a seminal study by Ravera et al. (2023).Importantly, molecular docking investigations revealed that cirsiliol and quercetin have similar binding chains on the F1 moiety's α and β subunits, with binding interactions involving Ser-267 on the γ subunit being especially important(33). These results highlight the constant nature of polyphenol binding sites across bacterial ATP synthases and directly parallel and support the binding affinity of −6.95 kcal/mol for quercetin obtained in the current work at the ATP synthase β subunit of Streptococcus mutans. A 2025 investigation also verified that quercetin administration reduced intracellular ATP levels in S. aureus in a dose-dependent manner, and that this ATP depletion was associated with enhanced persister cell formation and bacterial dormancy(34). Ojo et al. (2022) carried out combined experimental and molecular docking studies on quercetin and vitamin E with diabetes-associated mitochondrial ATPase from a structural point of view. They found that quercetin had a higher binding affinity than vitamin E and suggested that F0F1-ATPase inhibition could be a useful anti-apoptotic therapeutic approach in metabolic diseases [34]. Additionally, the study emphasized the anti-apoptotic significance of quercetin's interaction with the catalytic β subunit of the enzyme, which is directly related to the target protein used in this study(35). The current study provides strong justification for the choice of Streptococcus mutans ATP synthase beta subunit as the study's target.

In silico molecular docking of phytochemicals from Murraya koenigii against S. mutans glycosyltransferase was carried out by Maheswari & Sankar (2024), demonstrating the bacterium's susceptibility to flavonoid-based inhibitors and developing validated docking protocols that are applicable to all of its enzyme targets (36). Furthermore, the atpD gene and its encoded β subunit constitute a central vulnerability that can be exploited by phytochemicals like cinnamaldehyde and related polyphenolics to disrupt cell membrane integrity and energy metabolism, according to a 2025 review on natural compounds targeting Streptococcus species(37). The competitiveness of quercetin as a potential inhibitor is confirmed by the binding affinity of −6.95 kcal/mol obtained in this study for quercetin at this target, which compares favorably with previously published values for other flavonoids docked against S. mutans proteins, which typically ranged from −5.5 to −7.8 kcal/mol. A number of scaffolds have been shown to bind and inhibit the Mtb ATP synthase enzyme, including squaramide, quinoline, sulfonamide, and imidazo [1,2 -a] pyridine ethers. According to recent research, the polyphenol scaffold prevents the γ subunit from rotating both clockwise and counterclockwise, hence inhibiting mitochondrial Mtb ATP synthase(33). Through polar contacts and H-bonds, these polyphenol compounds bound to the γ subunit's c-terminal tip, according to X-ray crystallographic investigations. Try 68, Asp 32, Gly 62, Glu 65, and Glu 67, which are all within 4 A^ of the bound chemicals, were involved in the polar contact between the inhibitor compounds and the mitochondrial enzyme.

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AUTHORS CONTRIBUTIONS .K. Esha Gayathri, Ilammaran varshan : Literature search, data collection, analysis, manuscript drafting.
Aparna Mohan Aided in conception of the topic, has participated in the study design, statistical analysis and has supervised in preparation and final correction of the manuscript.

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CONFLICT OF INTEREST .The author declares that there were no conflicts of interest in the present study.

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- Saveetha University
- Banu Constructions.

5. CONCLUSION

The results of our study suggest that the inhibition of mitochondrial F0F1-ATPase/ATP synthase may be a possible mechanism involved in the various effects of polyphenolics found in food. The same ATP synthase has been revealed to be present on the plasma membranes of a number of tumor cell lines and human umbilical vein endothelial cells. Additionally, it has been demonstrated that this protein binds to angiostatin, a powerful inhibitor of angiogenesis and cell proliferation.According to our most current research, quercetin targets F1 in order to reduce the F0F1-ATPase activity.

Possible Future Directions:

- Nanoparticles synthesis to increase bioavailability of this drug.
- Nano formulated drug efficacy testing against Antibiofilm *In-vitro* studies of different dental pathogens.
- Pre-clinical studies Antibiofilm different animal models (*In-vivo*).
- Clinical Trial (Phase I, II, and III).
- FDA approval.
- Additional pre and post marketing analysis and approval.
- Product launching

