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Original Research Article

Exploration of Novel Type 2 Antidiabetic Agents: Molecular Docking and Toxicity Assessment of Polyphenolic Compounds for Improved Therapeutic Potential

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ABSTRACT

Type 2 diabetes (DM2) poses significant global health challenges due to insulin resistance and impaired glucose metabolism. Dipeptidyl peptidase-4 (DPP4) inhibitors are key pharmacological agents used to manage DM2, but concerns over side effects prompt exploration of alternative therapies. This study investigates the potential of polyphenolic compounds as novel inhibitors of the dipeptidyl peptidase-4 (DPP4) enzyme for type 2 diabetes management. Polyphenolic ligands, including 3,4-Dicaffeoylquinic Acid, Apiin, Naringin, Cirsiliol, Cryptochlorogenic Acid, Cirsilineol, and Quercitrin, were subjected to molecular docking with the DPP4 receptor for the first time using Molecular Operating Environment (MOE) software. Our analysis reveals compelling binding interactions, with several ligands demonstrating notably low docking scores compared to synthetic inhibitors. Notably, 3,4-Dicaffeoylquinic Acid, Apiin, and Naringin exhibited docking scores of -7.7, -7.6, and -7.4, respectively, surpassing established synthetic inhibitors Sitagliptin (-7.4), Vildagliptin (-6.6), and Saxagliptin (-5.9). Furthermore, a toxicity assessment of the polyphenolic ligands showed elevated LD_{50} values, emphasizing their potential safety. Quinic Acid, 3,4-Dicaffeoylquinic Acid, and Apiin demonstrated LD_{50} values of 9800 mg/kg, 5000 mg/kg, and 5000 mg/kg, respectively, with high toxicity classes indicative of a favourable safety profile. This study signifies a significant advancement in exploring alternative therapies for type 2 diabetes, underscoring the promising efficacy and safety of polyphenolic ligands as potential DPP4 inhibitors. The findings highlight the transformative potential of these natural compounds in reshaping diabetes therapeutics and warrant further investigation into their molecular mechanisms and therapeutic applications.

***Keywords*:** Type 2 Diabetes mellitus, Polyphenolic ligands, Molecular docking, Toxicity assessment, Anti-diabetic agents

Introduction

Diabetes mellitus type 2 (DM2) has reached epidemic proportions, with the World Health Organization estimating that approximately 422 million people worldwide were living with diabetes in 2014, and the numbers continue to rise.[1] DM2 represents a significant global health challenge characterized by insulin resistance and disrupted glucose metabolism, leading to elevated blood sugar levels. The pathophysiology of DM2 involves a complex interplay of genetic, environmental, and lifestyle factors, contributing to insulin resistance and *β*-cell dysfunction, where cellular responsiveness to insulin diminishes, impairing glucose uptake and leading to hyperglycemia.[2,3] This multifaceted condition underpins a spectrum of long-term complications, including cardiovascular diseases, neuropathy, and kidney problems, which significantly impact patients' quality of life and increase healthcare costs.[4]

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Central to glucose metabolism regulation is the Dipeptidyl Peptidase-4 (DPP4) enzyme, which plays a pivotal role in degrading incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). In DM2, elevated DPP4 levels accelerate incretin hormone degradation, undermining insulin secretion and glucagon suppression crucial for blood glucose control.[5] Pharmacological interventions targeting DPP4 have become essential in DM2 management. Established DPP4 inhibitors like Sitagliptin, Vildagliptin, and Saxagliptin effectively enhance glycemic control but are associated with potential side effects such as gastrointestinal discomfort and pancreatitis, necessitating exploration of alternative agents.[6,7] Given the need for safer and more effective therapeutic options, there has been growing interest in natural compounds, particularly polyphenolic compounds, known for their biological activities. Polyphenolic compounds are a diverse group of naturally occurring organic compounds primarily found in fruits, vegetables, tea, coffee, and wine. They have been extensively studied for their health benefits, including their ability to modulate various biological pathways relevant to metabolic diseases.[8] In a pioneering endeavour, our study conducts a comparative analysis between natural polyphenolic compounds and synthetic inhibitors, typically employed in inhibiting DPP4 to manage DM2. Specifically, this study investigates polyphenolic compounds, including 3,4-Dicaffeoylquinic Acid, Apiin, Naringin, Cirsiliol, Cryptochlorogenic Acid, Cirsilineol, and Quercitrin. These compounds have never been previously studied for their interactions with the DPP4 receptor using molecular docking techniques. This investigation represents the first attempt to select new, safer potential inhibitors through molecular docking utilizing the

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Molecular Operating Environment (MOE) software and toxicity assessment conducted via the NewChart website. The primary aim is to identify alternative therapeutic options with enhanced safety profiles for managing DM2.

