Current Research on Biosciences and Biotechnology **8** (1) 2026 12-17

Current Research on Biosciences and Biotechnology

www.crbb-journal.com

Molecular docking and ADMET evaluation of punicalagin from pomegranate (*Punica granatum* L.) peel as a dipeptidyl peptidase-4 (DPP-IV) inhibitor

Ari Yuniarto[a*], Junaidin[b], Ikhsan Nazar Arrahman[c], Nita Rusdiana[b]

[a]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Muhammadiyah A.R. Fachruddin University, Tangerang, Indonesia
[b]Department of Pharmacochemistry and Science, Faculty of Pharmacy, Muhammadiyah A.R. Fachruddin University, Tangerang, Indonesia
[c]Department of Pharmaceutical and Natural Products Technology, Faculty of Pharmacy, Muhammadiyah A.R. Fachruddin University, Tangerang, Indonesia

ABSTRACT

Dipeptidyl peptidase-4 (DPP-IV) is an important therapeutic target in the management of type 2 diabetes mellitus. This study aimed to evaluate the potential of punicalagin, a major polyphenol from pomegranate peel, as a natural DPP-IV inhibitor using an in silico approach. Molecular docking was performed using AutoDock Vina, and the docking protocol was validated by redocking the native ligand, yielding an RMSD value of 0.8298 Å, indicating good agreement between the experimental and predicted ligand poses. Punicalagin exhibited a more favourable predicted binding affinity toward DPP-IV, with a docking score of –10.44 kcal/mol, compared with alogliptin (–8.11 kcal/mol) and the native ligand (–8.65 kcal/mol). This favourable predicted interaction was supported by multiple hydrogen-bond and hydrophobic interactions with residues within the DPP-IV binding site, particularly Glu206, Ser209, Arg356, Arg358, and Arg669. ADMET prediction indicated a relatively favourable safety profile for punicalagin, particularly given the absence of predicted hepatotoxicity and its limited blood–brain barrier permeability. However, its lower intestinal absorption and limited volume of distribution compared with alogliptin may represent potential challenges to systemic bioavailability. Overall, punicalagin demonstrated promising in silico potential as a natural DPP-IV inhibitor based on its predicted binding affinity and interaction profile. Nevertheless, these findings represent computational predictions and do not establish actual DPP-IV inhibitory activity. Further molecular dynamics simulations, in vitro DPP-IV enzyme inhibition assays, pharmacokinetic studies, and formulation optimization are required to validate its inhibitory activity, stability, bioavailability, and potential therapeutic relevance in the management of type 2 diabetes mellitus.

Article history:

Received 25 Apr 2026
Revised 15 Aug 2026
Accepted 20 Aug 2026
Available online 31 Aug 2026

Keywords:

Diabetes mellitus
docking
DPP-IV
punicalagin
pomegranate

*Corresponding authors:
ari.yuniarto18@gmail.com

DOI: 10.5614/crbb.2026.8.1/4XE1Q4WB

e-ISSN 2686-1623/

1. Introduction

Diabetes mellitus is a heterogeneous metabolic disorder characterized primarily by chronic hyperglycaemia (Petersmann et al., 2019), which results from defects in insulin secretion, insulin action, or both (Sharma et al., 2024). In 2017, approximately 462 million people worldwide were affected by type 2 diabetes mellitus (T2DM), corresponding to 6.28% of the global population, with a prevalence of 6,059 cases per 100,000 population. The global prevalence of T2DM is projected to increase to 7,079 cases per 100,000 population by 2030, reflecting a continuing rise across all regions of the world (Khan et al., 2020). This persistent increase in the global burden of T2DM highlights the urgent need for effective and safe therapeutic strategies.

Metformin remains the preferred first-line pharmacological treatment for T2DM because of its low cost, well-established safety profile, and potential cardiovascular benefits (Yang et al., 2019). Current treatment guidelines recommend metformin as initial therapy, with the addition of one or more oral antidiabetic agents, including sulfonylureas, α-glucosidase inhibitors, thiazolidinediones, and dipeptidyl peptidase-4 (DPP-4) inhibitors, when adequate glycaemic control is not achieved.

