Docking: Ellagic Acid and It’s Derivatives as 11𝛽–HSD1 Inhibitors

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**Abstract.** Overactivity of 11𝛽 Hydroxysteroid dehydrogenase (11𝛽–HSD1) has been studied and may contribute to the development of type 2 diabetes mellitus: a metabolic syndrome. Inhibiting 11𝛽–HSD1 activity can be used as a treatment of diabetes mellitus by reducing the regeneration of active glucocorticoids which is cortisol. By inhibiting 11𝛽–HSD1, insulin sensitivity and glucose tolerance can be improved. The structural configurations of 11β–HSD1 (PDB ID: 4k1l) and ligands were prepared using AutoDockTools 1.5.6 and Open Babel 3.1.1. Docking was performed with AutoDock 4 using the Lamarckian genetic algorithm. Ellagic acid (EA) and its derivatives such as trimethyl ellagic acid (TMEA) and tetraacetate ellagic acid (EATA) proposed to act as 11–𝛽–HSD1 inhibitors which show close to known inhibitors such as carbenoxolone (CBX) where are the inhibition constants CBX, EA, TMEA, and respectively 582,6 pM, 670,39 pM, 28,29 nm, and 7,5 nm with the strongest binding energy are CBX and EA –12,6 kcal/mol and –12,52 kcal/mol respectively. In comparison, CBX definitely has the smallest concentration to inhibit the protein but in molecular docking experiments, EA and its derivatives bind perfectly at the 11𝛽–HSD1 active site near the TYR183 area which indicates that the inhibitory activity of EA and its derivatives is very promising considering that EA compounds and their derivatives are natural sources, which can be obtained in nature such as berries.

**Keywords:** 11–𝛽–HSD1, type 2 diabetes mellitus, inhibitor, Ellagic acid and its derivatives

# INTRODUCTION

Diabetes mellitus (DM) is a serious metabolic condition that impacts the body's glucose metabolism. Insulin, which is synthesized by the pancreas, regulates glucose, an indispensable energy source for the body's cells [1]. In 2021, diabetes is projected to claim the lives of approximately 6.7 million individuals and affect 537 million individuals worldwide, according to the International Diabetes Federation. The number of diabetic patients is anticipated to increase by 642.7 million individuals in 2030 and 783.2 million individuals in 2045 if the rate of increase remains consistent [2]. Type 2 diabetes is a chronic metabolic disorder that is debilitating and common, it is a multifactorial disease that is influenced by genetic and environmental factors [3]. The dysregulation of glucocorticoid metabolism is one of the most critical pathophysiological mechanisms implicated in the development of insulin resistance and the subsequent dysregulation of glucose homeostasis [4].

Cortisol (glucocorticoids) are steroid hormones that have a variety of physiological functions, such as modulating glucose metabolism, inflammation, and the stress response [5, 6]. The activation of cortisone (inactive glucocorticoids) is significantly influenced by the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which catalyzes its conversion to cortisol (active form) [7–9]. The process take place in the liver and adipose tissue, expressed and utilizes cofactor NADPH to convert intracellular cortisone to active cortisol. Cortisol is a critical regulator of metabolic processes by activating glucocorticoid receptors, which in turn regulates the expression of tissue-specific genes [6, 10, 11]. The expression of gluconeogenesis and glycogenolysis genes in the liver is induced by cortisol, resulting in an increase in glucose production [12]. Excessive local accumulation of active glucocorticoids and the development of insulin resistance, a hallmark of type 2 diabetes, may result from defects in 11β-HSD1 activity, particularly in insulin-sensitive tissues like adipose tissue and liver [3, 4, 11, 13, 14].

Ellagic acid is a naturally occurring polyphenolic compound found in various fruits and plants, such as pomegranates, raspberries, and walnuts. Preclinical studies have shown the potential therapeutic properties of ellagic acid and its derivatives, including antioxidant, anti-inflammatory, antibacterial, anti aging, and anticancer activity [15, 16].

In contrast to ellagic acid, carbenoxolone, a compound derived from glycyrrhetinic acid, has been extensively investigated as an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) due to its potential therapeutic application in metabolic disorders [17, 18], but carbenoxolone's practical application remains restricted due to its low specificity and adverse side effects. These adverse effects include pseudo aldosteronism (causing water and salt retention), hypertension, and edema. Furthermore, the prolonged use of carbenoxolone can result in hypokalemia, which can result in neuromuscular dysfunction, muscle and kidney injury [4, 10, 19].

So, it is crucial to identify safer and more specific 11β-HSD1 inhibitors. Ellagic acid, a polyphenolic compound widely present in numerous fruits and plants in addition, it demonstrates advantageous pharmacokinetic characteristics and a favorable safety profile, which makes it a promising candidate for further research [16, 20]. Structure-based drug design can be used to create and improve derivatives of ellagic acid by taking advantage of its distinctive structural characteristics. Ellagic acid (EA), Trimethyl ellagic acid (TMEA) and ellagic acid tetraacetate () can be proposed to address the limitations of carbenoxolone which offer a more efficient and safer treatment option to treat type 2 diabetes mellitus a metabolic disorder caused by overexpressed 11β-HSD1 which structure is shown in **Fig 1a-d**.



a)

b)

c)

d)

**FIGURE 1.** The structure of (a) Carbenoxolone, (b) Ellagic acid, (c) Trimethyl Ellagic acid, and (d) Ellagic acid tetraacetate.

Computational docking studies investigating the interactions between 11β-HSD1 and ellagic acid, trimethyl ellagic acid, ellagic acid tetraacetate, carbenoxolone, and cortisone provide a good technique to acquire insights into the potential inhibitory interactions between these two compounds. Molecular docking simulations are capable of forecasting the binding configurations, strengths, and structural factors that control the suppression of 11β-HSD1 by ellagic acid. Recent findings shows that ellagic acid has the potential in controlling many components of metabolic syndrome, such as diabetes, hypertension, and hyperlipidemia [21]. The information can serve as a logical foundation for the creation and improvement of more powerful and specific inhibitors of 11β-HSD1, which are derived from the structure of ellagic acid and can potentially be used as a new treatment approach to regulate the activity of 11β-HSD1. This can help reduce the harmful effects of excessive glucocorticoid exposure and improve metabolic results.