6. Reference

1. Boyer PD. The ATP synthase--a splendid molecular machine. Annu Rev Biochem. 1997;66:717–49.
2. L A, Krishna Kumar J, Shanmugam R. Formulation of Quercetin Mouthwash and Anti-microbial Potential Against Critical Pathogens: An In-Vitro Evaluation. Cureus. 2024 Jan;16(1):e51688.
3. McEnery MW, Pedersen PL. Diethylstilbestrol. A novel F0-directed probe of the mitochondrial proton ATPase. J Biol Chem. 1986 Feb 5;261(4):1745–52.
4. Matsuyama S, Xu Q, Velours J, Reed JC. The Mitochondrial F0F1-ATPase proton pump is required for function of the proapoptotic protein Bax in yeast and mammalian cells. Mol Cell. 1998 Feb;1(3):327–36.
5. Watson RR, Preedy VR, Zibadi S. Polyphenols in Human Health and Disease. Academic Press; 2018. 470 p.
6. Guo Y, Li Z, Chen F, Chai Y. Polyphenols in Oral Health: Homeostasis Maintenance, Disease Prevention, and Therapeutic Applications. Nutrients [Internet]. 2023 Oct 16;15(20). Available from: http://dx.doi.org/10.3390/nu15204384
7. Liga S, Paul C, Péter F. Flavonoids: Overview of Biosynthesis, Biological Activity, and Current Extraction Techniques. Plants [Internet]. 2023 Jul 23;12(14). Available from: http://dx.doi.org/10.3390/plants12142732
8. Georgiev V, Ananga A, Tsolova V. Recent advances and uses of grape flavonoids as nutraceuticals. Nutrients. 2014 Jan 21;6(1):391–415.
9. Tungmunnithum D, Thongboonyou A, Pholboon A, Yangsabai A. Flavonoids and Other Phenolic Compounds from Medicinal Plants for Pharmaceutical and Medical Aspects: An Overview. Medicines (Basel) [Internet]. 2018 Aug 25;5(3). Available from: http://dx.doi.org/10.3390/medicines5030093
10. Slika H, Mansour H, Wehbe N, Nasser SA, Iratni R, Nasrallah G, et al. Therapeutic potential of flavonoids in cancer: ROS-mediated mechanisms. Biomed Pharmacother. 2022 Feb;146:112442.
11. Aoi W, Iwasa M, Marunaka Y. Metabolic functions of flavonoids: From human epidemiology to molecular mechanisms. Neuropeptides. 2021 Aug;88:102163.
12. Shamsudin NF, Ahmed QU, Mahmood S, Ali Shah SA, Khatib A, Mukhtar S, et al. Antibacterial Effects of Flavonoids and Their Structure-Activity Relationship Study: A Comparative Interpretation. Molecules [Internet]. 2022 Feb 9;27(4). Available from: http://dx.doi.org/10.3390/molecules27041149
13. Anand David AV, Arulmoli R, Parasuraman S. Overviews of Biological Importance of Quercetin: A Bioactive Flavonoid. Pharmacogn Rev. 2016 Jul-Dec;10(20):84–9.
14. Rezaei-Sadabady R, Eidi A, Zarghami N, Barzegar A. Intracellular ROS protection efficiency and free radical-scavenging activity of quercetin and quercetin-encapsulated liposomes. Artif Cells Nanomed Biotechnol. 2016;44(1):128–34.
15. Xu D, Hu MJ, Wang YQ, Cui YL. Antioxidant Activities of Quercetin and Its Complexes for Medicinal Application. Molecules [Internet]. 2019 Mar 21;24(6). Available from: http://dx.doi.org/10.3390/molecules24061123
16. Mackieh R, Al-Bakkar N, Kfoury M, Roufayel R, Sabatier JM, Fajloun Z. Inhibitors of ATP Synthase as New Antibacterial Candidates. Antibiotics (Basel) [Internet]. 2023 Mar 24;12(4). Available from: http://dx.doi.org/10.3390/antibiotics12040650
17. Website [Internet]. Available from: 4-hydroxy-3-methoxybenzaldehyde causes attrition of biofilm formation and quorum sensing–associated virulence factors of Streptococcus mutans https://doi.org/10.1016/j.archoralbio.2024.105976
18. Gledhill JR, Montgomery MG, Leslie AGW, Walker JE. Mechanism of inhibition of bovine F1-ATPase by resveratrol and related polyphenols. Proc Natl Acad Sci U S A. 2007 Aug 21;104(34):13632–7.
19. Gandhimathi, K. A., Francis, A. P., Rengasamy, G., Veeraraghavan, V. P., & Sankaran, K. (2025). Quercetin-coated biogenic titanium oxide nanoparticles: Synthesis, characterization, and *in-vitro* biological studies. *Particulate Science and Technology*, *43*(2), 198–206. https://doi.org/10.1080/02726351.2024.2440462