DPP-4 inhibitors are a class of oral antidiabetic drugs that inhibit the DPP-4 enzyme, thereby enhancing incretin activity and improving glycaemic control. Several DPP-4 inhibitors, including sitagliptin, saxagliptin, vildagliptin, and linagliptin, are available in Indonesia and other countries. Compared with other oral antidiabetic drugs, DPP-4 inhibitors generally provide moderate improvements in glycated haemoglobin (HbA1c) and are well tolerated in short-term studies; however, adverse effects may still occur during their use (Kristin, 2016). In addition, the long-term use of established

pharmacotherapies may be constrained by suboptimal glycaemic control and treatment-related adverse effects (Młynarska et al., 2025). These limitations have encouraged increasing interest in natural products as potential sources of complementary or alternative antidiabetic agents.

Natural products have attracted considerable attention as potential sources of antidiabetic compounds because of their structural diversity and broad spectrum of biological activities. Among medicinal plants, pomegranate (*Punica granatum* L.) has been extensively investigated for its pharmacological properties. Pomegranate has traditionally been used in several medicinal systems, including Ayurveda and traditional Chinese medicine, and various studies have reported antimicrobial, antioxidant, anticancer, anti-inflammatory, and metabolic activities associated with different parts of the plant (Miguel et al., 2010). Consequently, pomegranate and its bioactive constituents represent promising candidates for the development of novel antihyperglycemic agents (Ye et al., 2023).

Pomegranate peel, a major by-product of pomegranate processing, is particularly rich in bioactive polyphenolic compounds. Although the peel is generally not consumed as a food component, it contains a variety of phytochemicals, including ellagic acid, catechin, caffeic acid, and tannins such as punicalagin (Singh et al., 2023). Among these constituents, punicalagin is a major ellagitannin found in pomegranate peel and has attracted considerable scientific interest because of its diverse biological activities (Venusova et al., 2021). Its complex polyphenolic structure and numerous hydroxyl groups provide multiple opportunities for interactions with biological macromolecules, suggesting its potential to modulate molecular targets involved in metabolic regulation (Xu et al., 2022).

Given these structural characteristics and reported biological activities, punicalagin may interact with molecular targets associated with glucose homeostasis, including DPP-IV. Although the antidiabetic potential of pomegranate and its bioactive constituents has been reported, previous studies have primarily investigated mechanisms such as carbohydrate-hydrolysing enzyme inhibition and antioxidant activity. However, to the best of our knowledge, the molecular interaction between punicalagin and DPP-IV has not yet been evaluated using molecular docking.

Molecular docking provides a computational approach for investigating ligand–protein interactions, including binding modes, key interacting residues, and relative binding affinity within a target binding site. Therefore, this approach can provide preliminary mechanistic insights into the potential interaction of punicalagin with DPP-IV before experimental validation. This study aimed to evaluate the predicted interaction of punicalagin derived from pomegranate peel with DPP-IV using molecular docking and to characterize its pharmacokinetic and safety profiles using the pkCSM platform. Alogliptin, a clinically established DPP-IV inhibitor, was included as a reference compound, while the crystallographic native ligand was used to validate the docking protocol and provide a comparative reference for the interactions. The findings are expected to provide computational evidence supporting further experimental investigation of punicalagin as a potential natural DPP-IV inhibitor.

2. Materials and methods

2.1. Materials

2.1.1. Instruments

The hardware used for the *in silico* analysis was an ASUS A456U notebook equipped with Microsoft Windows 10 Pro 64-bit, 4 GB of memory, and an Intel Core i5-7200U processor. The software used in this study included AutoDock Tools 1.5.6, AutoDock Vina 1.2.3, Avogadro 1.2.0, Chimera 1.17.3, Discovery Studio 2016, LigPlot+ 2.2.8, and ORCA 5.0.3.