# MEtHODS

Human 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) structural configuration was retrieved from the Protein Data Bank (PDB ID: 4k1l) of the Research Collaboratory for Structural Bioinformatics (RCSB) [9]. Using AutoDockTools version 1.5.6, the protein structure underwent pre-processing that included assigning Kollman charges, adding polar hydrogens, and removing water molecules [22, 23]. To have the protein ready to accept a new ligand later on, the ligand (NDP and SFF) was removed from the structure. Furthermore, the protein consists of four identical parts (A, B, C, and D), of which three are cleaved to leave just part A. The prepared proteins were then scored for their binding sites using DoGSiteScorer [24] tool by ProteinsPlus [25–27] to evaluate potential binding site with 0 – 1 scale which 1 represent the best possible score.

We obtained the chemical structures of cortisone, carbenoxolone, ellagic acid, trimethyl ellagic acid, and ellagic acid tetraacetate from the PubChem database, specific inclusion of cortisone and carbenoxolone was made to look into how they, as known inhibitors and inactive hormones, interact with the protein [28–32]. The acquired structures were next transformed into formats that could be used with Open Babel 3.1.1 [33, 34]. Later on, the improved ligand structures were kept in AutoDock-compatible PDBQT format.

Every ligand was docked separately into the 11β-HSD1 binding site using Lamarckian genetic algorithm with autodock 4 [22]. The conformations having the greatest scores were then identified by using their predicted binding affinities. The docking results were investigated and displayed using PyMOL version 3.0 [35], also with Protein-Ligand Interaction Profiler (PLIP) [36]. Finding potential hydrophobic, hydrogen bond, and other important interactions between the ligands and the active site residues was the primary goals.

# RESULT & DISCUSSION

The ligands interaction between 11β-HSD1 docking analysis revealed different ways in which these compounds bind to the protein, providing useful information about biological activity as promising inhibitor for 11β-HSD1. All ligands show 0 value in cluster RMSD that indicates convergence in the docking simulation, the results shows that each ligand consistently assumed a single, well-positioned binding in multiple docking runs, which also translate enhanced confidence in the predicted binding modes and suggests that the interactions are energetically favorable and stable [37, 38]. The consistent docking data serve as a basis for comparing the binding properties of the various ligands.

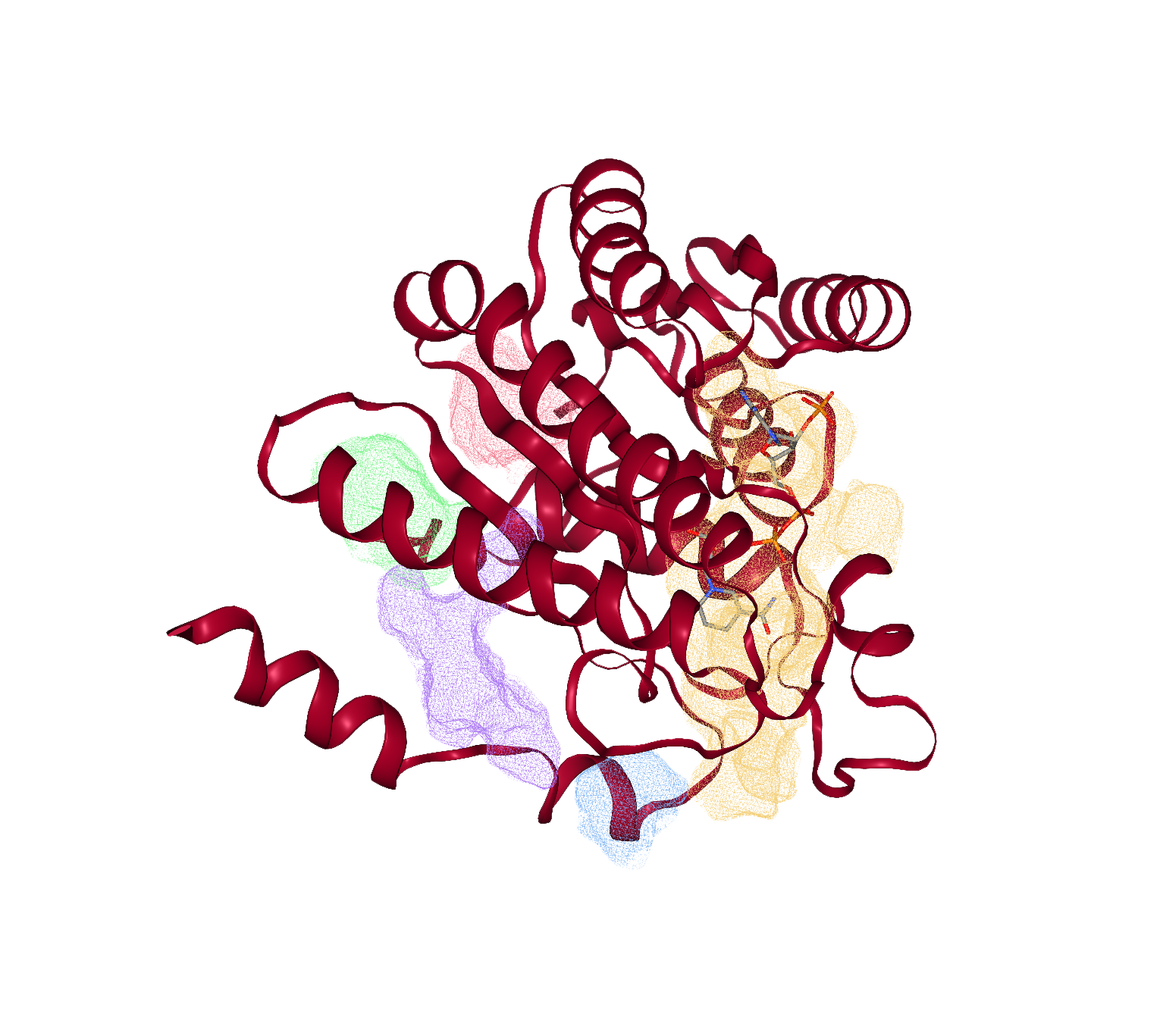
**TABLE 1.** Protein binding pocket/site prediction