Materials and Methods

Polyphenolic Compounds (Ligands)

Identifying Novel Ligands as Potential DPP4 Inhibitors in Type 2 Diabetes. Our investigation centres on exploring 11 meticulously chosen polyphenolic compounds with promising potential as novel inhibitors for the dipeptidyl peptidase-4 (DPP4) enzyme in the context of type 2 diabetes. These ligands, namely 3,4-Dicaffeoylquinic Acid, Caffeic Acid, Ferulic Acid, Cryptochlorogenic Acid, P-Coumaric Acid, Quinic Acid, Apiin, Cirsilineol, Cirsiliol, Naringin, and Quercitrin, have been selected following a thorough literature review, considering their relevance to diabetes and their unexplored interactions with DPP4. The detailed structures of these ligands and their corresponding PubChem Compound Identifiers (CID) are outlined in Table 1. Notably, this set of ligands represents a departure from commonly used compounds, as they will be investigated as potential replacements for established inhibitors. This novel approach aims to contribute new perspectives to the field by introducing alternative candidates for DPP4 inhibition in managing type 2 diabetes.[9]

DPP4 Inhibitors

DPP4 inhibitors, including Sitagliptin, Vildagliptin and Saxagliptin, are each identified by their unique CID numbers. This data is vital for conducting molecular docking and toxicity assessments, particularly in a comparative study with polyphenolic ligands. These standard inhibitors are listed in Table 2.[9]

Protein Structure

The crystal structure of DPP4 (PDB code: 5t4e) was downloaded from the Protein Data Bank (PDB; https://www.rcsb.org) to ensure the accuracy of the molecular docking simulations. Details regarding the enzyme source and its corresponding PDB code are in Table 3.[10]

Table 1: Ligands Explored for Potential Anti-Diabetic Type 2 Agents

Number	Ligand	CID
1	3,4-Dicaffeoylquinic Acid	5281780
2	Caffeic Acid	689043
3	Ferulic Acid	445858
4	Cryptochlorogenic Acid	9798666
5	P-Coumaric Acid	637542
6	Quinic Acid	6508
7	Apiin	5280746
8	Cirsilineol	162464
9	Cirsiliol	160237
10	Naringin	442428
11	Quercitrin	5280459

Table 2: DPP4 Inhibitors and their CID Numbers

Number	DPP4 Inhibitors	CID
1	Sitagliptin	4369359
2	Vildagliptin	6918537
3	Saxagliptin	11243969

Table 3: Enzyme Structure Used in Molecular Docking: PDB Code for DPP4

Enzyme	PDB Code
DPP4	5t4e

Molecular Docking

Molecular docking analyses were conducted using the Molecular Operating Environment (MOE) software version 2014.0901 (Chemical Computing Group, Montreal, Canada).[11] This software facilitated comprehensive preparation, optimization, and docking simulations of ligands and synthetic DPP4 inhibitors with the DPP4 enzyme. Before docking simulations, ligands and DPP4 inhibitors were prepared and optimized within the MOE platform to ensure appropriate structural alignment and conformational stability. Similarly, the DPP4 enzyme structure was prepared using MOE software to maintain uniformity and consistency in the simulation environment. Binding affinities between ligands/inhibitors and the DPP4 enzyme were quantified using docking scores, providing insights into the strength and feasibility of ligand interactions with the receptor. MOE software ensured a robust and reliable simulation environment, enhancing the accuracy and reliability of our docking analyses.[12-15]

Toxicity Prediction

A toxicity assessment was conducted using the ProTox-3.0 (https://tox.charite.de/protox3/) website to evaluate the potential toxicity of both ligands and synthetic inhibitors.[16] This web-based platform employs predictive models to estimate LD_{50} values and assign toxicity classes based on established criteria. The compounds were inputted into the website, and the resulting data, including LD_{50} values and toxicity classes, were retrieved for further analysis. This approach yielded valuable insights into the safety profiles of the compounds, facilitating a comparative assessment of their toxicological aspects.[17-18]

Results and Discussion

The study aimed to explore polyphenolic compounds as novel inhibitors of dipeptidyl peptidase-4 (DPP4) for managing type 2 diabetes mellitus (DM2). Given the side effects associated with synthetic DPP4 inhibitors, this research sought to identify alternative compounds with potentially improved safety and efficacy profiles. Utilizing the Molecular Operating Environment (MOE) software, molecular docking simulations were performed to evaluate the binding interactions of selected polyphenolic ligands with the DPP4 receptor.