2.1.2. Materials

The test compound analyzed in this study was punicalagin. The three-dimensional structure of punicalagin was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The molecular target used in the docking study was dipeptidyl peptidase-4 (DPP-IV; PDB ID: 3F8S), which was obtained from the Protein Data Bank (https://www.rcsb.org/) in complex with its crystallographic native ligand. Alogliptin was used as the reference ligand for comparison.

2.2. Methods

2.2.1. Geometry optimization

The three-dimensional structure of punicalagin was prepared using Avogadro. Geometry optimization was subsequently performed using the semi-empirical PM3 method implemented in ORCA 5.0.3 (Hanwell et al., 2012; Neese, 2022; Neese et al., 2020). The optimized structure was then converted and saved in PDB format for subsequent molecular docking analysis.

2.2.2. Docking protocol validation

The docking protocol was validated by redocking the crystallographic native ligand into the active site of DPP-IV (PDB ID: 3F8S) using AutoDock Tools 1.5.6 and AutoDock Vina (Ammirati et al., 2009; Morris et al., 2009; Trott and Olson, 2010). The predicted pose obtained from redocking was compared with the experimentally determined crystallographic pose by calculating the root mean square deviation (RMSD). An RMSD value below 2.0 Å was considered indicative of an acceptable docking protocol because it indicates that the predicted ligand pose reasonably reproduces the experimentally observed binding orientation.

2.2.3. Molecular docking

Molecular docking was performed using the validated docking protocol. Punicalagin was docked into the DPP-IV binding site, with alogliptin included as a reference DPP-IV inhibitor. Molecular docking was performed using AutoDock Vina with nine binding modes (num_modes = 9) generated for each ligand–protein complex in a single docking run. The docking results were evaluated based on the predicted binding affinity (kcal/mol) and the resulting ligand poses within the DPP-IV binding site. A more negative predicted binding free energy was interpreted as indicating a stronger predicted binding affinity under the docking scoring function.

2.2.4. Analysis and visualization of docking results

The docking results were analysed based on the predicted binding affinity of the resulting ligand poses. The interaction profiles of punicalagin, alogliptin, and the native ligand within the DPP-IV binding site were subsequently analysed and visualized using LigPlot+ 2.2.8 (Laskowski and Swindells, 2011) and Discovery Studio 2020 (BIOVIA, 2020). Hydrogen-bond and hydrophobic interactions between the ligands and amino acid residues within the binding site were identified and compared.

2.2.5. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction

The predicted pharmacokinetic and toxicity profiles of punicalagin, the native ligand, and alogliptin were evaluated using the pkCSM web server (https://biosig.lab.uq.edu.au/pkcsm/) (Pires et al., 2015). The evaluated parameters included intestinal absorption, volume of distribution at steady state (VDss), blood–brain barrier (BBB) permeability, CYP2D6 substrate and inhibitor properties, total clearance, hepatotoxicity, and predicted LD_{50}. The resulting values were used to compare the predicted pharmacokinetic and safety profiles of the evaluated compounds.

3. Results and discussion

3.1. Docking protocol validation

Redocking of the crystallographic native ligand into the DPP-IV binding site produced an RMSD value of 0.8298 Å. This value was below the commonly accepted threshold of 2.0 Å, indicating that the docking protocol was able to reproduce the experimentally determined binding orientation of the native ligand with good agreement. Therefore, the validated docking protocol was considered suitable for subsequent evaluation of punicalagin and alogliptin against the DPP-IV binding site.