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Binding Site** | **Color** | **Volume (Å3)** | **Surface (Å2)** | **Druggability Score** | **Simple Score** |
| 1 |  | 1721.34 | 2290.91 | 0.8 | 0.64 |
| 2 |  | 404.48 | 734.04 | 0.74 | 0.2 |
| 3 |  | 298.05 | 454.46 | 0.49 | 0.09 |
| 4 |  | 226.18 | 310.33 | 0.39 | 0.07 |
| 5 |  | 116.29 | 216.43 | 0.23 | 0.05 |

The binding site predicted using DoGSiteScorer tool [24] by ProteinsPlus [25–27] shows that binding pocket number 1 predicted to be the most promising site for ligand or drug bind to the protein that have the highest druggability score, highest volume, and surface area, the binding site number 1 corresponds to the docking simulation results that also take place in the same site because the cofactor take place also in the site 1, so it more likely the docking and ligand attachment is happening in the site 1. The binding site can be seen in **Fig 2**.

Molecular docking experiments show that intermolecular, internal, and torsional energy variables impact the binding and stability of ligand-protein complexes. Intermolecular energy measures the interactions between active sites and ligands, which include hydrogen bonds, van der Waals forces, and hydrophobic contacts. A decrease in intermolecular energy suggests a stronger binding interaction. The energetic cost associated with the rotation around single bonds, known as torsional energy, serves as an important measure of ligand flexibility. The conformation of the ligand needs to be modified to attain the most effective binding configuration. Ellagic acid (EA) demonstrates significant intermolecular interactions (−13.71 kcal/mol) with the active site residues TYR183 and HIS130. The internal energy of carbenoxolone (CBX) was elevated, even though it exhibited the same intermolecular energy (-14.98 kcal/mol). This indicates that conformational strain took place during the binding phase. Trimethyl ellagic acid (TMEA) and tetraacetate ellagic acid (EATA) demonstrate increased flexibility due to elevated torsional energy values. This could result in a reduced binding affinity, even in the presence of hydrophobic interactions.

The data for ligand characteristics interaction with the protein is shown in **Table 1** and the detailed information according to interaction between the protein and the ligand is shown on **Table 2** and **Table 3**. Cortisone and carbenoxolone (CBX), used as reference compounds shown in **Fig 3a-b**, have strong binding affinities and similar binding energies. However, ellagic acid (EA) had the maximum ligand efficiency (-0.57), indicating that its molecular interactions were optimally utilized given its size. This is especially interesting because of its substantial hydrogen bonding network (11 bonds) and extra π-cation interaction, indicating a binding mechanism that effectively utilizes the protein active site shown in **Fig 3c**.

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**FIGURE 2.** Binding pocket/site prediction.

**TABLE 2.** Ligand characteristic (all energy unit are in kcal/mol)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ligand** | **Binding Energy** | **Ligand Efficiency** | **Inhibition Constant** | **Intermolecular Energy** | **Internal Energy** | **Torsional Energy** | **Cluster RMSD** |
| Cortisone | -12.85 | -0.49 | 377.73 pM | -14.05 | -0.68 | 1.19 | 0 |
| CBX | -12.6 | -0.31 | 582.6 pM | -14.98 | -2.25 | 2.39 | 0 |
| EA | -12.52 | -0.57 | 670.39 pM | -13.71 | -2.15 | 1.19 | 0 |
| TMEA | -10.3 | -0.41 | 28.29 nM | -11.49 | -1.19 | 1.19 | 0 |
| EATA | -11.08 | -0.33 | 7.5 nM | -13.47 | -2.54 | 2.39 | 0 |

The addition of three methyl groups to ellagic acid (TMEA) resulted in a considerable decrease in binding energy (-10.3 kcal/mol) and a greater inhibition constant (28.29 nM) than ellagic acid alone. This shows that the methyl changes could cause steric hindrances or impair ideal hydrogen bonding patterns [39]. However, the presence of π-cation and salt bridge interactions with 135HIS shown in Figure 2d suggests that these electrostatic interactions can be fine-tuned to increase binding affinity.

Ellagic acid tetraacetate (EATA) demonstrated an intermediate binding profile, with higher affinity than the trimethyl derivative but lower than ellagic acid. Its binding mode with 135HIS is characterized by fewer hydrogen bonds but more hydrophobic contacts, as well as two salt bridges, indicating a shift in the balance of polar and non-polar interactions shown in **Fig 3e**. This could improve membrane permeability while retaining a tolerable binding affinity.

