Available online on http://www.ijhacr.com

International Journal of Health Advancement and Clinical Research (tz) 2023; 1 (4); 98-105

Original Review Article

How to design a structure-based *In-silico* approach for the therapeutic drug development for diabetes mellitus or obesity: A Systemic Review

Rajesh Asija[1], Amandeep Swami[2], Yovin Chug[3]

[1] Principal & Professor, Maharshi Arvind Institute of Pharmacy, Jaipur, Rajasthan India

[2] Associate Professor, Maharshi Arvind Institute of Pharmacy, Jaipur, Rajasthan India

[3] PG Scholar, Maharshi Arvind Institute of Pharmacy, Jaipur, Rajasthan India.

Received: 15-10-2023 / Revised: 11-11-2023 / Accepted: 10-12-2023
Corresponding author: Rajesh Asija
Conflict of interest: Nil

Abstract:

Obesity is a major contributing factor to other chronic non-communicable diseases and is strongly associated with Diabetes Mellitus. Computer modelling tools facilitate the comprehension of the interaction mechanisms between specific targets and substances of interest, hence enhancing the optimization of medication development. This article outlines two systematic review processes that aim to find therapeutic targets and models for the treatment of obesity or diabetes mellitus through in silico investigations. The protocol adheres to the requirements outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) and has been published in the International Prospective Register of Systematic Reviews database.

Keywords: Diabetes Mellitus, Computer modelling, Silico investigations, Meta-Analyses Protocols.

Introduction

Search techniques will be formulated by combining descriptors and implemented in the following databases: PubMed, ScienceDirect, Scopus, Web of Science, Virtual Health Library, and EMBASE. Only original in silico works utilizing molecular dynamics, molecular docking, or both will be included. Two proficient researchers will autonomously choose the articles, extract the data, and evaluate the danger of bias. The assessment of quality will be conducted using a modified version of the Strengthening the Reporting of Empirical Simulation Studies (STRESS) framework, and the risk of bias will be evaluated using a checklist collected from independent literature sources. [1]

The execution of this protocol will lead to the development of two comprehensive evaluations that will establish the therapeutic objectives for addressing obesity or diabetes mellitus as utilised in computer simulation studies and their corresponding models.[2] The organization of information regarding these treatment objectives and their computer-generated structures is essential, primarily because computer simulation aids in more precise planning of future experiments conducted either in laboratory settings or in living organisms. Thus, the reviews derived from

this approach will inform decision-making on the selection of targets/models in future research aimed at developing therapies for obesity or Diabetes Mellitus. This will help reduce factors such as costs, time, and the need for *in vitro* and/or *in vivo* experiments.[3]

Table 1. Research question structure (What therapeutic targets have been used in in silico analysis for the treatment of obesity?) according to the PECo strategy for the systematic review

Description	Abbreviation	Elements
Problem	P	Therapeutic targets used in the treatment of obesity
Exposure	E	Obesity
Context	Co	In silico studies with molecular dynamics or molecular docking

PECo (P, problem; E, exposure; Co, context).

Review question [4,5]

The current protocol was implemented to address the following inquiries that will align with two separate systematic reviews:
Which therapeutic targets have been utilised in computational analysis for the treatment of obesity?
Which therapeutic targets have been utilised in computational analysis for the treatment of diabetes mellitus?
The questions were designed based on the PECo method, which stands for Problem, Exposure, and Context. You can find more details in Tables 1 and 2.

Requirements for eligibility [6,7,8]

Issue. The inclusion criteria will encompass studies focusing on therapeutic targets for combating obesity or diabetes.
Exclusion criteria will encompass studies focusing on therapeutic targets utilized in the treatment of other comorbidities.
Exposure. Inclusion criteria encompass studies pertaining to obesity or diabetes mellitus. Studies examining additional comorbidities will be excluded.
The given information. Only the initial in silico investigations utilizing molecular dynamics, molecular docking, or both will be included. Only studies including in vivo, in vitro, and other types of in silico research that specifically pertain to molecular dynamics or molecular docking will be considered. Furthermore, studies that are in the form of preprints, review articles, theses, dissertations, letters, conference abstracts, and grey literature will not be included.

