International Journal Of Health, Engineering And Technology (IJHET) *E-ISSN 2829 - 8683*
Volume 5, Number 1, May 2026, *Page. 902 - 907*
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Literature Review Of Drug-Receptor Interactions Based On Molecular Docking From The Perspective Of Lock And Key Theory

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Abstract

Drug-receptor interactions are the primary basis for determining the effectiveness of a therapy. Understanding the mechanisms of these interactions continues to evolve with advances in computational technology, one of which is through the molecular docking approach. This method enables in silico analysis of ligand-receptor interactions, including predictions of binding affinity, complex stability, and the types of molecular interactions that occur. Furthermore, the lock and key theory is a fundamental concept in explaining the structural compatibility between drugs and receptors, which influences bond strength and specificity. The method used in this review is a literature review from various scientific databases such as PubMed, Google Scholar, and ScienceDirect, with journals published in 2020 or later as inclusion criteria. The results show that oseltamivir has high affinity for neuraminidase through specific interactions such as hydrogen bonding and electrostatic binding. However, mutations in the receptor can lead to drug resistance. Therefore, understanding the mechanisms of molecular interactions is crucial for the development of more effective antiviral drugs.

Keywords: Docking, Drug, Receptor, Molecular, Interaction.

INTRODUCTION

The interaction between drugs and receptors is a fundamental concept in pharmacology that explains how a drug produces biological effects in the body. Receptors have a specific three-dimensional structure, allowing only ligands with specific characteristics to bind effectively. This concept is known as the lock and key theory, where the drug is likened to a "key" and the receptor to a "lock." The suitability of shape, size, and chemical properties are key factors in determining the success of the interaction, which is also supported by various non-covalent forces such as hydrogen bonds and hydrophobic interactions (Sharma et al., 2021; Kumari et al., 2023; Torres et al., 2022).

The development of medicinal chemistry has encouraged the use of computational methods to better understand drug-receptor interactions. One widely used method is molecular docking, a simulation technique used to predict the orientation and binding affinity between a ligand and a target protein. This method allows the identification of the best binding sites based on the lowest interaction energy, making it an important tool in the early stages of drug discovery due to its efficiency in screening candidate (Morris & Lim-Wilby, 2021; El Aissaoui et al., 2022; Sabe et al., 2023).

Molecular docking has been widely applied in antidiabetic research, particularly in evaluating the interactions of bioactive compounds with enzymes involved in glucose metabolism. Research by Akinyede et al. (2022) demonstrated the potential of Helichrysum petiolare extract as an antidiabetic agent through its interaction with specific enzyme targets. Other studies have combined in vitro and in silico assays to evaluate the inhibition of enzymes such as α-glucosidase and DPP-IV (Sadiq, 2020; Siddique, 2022; Zabidi, 2021).

In virology, particularly with regard to SARS-CoV-2, molecular docking plays a crucial role in identifying antiviral drug candidates. Various studies have evaluated the ability of compounds to inhibit key viral proteins such as the spike protein and the main protease. A study by Biswas et al. (2022) demonstrated the potential of peptides as receptor-binding domain inhibitors, while other studies have reported the effectiveness of bioactive compounds against viral proteases (Sharon & Kris, 2021; Prayogi et al., 2023).

Exploration of herbal compounds as antiviral candidates is also progressing through virtual screening and docking approaches. Karuna Sugito et al. (2023) demonstrated the potential of

Indonesian herbal compounds as inhibitors of the SARS-CoV-2 spike protein. Research by Prasetio et al. (2021) and Amin et al. (2025) also supports that certain compounds, including umifenovir, have high affinity for the viral protein target.

The application of molecular docking provides strong support for the lock and key theory in explaining drug-receptor interactions. Visualization of ligand-receptor complexes helps understand the relationship between structure and biological activity, and supports the development of more rational and specific drug designs. The integration of in silico approaches with experimental methods further strengthens the role of molecular docking in modern pharmaceutical research (Kumari et al., 2023; Sabe et al., 2023; Torres et al., 2022).

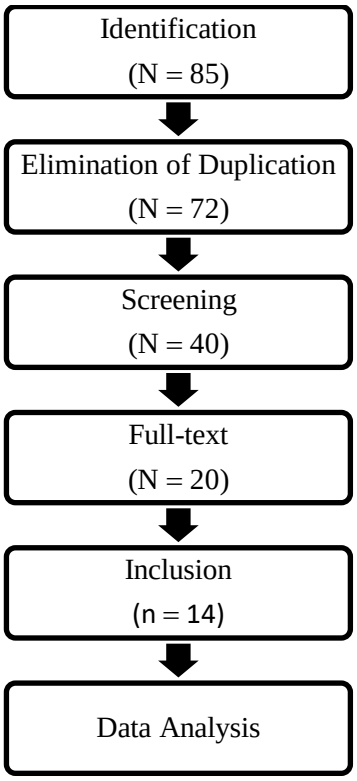
RESEARCH METHODS

This research is a systematic literature review conducted by searching scientific articles in several leading databases, including Google Scholar, PubMed, and ScienceDirect. The search strategy used a combination of key keywords, including "molecular docking," "drug-receptor interaction," and "lock and key theory," with the help of Boolean operators (AND/OR). The literature search timeframe was limited to 2020 to 2025 to ensure the relevance and currency of the analyzed data.