Our molecular docking analysis, as detailed in Table 4, revealed that several polyphenolic ligands exhibited notably low docking scores, indicating strong binding affinities. Specifically, 3,4-Dicaffeoylquinic Acid, Apiin, and Naringin demonstrated docking scores of -7.7283, -7.6299, and -7.4193, respectively. These scores surpassed those of the synthetic inhibitors Sitagliptin (-7.3681), Vildagliptin (-6.6456), and Saxagliptin (-5.8880), as shown in Table 5. This suggests that the polyphenolic compounds have a higher potential to inhibit DPP4 effectively, thereby offering a promising alternative to conventional synthetic inhibitors. The findings align with previous research, such as Liu et al. (2021)[19], who demonstrated the inhibitory effects of polyphenolic ligands on the DPP4 enzyme. To evaluate the binding interactions, the ligand-DPP4 interactions were examined in detail (see Figure 1 and Figure 2). 3,4-Dicaffeoylquinic Acid engaged in Van der Waals interactions and formed hydrogen bonds with Val207 (as a donor) and Arg125 (as an acceptor). The binding was robust despite a noticeable loss of part of the contour, indicating potential solvent interaction. Similarly, Apiin exhibited Van der Waals interactions and formed hydrogen bonds with Val546 and Glu206 (both as donors), with a loss of contour suggesting solvent interaction. Cirsilineol demonstrated stable Van der Waals interactions and acted as a hydrogen bond acceptor with Arg125, showing a complete contour that signifies stable interaction with the DPP4 receptor. Cirsiliol formed Van der Waals interactions and a hydrogen bond with

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Glu206 (as a donor) but also showed a loss of contour, indicating solvent interaction.

In comparison, Figure 3 shows the interactions of Sitagliptin, Vildagliptin, and Saxagliptin with the DPP4 receptor. Sitagliptin engaged the DPP4 receptor through diverse interactions, including Van der Waals interactions, hydrogen bonding with Glu206, ionic bonding with Glu205, and arene-H interactions with Ser630. Despite these interactions, a discernible loss of contour suggested potential solvent interaction. Vildagliptin exhibited stable and intricate interactions, forming Van der Waals interactions, acting as a hydrogen bond acceptor with Arg669 and both a donor and acceptor with Glu205 and Glu206. Notably, an ionic bond with Glu205 contributed to the stability of the interaction, with a complete contour around the compound signifying a robust and stable binding interface. However, despite forming Van der Waals interactions and acting as a hydrogen bond acceptor with Arg125 and Tyr631, Saxagliptin showed a noticeable loss of contour, suggesting potential solvent interaction. The findings align with previous research by Patel et al. (2018), who emphasized the importance of hydrogen bonding and Van der Waals interactions in the stability and activity of DPP4 inhibitors.[20]

The favourable binding interactions of the polyphenolic compounds with the DPP4 receptor were further supported by toxicity assessments conducted using the ProTox-II website. As shown in Table 6, Quinic Acid, 3,4-Dicaffeoylquinic Acid and Apiin demonstrated LD_{50} values of 9800 mg/kg, 5000 mg/kg, and 5000 mg/kg, respectively, indicating a favourable safety profile. These values suggest a higher safety margin than some synthetic inhibitors, such as Vildagliptin (LD_{50} of 80 mg/kg, toxicity class 3) and Saxagliptin (LD_{50} of 3 mg/kg, toxicity class 1), as shown in Table 7. These findings align with recent research highlighting polyphenolic compounds' lower toxicity than synthetic drugs. A study by Scalbert et al. (2005) emphasized the general safety of dietary polyphenols, supporting their potential therapeutic application.[21]

The polyphenolic compounds' compelling docking scores and favourable toxicity profiles underscore their potential as effective and safe DPP4 inhibitors. This study represents a pioneering effort to explore these natural compounds in the context of DM2 management.

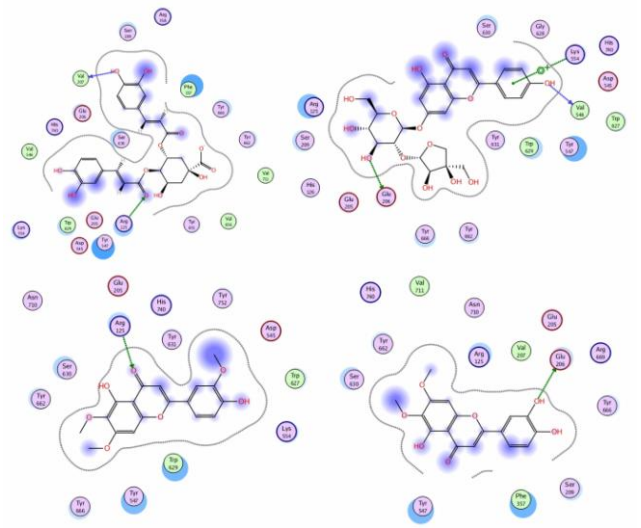

Figure 1: 2D ligand interactions of 3,4-Dicaffeoylquinic Acid, Apiin, Cirsilineol and Cirsiliol with DPP4 Receptor.