Information sources and bibliographic research [9,10,11,12]

Two systematic reviews will be conducted according to the registered methodology on PROSPERO. One study will focus on therapeutic targets utilised in in silico research for the treatment of obesity, while the other will focus on the treatment of Diabetes Mellitus.
A thorough search will be conducted by combining MESH and EMTREE phrases using Boolean operators (AND and OR) on databases, with no limitations on time or language. The searches will be performed in the electronic bibliographic databases: PubMed, ScienceDirect, Scopus, Web of Science, Virtual Health Library, and EMBASE. [13]
In addition, a manual search will be conducted to include articles that may have been missed in the aforementioned databases. The search equation for the systematic review will be determined based on the components of the PECo method, as outlined in Tables 3 and 4. Modifications might be required for the search method, taking into account the attributes of the electronic databases, and terms may be added or modified. [14,15]

Table 2. Research question structure (What therapeutic targets have been used in in silico analysis for the treatment of diabetes mellitus?) according to the PECo strategy for the systematic review.

Description	Abbreviation	Elements
Problem	P	Therapeutic targets used in the treatment of Diabetes Mellitus
Exposure	E	Diabetes Mellitus
Context	Co	In silico studies with molecular dynamics or molecular docking

PECo (P, problem; E, exposure; Co, context).

Table 3. Search strategy for the Pubmed database to recover articles to answer the systematic review's question: What therapeutic targets have been used in in silico analysis for the treatment of obesity?

	Terms
Problem	"Therapeutic target" OR target OR treatment
Exposure	obesity
Context	("in silico" OR "computer simulation") AND ("molecular dynamics simulation" OR "molecular dynamics" OR "molecular docking simulation" OR "molecular docking")

Study selection

Two reviewers will independently evaluate the works. At first, the titles and abstracts of the books will be examined. Afterward, the chosen pieces will be read in their entirety. Conflicts will be settled by a third reviewer.[17]

Following the screening process, all articles will be imported into the Rayyan app (version 0.1.0) [20]. Transferring publications to this platform would simplify the process of eliminating duplicate studies, as per the defined criteria for inclusion. The rationales for being excluded from trials shall be documented. The report detailing the selection or exclusion of studies will be presented using the PRISMA-P flowchart (Fig 1). [18]

Data extraction

Two reviewers will independently conduct data extraction. The selected articles will be analyzed to extract the following characteristics: authors, country, in silico model, docking and molecular dynamics techniques used, docking score, the potential energy of interaction, amino acids with significant interaction, therapeutic targets, the therapeutic agent used, effects in vitro/in vivo, potential applications, and other relevant data. Incomplete works will be sought from the authors by email (up to two attempts). The articles and their corresponding data will be organized and displayed in a predetermined table using the Microsoft Excel Programme.[19]

Data analysis and synthesis

The data will be condensed using a narrative method, and the attributes of the research that are included will be detailed in tables. The reviews will be organized based on the therapeutic targets for treating obesity or diabetes that have been studied using in silico simulations. Both evaluations will include comprehensive summaries of the findings and methodologies employed in the investigations. The data will be given in concise tables and written descriptions to accurately depict the characteristics of the research that have been included. The data provided will be categorised based on the therapeutic targets for treating obesity or diabetes, together with three-dimensional models of the molecules or chemicals used

in computer simulations to study their interactions. The references will be arranged using the Mendeley programme [21]. As a result of the technique used in the studies being examined, a meta-analysis will not be conducted.

Table 4. Search strategy for the Pubmed database to recover to answer the systematic review's question: What therapeutic targets have been used in in silico analysis for the treatment of diabetes mellitus?

Terms	
Problem	"Therapeutic target" OR target OR treatment
Exposure	"Diabetes mellitus"
Context	("in silico" OR "computer simulation") AND ("molecular dynamics simulation" OR "molecular dynamics" OR "molecular docking simulation" OR "molecular docking")