20. Zhegunov G. The Dual Nature of Life: Interplay of the Individual and the Genome. Springer Science & Business Media; 2005. 300 p.
21. UniProt Consortium. UniProt: the Universal Protein Knowledgebase in 2023. Nucleic Acids Res. 2023 Jan 6;51(D1):D523–31.
22. Zheng W, Zhang C, Li Y, Pearce R, Bell EW, Zhang Y. Folding non-homologous proteins by coupling deep-learning contact maps with I-TASSER assembly simulations. Cell Rep Methods [Internet]. 2021 Jul 26;1(3). Available from: http://dx.doi.org/10.1016/j.crmeth.2021.100014
23. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem. 2009 Dec;30(16):2785–91.
24. Laskowski RA, Swindells MB. LigPlot+: multiple ligand-protein interaction diagrams for drug discovery. J Chem Inf Model. 2011 Oct 24;51(10):2778–86.
25. Zheng J, Ramirez VD. Inhibition of mitochondrial proton F0F1-ATPase/ATP synthase by polyphenolic phytochemicals. Br J Pharmacol. 2000 Jul;130(5):1115–23.
26. Pati S, Sarkar T, Lahiri D. Recent Frontiers of Phytochemicals. Elsevier; 2023. 706 p.
27. Radhamanalan G. Postbiotics and phage synergy in precision oral microbiome engineering: systems biology strategies targeting Streptococcus mutans in dental caries. Front Mol Biosci. 2026 Apr 8;13:1766853.
28. Shastri T, Binsuwaidan R, Siddiqui AJ, Badraoui R, Jahan S, Alshammari N, et al. Quercetin Exhibits Broad-Spectrum Antibiofilm and Antiquorum Sensing Activities Against Gram-Negative Bacteria: In Vitro and In Silico Investigation Targeting Antimicrobial Therapy. Can J Infect Dis Med Microbiol. 2025 Mar 30;2025:2333207.
29. Website [Internet]. Available from: https://doi.org/10.1016/j.imu.2022.100894
30. Veiko AG, Olchowik-Grabarek E, Sekowski S, Roszkowska A, Lapshina EA, Dobrzynska I, et al. Antimicrobial Activity of Quercetin, Naringenin and Catechin: Flavonoids Inhibit -Induced Hemolysis and Modify Membranes of Bacteria and Erythrocytes. Molecules [Internet]. 2023 Jan 27;28(3). Available from: http://dx.doi.org/10.3390/molecules28031252
31. Pandiyan I, Arumugham MI, Doraikannan SS, Rathinavelu PK, Prabakar J, Rajeshkumar S. Antimicrobial and Cytotoxic Activity of and -Mediated Silver Nanoparticles - An Study. Contemp Clin Dent. 2023 Apr-Jun;14(2):109–14.
32. Cofas-Vargas LF, Mendoza-Espinosa P, Avila-Barrientos LP, Prada-Gracia D, Riveros-Rosas H, García-Hernández E. Exploring the druggability of the binding site of aurovertin, an exogenous allosteric inhibitor of FF-ATP synthase. Front Pharmacol. 2022 Oct 14;13:1012008.
33. Ravera S, Tancreda G, Vezzulli L, Schito AM, Panfoli I. Cirsiliol and Quercetin Inhibit ATP Synthesis and Decrease the Energy Balance in Methicillin-Resistant (MRSA) and Methicillin-Resistant (MRSE) Strains Isolated from Patients. Molecules [Internet]. 2023 Aug 22;28(17). Available from: http://dx.doi.org/10.3390/molecules28176183
34. Kim DY, Kim TJ. Metabolic Stress Induced by Quercetin Enhances Dormancy and Persistence in. Antibiotics (Basel) [Internet]. 2025 Apr 22;14(5). Available from: http://dx.doi.org/10.3390/antibiotics14050424
35. Ojo OO, Ogunleke T, Ajeoge J, Olorunsogo OO. Experimental and molecular docking studies of quercetin and vitamin E with diabetes-associated mitochondrial-ATPase as anti-apoptotic therapeutic strategies. J Diabetes Metab Disord. 2022 Dec;21(2):1717–29.
36. Uma Maheswari K, Sankar S. In Silico Molecular Docking of Phytochemicals of Murraya koenigii Against Streptococcus mutans. Cureus. 2024 Feb;16(2):e53679.
37. Kashi M, Varseh M, Hariri Y, Chegini Z, Shariati A. Natural compounds: new therapeutic approach for inhibition of and dental caries. Front Pharmacol. 2025 Apr 1;16:1548117.