Table 4: Molecular Docking Scores for Ligands with DPP4 Enzyme

Ligands	Score
3,4-Dicaffeoylquinic Acid	-7.7283
Apiin	-7.6299
Naringin	-7.4193
Cirsiliol	-6.2493
Cryptochlorogenic Acid	-6.2013
Cirsilineol	-6.1966
Quercitrin	-6.1917
Ferulic Acid	-5.1580
Quinic Acid	-4.4000
P-Coumaric Acid	-4.3433
Caffeic Acid	-4.3196

Table 5: Molecular Docking Scores for Synthetic Inhibitors with DPP4 Enzyme

Synthetic Inhibitors	Score
Sitagliptin	-7.3681
Vildagliptin	-6.6456
Saxagliptin	-5.8880

Table 6: Toxicity Assessment of Ligands: LD_{50} Values and Toxicity Classes

Ligand	LD_{50} (mg/kg)	Toxicity Class
Quinic Acid	9800	6
3,4-Dicaffeoylquinic Acid	5000	5
Apiin	5000	5
Cryptochlorogenic Acid	5000	5
Cirsilineol	5000	5
Quercitrin	5000	5
Cirsiliol	4000	5
Caffeic Acid	2980	5
P-Coumaric Acid	2850	5
Naringin	2300	5
Ferulic Acid	1772	4

Table 7: Toxicity Assessment of Synthetic Inhibitors: LD_{50} Values and Toxicity Classes

Synthetic Inhibitors	LD_{50} (mg/kg)	Toxicity Class
Sitagliptin	2500	5
Vildagliptin	80	3
Saxagliptin	3	1

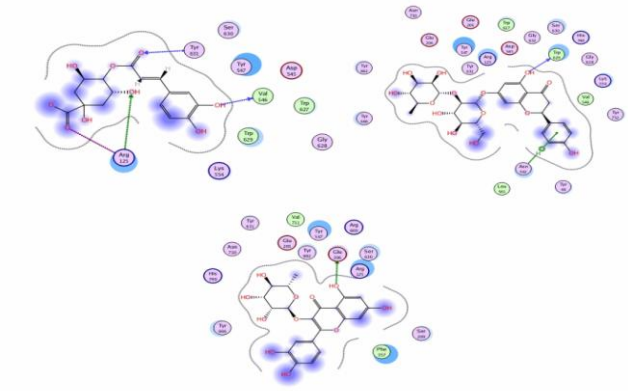

Figure 2: 2D ligand interactions of Cryptochlorogenic Acid, Naringin and Quercitrin with DPP4 Receptor.

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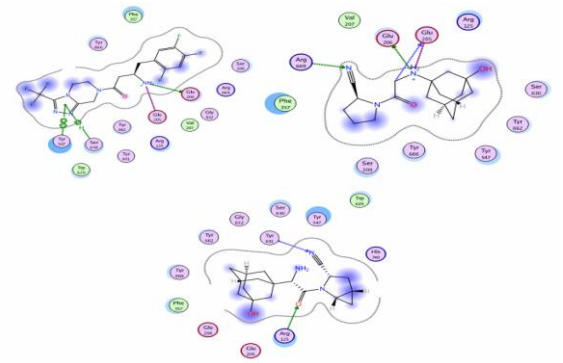

Figure 3: 2D Synthetic Inhibitors interactions of Sitagliptin, Vildagliptin and Saxagliptin with DPP4 Receptor.

Conclusion

Exploring novel type 2 antidiabetic agents, we've uncovered promising pathways for managing type 2 diabetes mellitus (DM2) through polyphenolic ligands. Analyzing the molecular interactions of 3,4-Dicaffeoylquinic Acid, Apiin, Naringin, Cirsiliol, Cryptochlorogenic Acid, Cirsilineol, and Quercitrin with the Dipeptidyl Peptidase-4 (DPP4) receptor for the first time revealed insights into their potential for DM2 management. Notably, these ligands exhibited high binding affinities, comparable to or surpassing synthetic inhibitors. Detailed analyses elucidated crucial ligand-receptor interactions, while toxicity assessments indicated a favourable safety profile. *In vivo* studies, structure-activity relationship investigations, and clinical trials are necessary to validate the efficacy and safety of these compounds, offering new horizons for DM2 therapeutics.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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