Articles selected for this study must meet the inclusion criteria: relevant to the topic of molecular docking-based drug–receptor interactions, published between 2020 and 2025, using an in silico approach, and available in full-text form. Conversely, articles that were irrelevant, duplicate, outside the publication year range, or lacked complete data were excluded from the analysis process. The article selection process was carried out systematically, adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) principles to ensure transparency and validity of the literature selection, as shown in Figure 1.

Based on the initial search results, 85 articles were obtained from all databases used. After removing 13 duplicate articles, the remaining number of articles was 72. A screening stage based on titles and abstracts was then carried out to eliminate irrelevant articles, resulting in 40 articles. Next, a feasibility evaluation was conducted through full-text reading, resulting in 20 articles. After going through the final selection stage based on inclusion and exclusion criteria, 14 articles were obtained that met the criteria and were used as samples in this study.

Data obtained from selected articles were analyzed using a descriptive qualitative synthesis method by reviewing and comparing various key parameters, such as binding affinity values, types of molecular interactions including hydrogen bonds, hydrophobic interactions, and electrostatic interactions, and the stability of ligand-receptor complexes. The analysis results were then systematically arranged in the form of comparative tables and supported by flowcharts to provide a clear overview of the literature selection process. This approach is expected to identify molecular interaction patterns that support the lock and key theory concept and contribute to the development of molecular docking-based drug candidates.



Picture 1. Flow Research

RESULTS AND DISCUSSION

Table 1 Summary of Literature Search Results

Researchers	Title	Results
Amin et al. (2025)	Molecular Docking Exploration of Antiviral Compounds against SARS-CoV-2	Umifenovir shows high affinity to PLpro and Nsp10 through hydrogen bonding and hydrophobic interactions, indicating a strong bond according to the lock and key concept.
Azahra & Amin (2025)	Systematic Analysis of Molecular Docking of Natural Compounds as Antidiabetics	Flavonoid compounds have a strong affinity (-6.5 to -11.2 kcal/mol) for glucose metabolism enzymes through hydrogen bonds and other interactions, thereby inhibiting enzyme activity.
Ahmad & Amin (2025)	Molecular Docking Literature as Anti-SARS-CoV-2 Agent	Natural and synthetic compounds exhibit high affinity (up to -10.523 kcal/mol) and are able to inhibit Mpro and RdRp function through ligand–receptor structural compatibility.
Karuna Sugito et al. (2023)	Virtual Screening of Indonesian Herbal Compounds as Spike Inhibitors	Compounds such as octopamine and L-noradrenaline show quite good affinity and are able to inhibit the spike protein through structural compatibility.
Prayogi et al. (2023)	Docking of Bicycloproline Compounds on Envelope Proteins	MI-30 has the highest affinity (-10.33 kcal/mol) and shows strong interaction with protein E via a lock and key mechanism.
Prasetio et al. (2021)	Docking of Isoeleutherin and Isoeleutherol	Both compounds have affinity (-6.9 kcal/mol) but are weaker than remdesivir, although they still show interaction at the active site.
Biswas et al. (2022)	Peptide Docking to SARS-CoV-2 Spike RBD	Peptides exhibit high affinity and interaction stability through hydrogen bonds, thus inhibiting the binding of viruses to cells.

Akinyede et al. (2022)	Anti-diabetic Helichrysum petiolare with Docking	Flavonoid compounds show strong affinity (-7.2 to -9.6 kcal/mol) towards α-amylase and α-glucosidase, better than acarbose.
Feunaing (2024)	Terminalia macroptera Compound Docking	The compound exhibits negative binding energy and forms a stable complex with the target enzyme according to the lock and key theory.
kun (2023)	Docking of Ficus lutea Compounds as Antidiabetic	Compounds such as epicatechin show high affinity and potential as drug candidates with good ADMET profiles.
Zabidi (2021)	Curculigo latifolia as an Antidiabetic	Compounds such as phlorizin show high affinity for α-glucosidase and DPP-IV and form stable complexes.
Siddique (2022)	Abelmoschus esculentus as Antidiabetic	Antidiabetic activity through inhibition of α-glucosidase and α-amylase and support from docking results showing strong interactions.
Sadiq (2020)	Eryngium caeruleum as Antidiabetic	Demonstrates antidiabetic activity through enzyme inhibition and is supported by docking results and in vivo tests.
Sharon & Kris (2021)	Docking of Plant Compounds against SARS-CoV-2 Protease	Phytochemical compounds show good affinity to Mpro and are able to inhibit viral replication through structural compatibility.