**TABLE 3.** Ligand Interaction

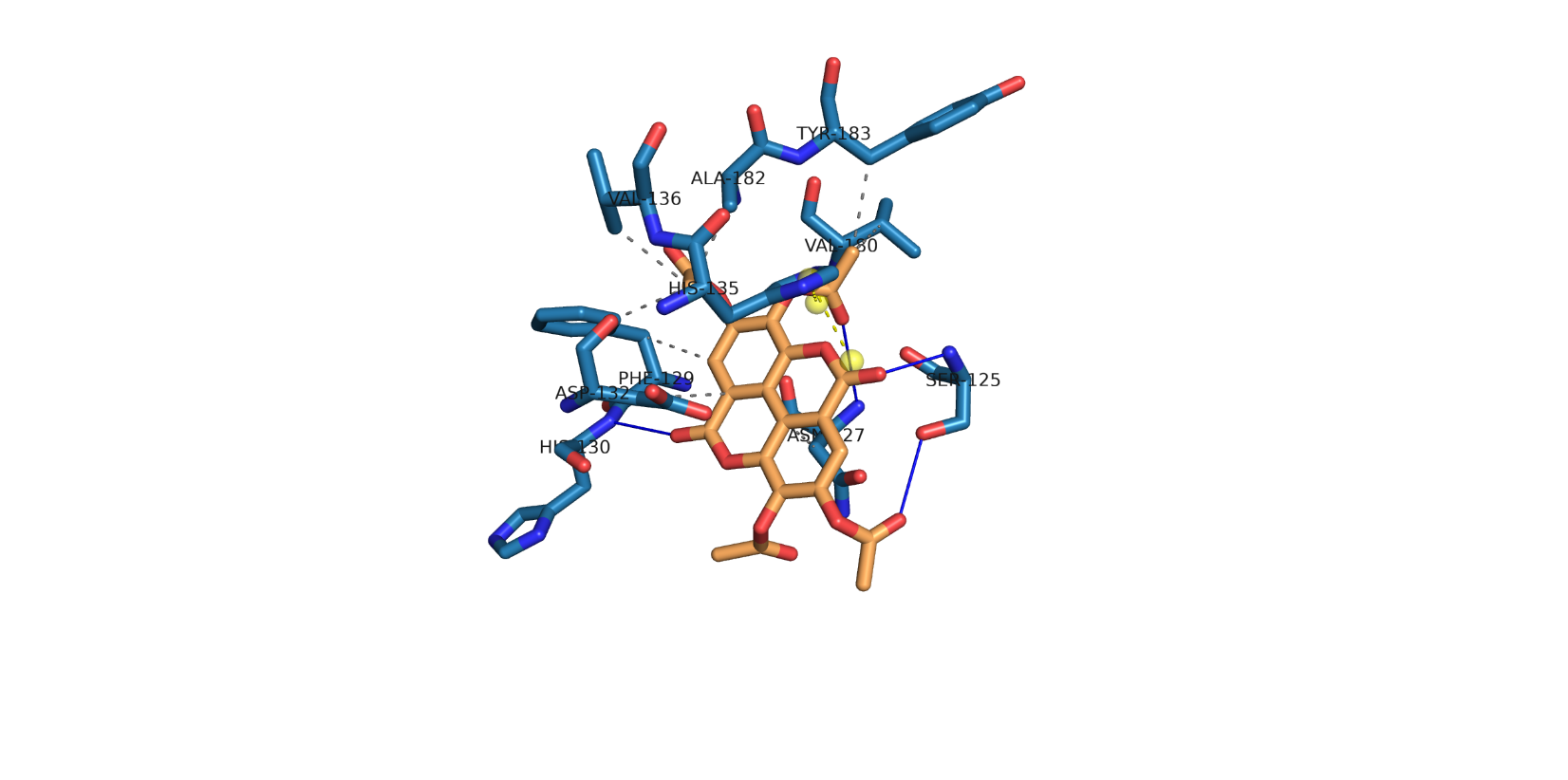
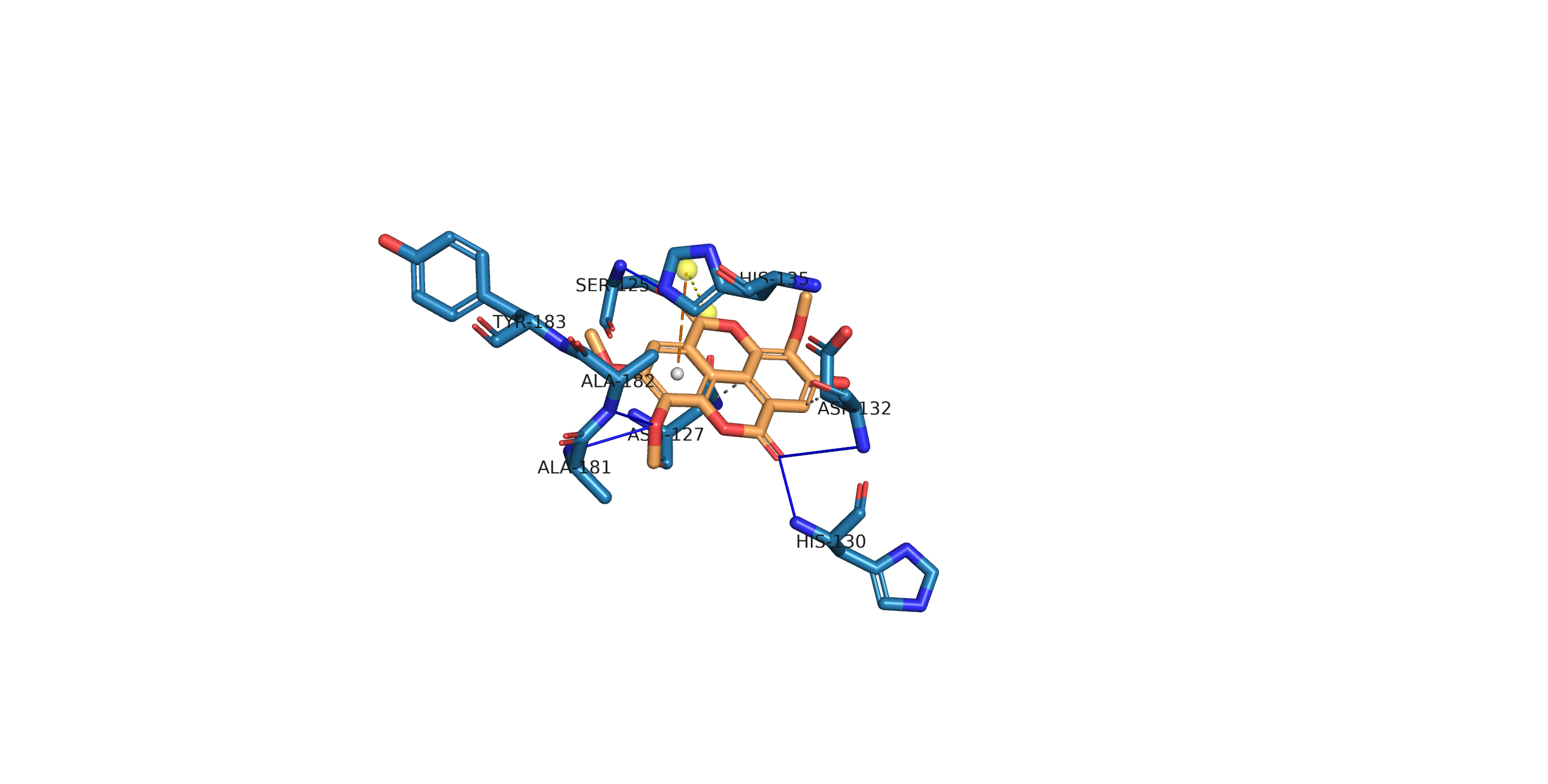
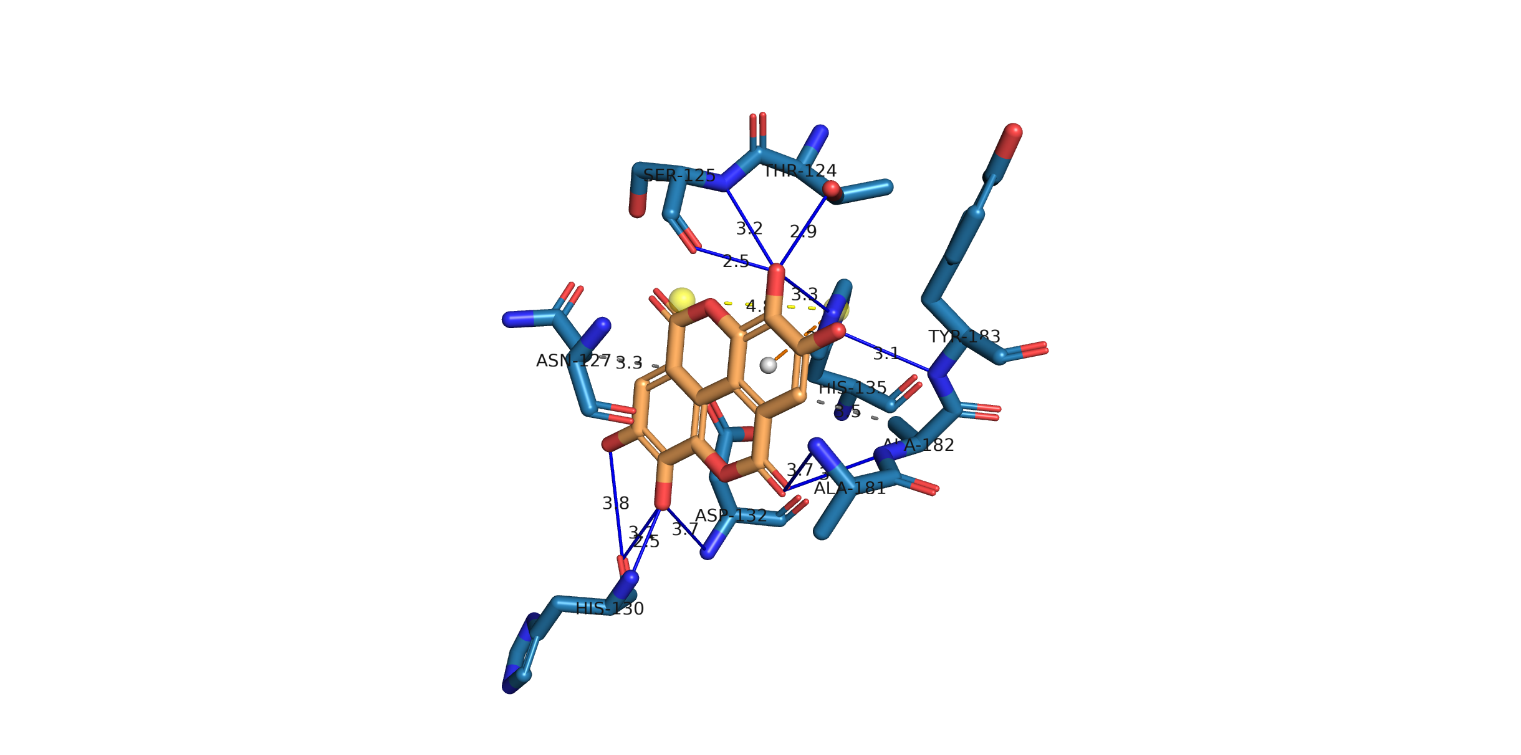
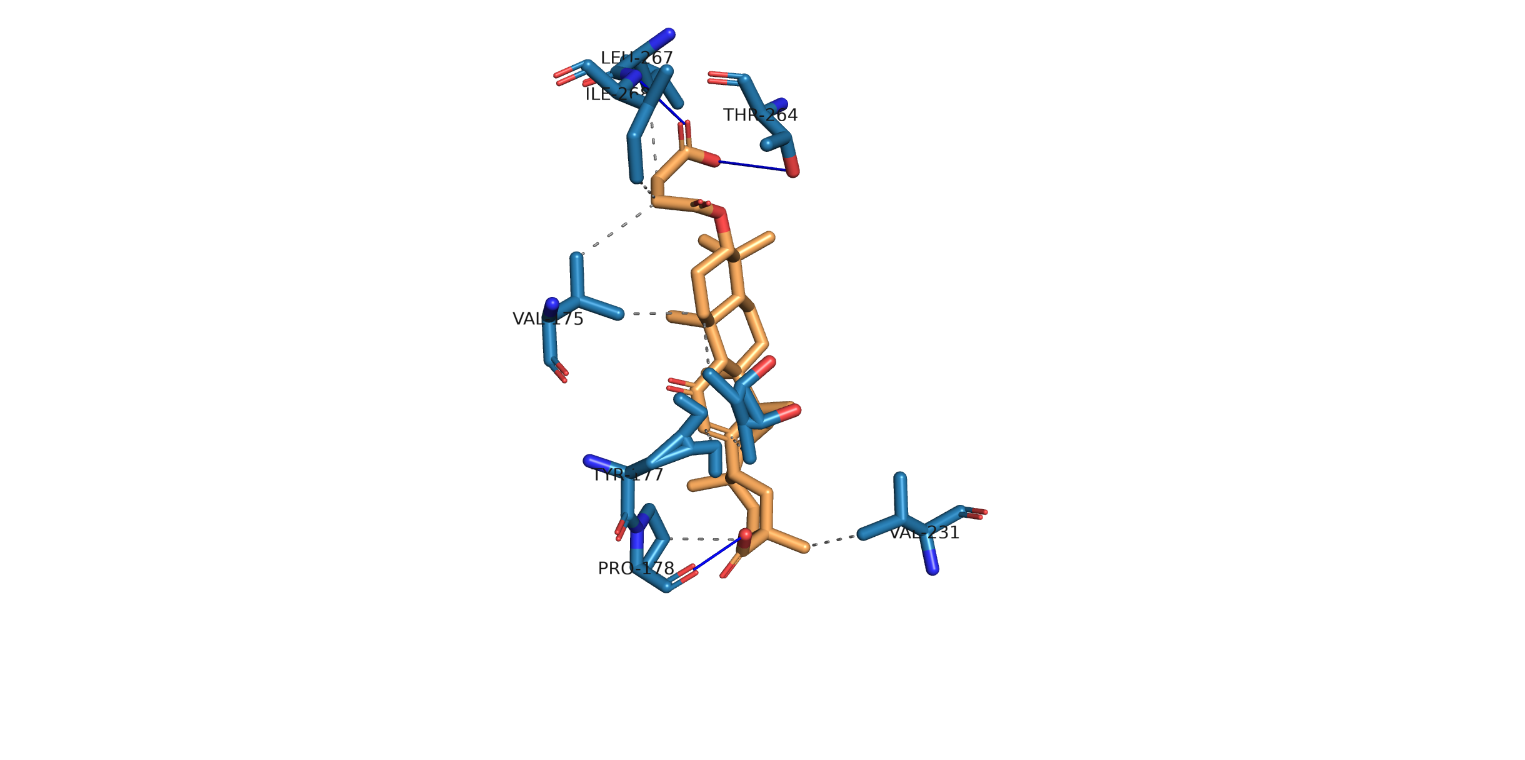
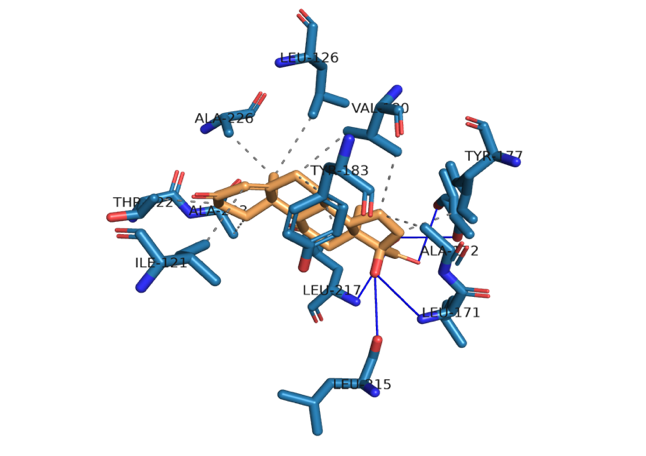
|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ligand** | **Cluster RMSD** | **Number of interactions** | | | | | **Amino Acid Involved in Interaction** | | | | |