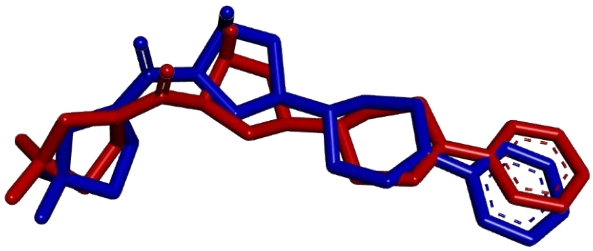

Fig. 1. Overlay RMSD of native ligand: blue before redocking and red after redocking RMSD

3.2. Molecular docking of punicalagin against DPP-IV

Molecular docking analysis showed that punicalagin exhibited the most negative predicted binding affinity among the evaluated compounds, with a docking score of –10.44 kcal/mol, compared with –8.65 kcal/mol for the native ligand and –8.11 kcal/mol for alogliptin. The more negative docking score indicates a stronger predicted binding affinity within the DPP-IV binding site according to the AutoDock Vina scoring function. However, docking scores should be interpreted as computational estimates rather than direct experimental measurements of binding free energy or complex stability.

The interaction profile further supported the favourable predicted binding of punicalagin. Punicalagin formed hydrogen-bond interactions with Arg125, His126, Glu206, Ser209, Arg356, Phe357, Arg358, and Arg669, as well as hydrophobic interactions with Glu205, Gly355, and Tyr666. In comparison, the native ligand formed hydrogen-bond interactions with Glu206 and Ser630 and hydrophobic interactions with His126, Glu205, Ser209, Val656, Tyr662, Tyr631, Tyr666, and Val711. Alogliptin formed a hydrogen-bond interaction with Glu205 and hydrophobic interactions with Arg125, Glu206, Phe357, Tyr547, Gly549, Pro550, Cys551, Ser552, and Tyr666.

The relatively extensive interaction profile of punicalagin may contribute to its favourable predicted binding affinity by providing multiple polar and nonpolar contacts within the DPP-IV binding site. In particular, interactions involving residues such as Glu206 and Ser209 may contribute to ligand recognition and positioning within the binding pocket. Previous structural studies have highlighted the importance of residues within the DPP-IV catalytic region for ligand recognition and inhibitor binding (Nabeno et al., 2013; Metzler et al., 2008). Nevertheless, the present docking results represent computational predictions and cannot independently establish the enzymatic inhibitory activity or thermodynamic stability of the punicalagin–DPP-IV complex.

3.3. Visualization of the docking interactions

The predicted binding interactions of punicalagin within the DPP-IV binding site are shown in Fig. 2 using Chimera 1.17.3. The visualization illustrates the hydrogen-bond and hydrophobic interactions between punicalagin and amino acid residues located within the binding pocket.

Punicalagin showed an intestinal absorption of 75.4%, which was lower than that of the native ligand (90.207%) and alogliptin (98.401%). This result suggests that the predicted oral absorption of punicalagin may be less favourable than that of the reference compound. Punicalagin also showed a lower predicted VDss value (0.013) than alogliptin (0.759), suggesting a potentially more limited distribution into body tissues.

The predicted BBB permeability of punicalagin was –4.181, indicating low predicted penetration across the blood–brain barrier. Limited central nervous system exposure may be favourable when central nervous system activity is not required for the intended pharmacological effect. However, this prediction should be interpreted cautiously because BBB permeability is influenced by multiple physicochemical and biological factors that may not be fully captured by computational models.

Punicalagin was not predicted to be a substrate or inhibitor of CYP2D6, suggesting a low predicted potential for CYP2D6-mediated metabolic interactions. Its total clearance value was –4.248, compared with 0.636 for the native ligand and 0.701 for alogliptin. Because the pkCSM total clearance output is reported on a logarithmic prediction scale, the negative value should not be interpreted as a physically negative clearance. Rather, it represents a relatively low predicted clearance on the logarithmic scale. These computational predictions should nevertheless be interpreted cautiously because they do not directly represent experimentally measured pharmacokinetic elimination rates.