Based on the results of the summarized literature review, it can be seen that molecular docking is a method that is often used to analyze the interaction between ligands (drugs or bioactive compounds) and receptors (target proteins) in various fields, especially antidiabetic and antiviral. In general, all studies show that the strength of the interaction is determined by the binding affinity value, where the lower (more negative) the binding energy value, the stronger and more stable the ligand-receptor complex formed. This is in accordance with the basic principles of medicinal chemistry and supports the concept of the lock and key theory, where the structural match between the ligand and receptor is the main factor in determining the success of the interaction.

In antiviral research, particularly on SARS-CoV-2, most studies have shown that both natural and synthetic compounds have the potential to act as viral protein inhibitors. Amin et al. (2025) reported that umifenovir has a high affinity for the PLpro and Nsp10 proteins through hydrogen bond formation and hydrophobic interactions. Similar results were also shown by Prayogi et al. (2023) and Biswas et al. (2022), where synthetic compounds and peptides were able to bind strongly to viral proteins such as the envelope and spike RBD. Furthermore, studies by Ahmad & Amin (2025) and Sharon & Kris (2021) showed that various bioactive compounds can inhibit important enzymes such as Mpro and RdRp by filling the protein's active site. This mechanism demonstrates the suitability of the ligand structure to the receptor, thus disrupting the viral replication process.

Meanwhile, in the field of antidiabetics, research shows that many bioactive compounds, especially those from natural sources, have the potential to inhibit enzymes involved in glucose metabolism. Studies by Akinyede et al. (2022) and Azahra & Amin (2025) showed that flavonoid compounds have a high affinity for the enzymes α-amylase and α-glucosidase. Other studies, such as those by Olaokun (2023), Zabidi (2021), and Siddique (2022), also confirmed that compounds such as epicatechin and phlorizin are able to bind strongly to target receptors and inhibit enzyme activity. Furthermore, Sadiq (2020) demonstrated that a combined approach with in vivo testing provides more comprehensive evidence regarding the effectiveness of the compounds. This inhibitory mechanism occurs because the ligand is able to occupy the active site of the enzyme, thereby preventing substrate binding.

When viewed from the interaction mechanism, almost all studies show that the bond between the ligand and receptor occurs through a combination of non-covalent interactions such as hydrogen bonds, hydrophobic interactions, π-stacking, and salt bridges. These interactions play a role in stabilizing the ligand-receptor complex, thereby increasing the binding affinity. For example, in the

study by Amin et al. (2025), the interaction occurs through hydrogen bonds with specific amino acid residues, while in the study by Azahra & Amin (2025), the interaction involves several types of forces simultaneously. This indicates that the more types of interactions formed, the more stable the resulting complex.

However, not all compounds exhibited superior affinity compared to positive controls. Research by Prasetio et al. (2021) showed that isoeleutherine and isoeleutherol had lower affinity than remdesivir, although they were still able to bind to the receptor. This indicates that even though a ligand can enter the receptor's active site (according to the lock and key concept), the strength of the bond remains a determining factor in its biological effectiveness. Therefore, the binding affinity value needs to be considered along with other parameters such as interaction stability and pharmacokinetic profile.

Overall, the results of this study demonstrate that molecular docking is highly effective in explaining drug-receptor interactions from a lock and key theory perspective. This method is not only capable of predicting the strength and stability of interactions but also provides insight into the mechanism of action of compounds at the molecular level. Thus, molecular docking is an important tool in supporting modern drug development, particularly in the identification and optimization of candidate compounds with high therapeutic potential.

CONCLUSION

Based on the literature review, it can be concluded that molecular docking is an effective method for analyzing drug-receptor interactions at the molecular level. This method can predict the strength and stability of the bond between a ligand and a receptor through binding affinity values, where a lower bond energy indicates a stronger and more stable interaction.

The results of various studies indicate that both natural and synthetic compounds have potential as drug candidates, particularly in the fields of antidiabetic and antiviral. These compounds work by binding to the active site of receptors such as glucose-metabolizing enzymes or viral proteins, thereby inhibiting their biological activity. The interaction mechanisms that occur generally involve hydrogen bonds, hydrophobic interactions, and other non-covalent forces that support the formation of a stable ligand-receptor complex. Overall, these findings strengthen the concept of the lock and key theory, where the success of an interaction is greatly influenced by the structural compatibility between the ligand and the receptor. Thus, molecular docking not only plays a role in predicting interactions but also becomes an important tool in supporting the development of more effective, specific, and efficient drugs.

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