| **H-Bonds** | **Hydrophobic** | **π-Cation** | **Salt Bridges** | **H-Bonds** | | **Hydrophobic** | **π-Cation** | **Salt Bridges** |
| Cortisone | 0 | 5 | 11 | - | - | 171LEU, 2 177TYR, 215LEU, 217LEU | | 121ILE, 126LEU, 172ALA, 177TYR, 2 180VAL, 2 183TYR, 222THR, 223ALA, 226ALA | - | - |
| CBX | 0 | 3 | 9 | - | - | PRO178; 264THR; ILE268 | | 2 175VAL, 3 177TYR, 178PRO, 231VAL, 267LEU, 268ILE | - | - |
| EA | 0 | 11 | 2 | 1 | 1 | 124THR, 2 125SER, 3 130HIS, 132ASP, 135HIS, 181ALA, 182ALA, 183TYR | | 127ASN, 182ALA | 135HIS | 135HIS |
| TMEA | 0 | 6 | 2 | 1 | 1 | SER125; HIS130; ASP132; ALA181; ALA182; TYR183 | | 127ASN, 132ASP | 135HIS | 135HIS |
| EATA | 0 | 4 | 8 | - | 2 | 2 125SER; 127ASN; 130HIS | | 127ASN, 2 129PHE, 132ASP, 136VAL, 180VAL, 182ALA, 183TYR | - | 2 135HIS |