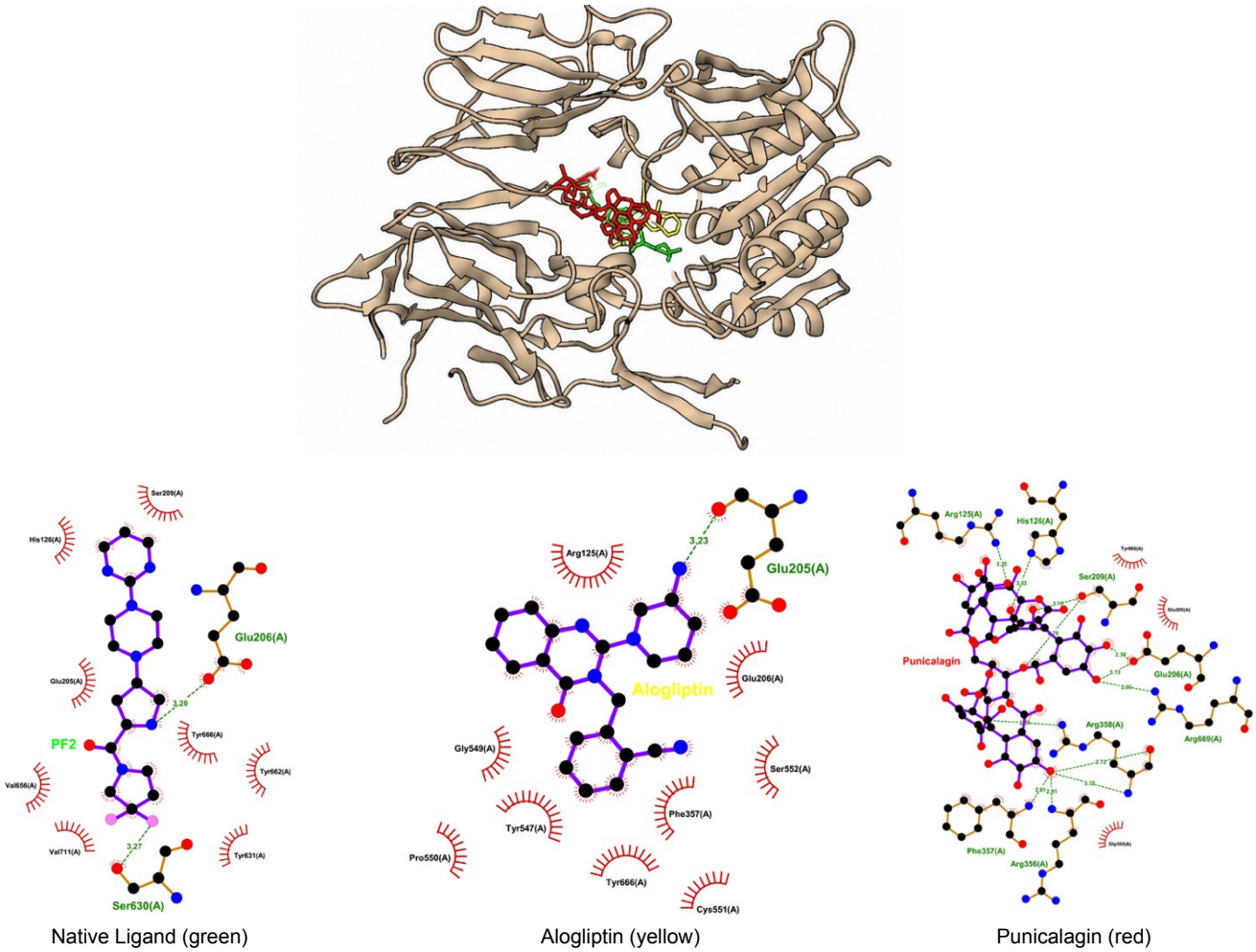

Fig. 2. Predicted binding interactions of punicalagin within the DPP-IV binding site.