The 11β-HSD1 binding site may support a wide range of ligands, as seen by the various interaction patterns observed in these molecules. The continuous participation of residues such as 125SER, 130HIS, and 183TYR across various ligands implies that they play an important role in ligand recognition and binding.

Ellagic acid's greater ligand efficiency over carbenoxolone, combined with its distinct interaction profile, making it an attractive candidate for further study. Its binding style could be used to develop new inhibitors that optimize hydrogen bonding and electrostatic interactions at the active site. The lower affinity of the trimethyl and tetraacetate derivatives, while potentially disappointing from an inhibitory standpoint, reveals important information about the structure-activity connection. These alterations expose the binding site's sensitivity to steric and electronic perturbations, providing guidance for future optimization strategies.

A comparison of binding energies with those reported in literature highlights EA's great potential as a very powerful inhibitor. For their top inhibitors, Cabrera-Pérez et al. (2020) showed binding energies between -8.46 and -8.91 kcal/mol, therefore stressing important hydrogen bonding interactions with residues like TYR183 and S170 [40]. EA's binding energy of −12.52 kcal/mol shows more affinity for the 11β-HSD1 active site than these values. Benzothiazole derivatives displayed inhibition constants in the micromolar range, while EA had nanomolar inhibition constants, emphasizing its higher potency. Moreover, EA's adherence to Lipinski's Rule of Five shows favorable pharmacokinetics as opposed to synthetic inhibitors like CBX. Unlike benzothiazole derivatives, which showed different hydrophobic contributions depending on substituents, EA showed homogeneous hydrophobic interactions, particularly with residues LEU215 and VAL180, therefore improving its stability inside the binding pocket. Furthermore, compared to the more flexible ligands TMEA and EATA, investigations of torsional energy revealed that EA's lowered flexibility improved its accuracy in binding to the active site.

Ellagic acid had the best ligand efficiency (-0.57) of the substances tested, indicating that its molecular interactions were optimally utilized for its size. Importantly, ellagic acid follows Lipinski's Rule of Five, which predicts high oral bioavailability for drug-like compounds [41]. The compound fits the criteria with a molecular weight of 302.19 g/mol (< 500), a log P value of 1.1 (< 5), 4 hydrogen bond donors (≤ 5), and 8 hydrogen bond acceptors (≤ 10) [30]. This adherence to Lipinski's Rule suggests that ellagic acid possesses attractive drug-like qualities, thus improving its prospects as a lead molecule for further development. The docking research demonstrated that ellagic acid forms hydrogen bonds with eight amino acid residues in the binding site: 124THR, 125SER, 130HIS, 132ASP, 135HIS, 181ALA, 182ALA, and 183TYR. The 11 hydrogen bonds indicated earlier are most likely numerous hydrogen bonds produced with some of these residues, particularly those with side chains that can form multiple hydrogen bonds. This large hydrogen bonding network, together with its π-cation interaction, contributes to ellagic acid's high binding affinity and efficient use of the protein active site.



a)

b)

c)

d)

e)

**FIGURE 3.** The interaction of (a) Cortisone, (b) Carbenoxolone, (c) Ellagic Acid, (d) Trimethyl Ellagic acid, and (e) Ellagic acid tetraacetate Interaction with 11β-HSD1

# CONCLUSION

This thorough investigation analyzes the binding properties of ellagic acid and its derivatives with the 11β-HSD1 protein, comparing them to the natural substrate cortisone and the established inhibitor carbenoxolone. Our molecular docking investigations, backed by consistent RMSD values, have identified ellagic acid as a very promising lead chemical because to its superior ligand efficiency and attractive interaction profile. The trimethyl and tetraacetate derivatives show useful information about 11β-HSD1 binding site through structure-activity connections. The fact that ellagic acid adheres to Lipinski's Rule of Five improves its medical research potential even further. Despite their hopeful nature, these computational studies underline the importance of extensive experimental validation and optimization. Future study should focus on proving ellagic acid's inhibitory effect using cellular models, validating interaction properties, and researching structural alterations to improve its efficiency and potential as a safe inhibitor for patients. This finding might pave the way for the development of 11β-HSD1 inhibitors, perhaps leading to novel treatments for type 2 diabetes.