Table 1. Results of docking punicalagin to the DPP IV target

Compounds	**Affinity (kcal/mol)**	**Hydrophobic Interaction**	**Hydrogen Interaction**
Punicalagin	–10.44	**Glu205**, Gly355, **Tyr666**	Arg125, His126, **Glu206**, Ser209, Arg356, Phe357, Arg358, Arg669
Native ligand	–8.65	His126, **Glu205**, Ser209, Val656, Tyr662, Tyr631, **Tyr666**, Val711	**Glu206**, Ser630
Alogliptin	–8.11	Arg125, Glu206, Phe357, Tyr547, Gly549, Pro550, Cys551, Ser552, **Tyr666**	Glu205

Table 2. Prediction of ADMET of pomegranate using the pkCSM online tool program

Molecule Name	**Intestinal absorption (human)**	**VDss (human)**	**BBB permeability**	**CYP2D6 substrate**	**CYP2D6 inhibitor**	**Total Clearance**	**Hepatotoxicity**	**LD_{50} (mol/kg)**
Punicalagin	75.4	0.013	-4.181	No	No	-4.248	No	2.482
Native ligand	90.207	0.006	-0.047	No	No	0.636	Yes	2.5
Alogliptin	98.401	0.759	-0.536	No	No	0.701	Yes	2.563

Punicalagin was not predicted to exhibit hepatotoxicity, whereas hepatotoxicity was predicted for the native ligand and alogliptin. The predicted LD_{50} values were relatively similar among the evaluated compounds, with values of 2.482, 2.500, and 2.563 mol/kg for punicalagin, the native ligand, and alogliptin, respectively. Overall, punicalagin showed a relatively favourable predicted ADMET profile, particularly with respect to BBB permeability, CYP2D6 interaction, and hepatotoxicity. However, its lower predicted intestinal absorption and limited predicted tissue distribution may present challenges for systemic bioavailability.

The relatively lower predicted intestinal absorption of punicalagin compared with alogliptin may represent an important consideration for its potential systemic application. This finding is relevant to the traditional use of pomegranate preparations, which are commonly administered as plant-derived preparations or extracts rather than as purified punicalagin. The use of complex extracts may result in exposure to multiple phytochemicals that could collectively contribute to biological activity, although the present computational analysis cannot determine whether such effects compensate for the predicted limited absorption of

punicalagin. Therefore, the predicted pharmacokinetic limitations observed in this study should not be interpreted as evidence against the traditional use of pomegranate preparations.

Processing and pre-treatment conditions may also influence the phytochemical composition and bioactive compound content of pomegranate peel. Drying methods, including sun-drying, vacuum-drying, freeze-drying, oven-drying, and air-drying, may affect the recovery and preservation of bioactive compounds (Magangana et al., 2020). Freeze-drying has been reported to facilitate the preservation and recovery of bioactive compounds from pomegranate peel, although its relatively high processing cost may limit large-scale application (Kumar et al., 2022). Considering the predicted absorption characteristics of punicalagin, further studies investigating formulation and processing strategies, including encapsulation or other bioavailability-enhancement approaches, may be warranted to improve its pharmacokinetic performance (Rezagholizade-shirvan et al., 2024; Wen et al., 2025).

Importantly, the present findings remain limited to computational predictions. Experimental studies are required to determine whether the predicted interaction with DPP-IV translates into measurable enzyme inhibition and to establish the pharmacokinetic behaviour and biological activity of punicalagin in relevant experimental models.

4. Conclusion

Molecular docking analysis showed that punicalagin exhibited a more negative predicted binding affinity toward DPP-IV than alogliptin and the crystallographic native ligand, with docking scores of –10.44, –8.11, and –8.65 kcal/mol, respectively. Multiple hydrogen-bond and hydrophobic interactions with residues within the DPP-IV binding site supported the favourable predicted interaction of punicalagin. The docking protocol was successfully validated by redocking the native ligand, which produced an RMSD value of 0.8298 Å.

ADMET prediction indicated a relatively favourable predicted safety profile for punicalagin, particularly with respect to the absence of predicted hepatotoxicity, low predicted BBB permeability, and the absence of predicted CYP2D6 substrate or inhibitor activity. However, the lower predicted intestinal absorption and limited tissue distribution compared with alogliptin may represent potential challenges for its systemic bioavailability.