# REFERENCES

1. L. Poretsky, *Principles of diabetes mellitus*, Springer (2010).
2. D. Magliano and E. J. Boyko, *IDF diabetes atlas*, Brussels, International Diabetes Federation (2021).
3. R. Shukla, A. K. Basu, B. Mandal, P. Mukhopadhyay, A. Maity, S. Chakraborty, and P. K. Devrabhai, *BMC Endocr. Disord.* **19**, 15 (2019).
4. S. A. Morgan and J. W. Tomlinson, *Expert Opin. Investig. Drugs* **19**, 1067 (2010).
5. P. M. Stewart and J. I. Mason, *Aldosterone Hypertens.* **60**, 143 (1995).
6. A. J. Peckett, D. C. Wright, and M. C. Riddell, *Metabolism* **60**, 1500 (2011).
7. D. H. van Raalte and M. Diamant, *Netherlands The Journal of Medicine* **72**, 62 (2014).
8. S. Diederich, C. Grossmann, B. Hanke, M. Quinkler, M. Herrmann, V. Bahr, and W. Oelkers, *Eur J Endocrinol* **142**, 200 (2000).
9. T. Böhme, C. K. Engel, G. Farjot, S. Güssregen, T. Haack, G. Tschank, and K. Ritter, *Bioorg. Med. Chem. Lett.* **23**, 4685 (2013).
10. T. C. Sandeep, R. Andrew, N. Z. M. Homer, R. C. Andrews, K. Smith, and B. R. Walker, *Diabetes* **54**, 872 (2005).
11. L. Duplomb, Y. Lee, M. Y. Wang, B. H. Park, K. Takaishi, A. K. Agarwal, and R. H. Unger, *Biochem Biophys Res Commun* **313**, 594 (2004).
12. H.-S. Han, G. Kang, J. S. Kim, B. H. Choi, and S.-H. Koo, *Exp. Mol. Med.* **48**, e218 (2016).
13. B. M. Abdallah, H. Beck-Nielsen, and M. Gaster, *Eur J Clin Invest* **35**, 627 (2005).
14. K. Kannisto, K. H. Pietilainen, E. Ehrenborg, A. Rissanen, J. Kaprio, A. Hamsten, and H. Yki-Jarvinen, *J Clin Endocrinol Metab* **89**, 4414 (2004).
15. E. M. Daniel, A. S. Krupnick, Y.-H. Heur, J. A. Blinzler, R. W. Nims, and G. D. Stoner, *J. Food Compos. Anal.* **2**, 338 (1989).
16. J. Sharifi-Rad, C. Quispe, C. M. S. Castillo, R. Caroca, M. A. Lazo-Vélez, H. Antonyak, A. Polishchuk, R. Lysiuk, P. Oliinyk, L. De Masi, P. Bontempo, M. Martorell, S. D. Daştan, D. Rigano, M. Wink, and W. C. Cho, *Oxid. Med. Cell. Longev.* **2022**, 1 (2022).
17. B. R. Walker, A. A. Connacher, R. M. Lindsay, D. J. Webb, and C. R. W. Edwards, *J Clin Endocrinol Metab* **80**, 3155 (1995).
18. A. M. Nuotio-Antar, D. L. Hachey, and A. H. Hasty, *Am J Physiol Endocrinol Metab* **293**, E1517−E1528 (2007).
19. D. Armanini and C. Fiore, Carbenoxolone, in *Encyclopedia of Endocrine Diseases*, Edited by L. Martini, New York, Elsevier (2004), pp. 451–454.
20. A. González-Sarrías, R. García-Villalba, M. Á. Núñez-Sánchez, J. Tomé-Carneiro, P. Zafrilla, J. Mulero, F. A. Tomás-Barberán, and J. C. Espín, *J. Funct. Foods* **19**, 225 (2015).
21. K. Naraki, M. Ghasemzadeh Rahbardar, B. O. Ajiboye, and H. Hosseinzadeh, *Heliyon* **9**, e21844 (2023).
22. G. M. Morris, D. S. Goodsell, R. S. Halliday, R. Huey, W. E. Hart, R. K. Belew, and A. J. Olson, *J. Comput. Chem.* **19**, 1639 (1998).
23. R. Huey, G. M. Morris, A. J. Olson, and D. S. Goodsell, *J. Comput. Chem.* **28**, 1145 (2007).
24. A. Volkamer, D. Kuhn, T. Grombacher, F. Rippmann, and M. Rarey, *J. Chem. Inf. Model.* **52**, 360 (2012).
25. R. Fährrolfes, S. Bietz, F. Flachsenberg, A. Meyder, E. Nittinger, T. Otto, A. Volkamer, and M. Rarey, *Nucleic Acids Res.* **45**, W337 (2017).
26. K. Schöning-Stierand, K. Diedrich, R. Fährrolfes, F. Flachsenberg, A. Meyder, E. Nittinger, R. Steinegger, and M. Rarey, *Nucleic Acids Res.* **48**, W48 (2020).
27. K. Schöning-Stierand, K. Diedrich, C. Ehrt, F. Flachsenberg, J. Graef, J. Sieg, P. Penner, M. Poppinga, A. Ungethüm, and M. Rarey, *Nucleic Acids Res.* **50**, W611 (2022).
28. National Center for Biotechnology Information, PubChem Compound Summary for CID 222786, Cortisone, (2024).at <https://pubchem.ncbi.nlm.nih.gov/compound/Cortisone>
29. National Center for Biotechnology Information, PubChem Compound Summary for CID 636403, Carbenoxolone, (2024).at <https://pubchem.ncbi.nlm.nih.gov/compound/Carbenoxolone>
30. National Center for Biotechnology Information, Pubchem Compound Summary ID 5281855, Ellagic Acid, (2024).at <https://pubchem.ncbi.nlm.nih.gov/compound/Ellagic-Acid>
31. National Center for Biotechnology Information, PubChem Compound Summary for CID 5281860, 2,3,8-Tri-O-methylellagic acid, (2024).at <https://pubchem.ncbi.nlm.nih.gov/compound/2_3_8-Tri-O-methylellagic-acid>
32. National Center for Biotechnology Information, PubChem Compound Summary for CID 14432358, Ellagic acid tetraacetate, (2024).at <https://pubchem.ncbi.nlm.nih.gov/compound/Ellagic-acid-tetraacetate>
33. N. M. O’Boyle, M. Banck, C. A. James, C. Morley, T. Vandermeersch, and G. R. Hutchison, *J. Cheminformatics* **3**, 33 (2011).
34. The Open Babel Package, version 3.1.1at <http://openbabel.org>
35. The PyMOL Molecular Graphics System, Version 3.0 Schrödinger, LLC.
36. M. F. Adasme, K. L. Linnemann, S. N. Bolz, F. Kaiser, S. Salentin, V. J. Haupt, and M. Schroeder, *Nucleic Acids Res.* **49**, W530 (2021).
37. I. Kufareva and R. Abagyan, Methods of Protein Structure Comparison, in *Homology Modeling*, Edited by A. J. W. Orry and R. Abagyan, Totowa, NJ, Humana Press (2011), pp. 231–257.
38. M. T. Khan, A. Ali, Q. Wang, M. Irfan, A. Khan, M. T. Zeb, Y.-J. Zhang, S. Chinnasamy, and D.-Q. Wei, *J. Biomol. Struct. Dyn.* **39**, 3627 (2021).
39. S. Neupane, J. Khadka, S. Rayamajhi, and A. S. Pandey, *J. Ayurveda Integr. Med.* **14**, 100750 (2023).
40. L. C. Cabrera Pérez, I. I. Padilla-Martínez, A. Cruz, J. Correa Basurto, Á. Miliar García, A. A. Hernández Zavala, M. Gómez López, and M. C. Rosales Hernández, *Mol. Divers.* **24**, 1 (2020).
41. Abd. K. Umar, J. H. Zothantluanga, K. Aswin, S. Maulana, M. Sulaiman Zubair, H. Lalhlenmawia, M. Rudrapal, and D. Chetia, *Struct. Chem.* **33**, 1445 (2022).