Overall, punicalagin from pomegranate peel demonstrated promising in silico potential as a natural DPP-IV inhibitor. However, these findings are computational predictions and do not establish actual DPP-IV inhibitory activity or therapeutic efficacy. Therefore, confirmatory in vitro DPP-IV enzyme inhibition assays, followed by molecular dynamics simulations, pharmacokinetic studies, and further in vivo evaluation, are required to validate the predicted molecular interactions, inhibitory activity, bioavailability, and potential therapeutic relevance of punicalagin.

Acknowledgements

The author would like to thank the LPPM of Muhammadiyah A.R. Fachruddin University for funding this research through internal research funding.

Conflict of interest

The authors declare no conflict of interest in this research.

References

Ammirati MJ, Andrews KM, Boyer DD, Brodeur AM, Danley DE, Doran SD, Hulin B, Liu S, McPherson RK, Orena SJ, Parker JC, Polivkova J, Qiu X, Soglia CB, Treadway JL, Vanvolkenburg MA, Wilder DC, Piotrowski DW. 2009. (3,3-Difluoro-pyrrolidin-1-yl)-[(2S,4S)-(4-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrrolidin-2-yl]-methanone: a potent, selective, orally active dipeptidyl peptidase IV inhibitor. *Bioorg Med Chem Lett* 19(9): 2472-2476. doi: 10.1016/j.bmcl.2009.02.041

BIOVIA, Dassault Systèmes. 2020. BIOVIA Discovery Studio Visualizer, version 20.1.0.19295. San Diego: Dassault Systèmes.

Hanwell MD, Curtis DE, Lonie DC, Vandermeersch T, Zurek E, Hutchison GR. 2012. Avogadro: An advanced semantic chemical editor, visualization, and analysis platform. *J Cheminform* 4(1): 17. doi: 10.1186/1758-2946-4-17

Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. 2020. Epidemiology of Type 2 diabetes - Global burden of disease and forecasted trends. *J Epidemiol Glob Health* 10(1): 107-111. doi: 10.2991/JEGH.K.191028.001

Kristin E. 2016. Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus. *J Med Sci* 48(2): 119-130. doi: 10.19106/JMedSci004802201606

Kumar N, Pratibha, Neeraj, Sami R, Khojah E, Aljahani AH, Al-Mushhin AAM. 2022. Effects of drying methods and solvent extraction on quantification of major bioactive compounds in pomegranate peel waste using HPLC. *Sci Rep* 12(1): 8000. doi: 10.1038/s41598-022-11881-7

Laskowski RA, Swindells MB. 2011. LigPlot+: multiple ligand-protein interaction diagrams for drug discovery. *J Chem Inf Model* 51(10): 2778-2786. doi: 10.1021/ci200227u

Magangana TP, Makunga NP, Fawole OA, Opara UL. 2020. Processing Factors Affecting the Phytochemical and Nutritional Properties of Pomegranate (Punica granatum L.) Peel Waste: A Review. *Molecules* 25(20): 4690. doi: 10.3390/molecules25204690

Metzler WJ, Yanchunas J, Weigelt C, Kish K, Klei HE, Xie D, Zhang Y, Corbett M, Tamura JK, He B, Hamann LG, Sirby MS, Marcinkeviciene J. 2008. Involvement of DPP-IV catalytic residues in enzyme–saxagliptin complex formation. *Protein Sci* 17(2): 240-250. doi: 10.1110/ps.073253208

Miguel MG, Neves MA, Antunes MD. 2010. Pomegranate (Punica granatum L.): a medicinal plant with myriad biological properties-a short review. *J Med Plants Res* 425(25): 2836-2847.

Młynarska E, Czarnik W, Dzieża N, Jędraszak W, Majchrowicz G, Prusinowski F, Stabrawa M, Rysz J, Franczyk B. 2025. Type 2 Diabetes Mellitus: New Pathogenetic Mechanisms, Treatment and the Most Important Complications. *Int J Mol Sci* 26(3):1094. doi: 10.3390/ijms26031094

Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, Olson AJ. 2009. AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility. *J Comput Chem* 30(16): 2785-2791. doi:10.1002/jcc.21256

Nabeno M, Akahoshi F, Kishida H, Miyaguchi I, Tanaka Y, Ishii S, Kadowaki T. 2013. A comparative study of the binding modes of recently launched dipeptidyl peptidase IV inhibitors in the active site. *Biochem Biophys Res Commun* 434(2): 191-196. doi: 10.1016/j.bbrc.2013.03.010

Neese F, Wennmohs F, Becker U, Riplinger C. 2020. The ORCA quantum chemistry program package. *J Chem Phys* 152(22): 224108. doi: 10.1063/5.0004608

Neese F. 2022. Software update: The ORCA program system—Version 5.0. *WIREs Comput Mol Sci* 12(5): e1606. doi: 10.1002/wcms.1606

Petersmann A, Mueller-Wieland D, Muller UA, Landgraf R, Nauck M, Freckmann G, Heinemann L, Schleicher E. 2019. Definition, Classification and Diagnosis of Diabetes Mellitus. *Exp Clin Endocrinol Diabetes* 127 (S01): S1–S7. doi: 10.1055/a-1018-9078

Pires DEV, Blundell TL, Ascher DB. 2015. pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *J Med Chem* 58(9): 4066-4072. doi:10.1021/acs.jmedchem.5b00104

Rezagholizade-shirvan A, Soltani M, Shokri S, Radfar R, Arab M, Shamloo E. 2024. Bioactive compound encapsulation: Characteristics, applications in food systems, and implications for human health. *Food Chem X* 24: 101953. doi: 10.1016/j.fochx.2024.101953

Sharma UK, Pujani M, Anuradha J. 2024. Type-II-Diabetes Mellitus- Etiology, Epidemiology, Risk Factors and Diagnosis and Insight into Demography (Urban Versus Rural). *Int J Health Sci Res* 14(1): 283-290. doi: 10.52403/ijhsr.20240136

Singh J, Kaur HP, Verma A, Chahal AS, Jajoria K, Rasane P, Kaur S, Kaur J, Gunjal M, Ercisli S, Choudhary R, Bozhuyuk MR, Sakar E, Karatas N, Durul MS. 2023. Pomegranate Peel Phytochemistry, Pharmacological Properties, Methods of Extraction, and Its Application: A Comprehensive Review. *ACS Omega* 8(39): 35452-35469. doi: 10.1021/acsomega.3c02586

Trott O, Olson AJ. 2010. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J Comput Chem* 31(2): 455-461. doi:10.1002/jcc.21334

Venusova E, Kolesarova A, Horky P, Slama P. 2021. Physiological and Immune Functions of Punicalagin. *Nutrients* 13(7): 2150. doi: 10.3390/nu13072150

Wen C, Tang J, Cao L, Fan M, Lin X, Liu G, Liang L, Liu X, Zhang J, Li Y, Xu X. 2025. Strategic Approaches for Co-Encapsulation of Bioactive Compounds: Technological Advances and Mechanistic Insight. *Foods* 14(12): 2024. doi: 10.3390/foods14122024

Xu J, Cao K, Liu X, Zhao L, Feng Z, Liu J. 2022. Punicalagin regulates signaling pathways in inflammation-associated chronic diseases. *Antioxidants* 11(1): 29. doi: 10.3390/antiox11010029

Yang HK, Lee SH, Shin J, Choi YH, Ahn YB, Lee BW, Rhee UJ, Min KW, Yoon KH. 2019. Acarbose Add-on Therapy in Patients with Type 2 Diabetes Mellitus with Metformin and Sitagliptin Failure: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study. *Diabetes Metab J* 43(3): 287-301. doi: 10.4093/dmj.2018.0054

Ye J, Wu Y, Yang S, Zhu D, Chen F, Chen J, Ji X, Hou K. 2023. The global, regional and national burden of type 2 diabetes mellitus in the past, present and future: a systematic analysis of the Global Burden of Disease Study 2019. *Front Endocrinol* 14: 1192629. doi: 10.3389/fendo.2023.1192629