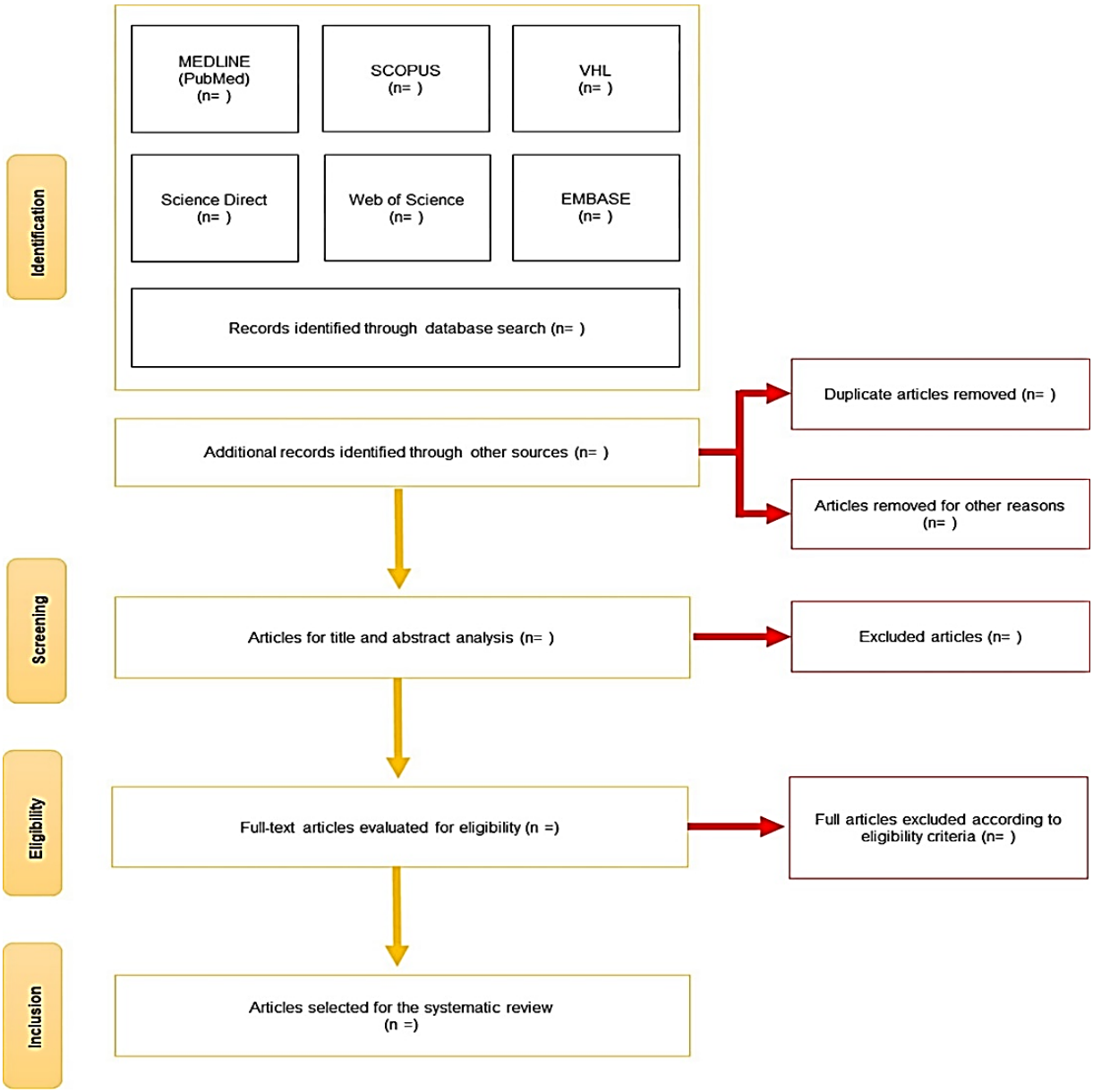

Fig 1. Article selection flowchart adapted from Preferred Reporting Items for Systematic Reviews (PRISMA-P).

Risk of bias

Two reviewers will autonomously evaluate the calibre of the studies and the potential for bias. An additional assessor will resolve any inconsistencies. To assess the quality of the modelling, we will use a checklist established from standardised criteria for simulation called "Strengthening the reporting of empirical simulation studies (STRESS)" [22], as there is currently no standardised instrument available for this sort of study. The assessment of bias will be conducted utilising a pre-existing checklist. and implemented by Taldaev et al. [18]. Evaluators will undergo training to guarantee consistent application of both instruments.

Discussion

The purpose is to provide detailed analysis of two systematic literature reviews that rely on papers employing bioinformatics techniques in their methodology. Both reviews will primarily aim to identify therapeutic targets that have been examined using computational methods. Additionally, the corresponding three-dimensional models employed in these studies will be organised systematically.

The initial review will ascertain the therapeutic targets pertaining to obesity, while the subsequent review will endeavour to unveil the targets associated with diabetes.

The understanding of targets and their structures, along with the advancements in bioinformatics tools, surpasses theoretical boundaries and has a significant impact on public health. The potential for successfully creating viable treatments for challenging comorbidities, such as diabetes and obesity, is enhanced [23, 24].

The process of discovering and developing new pharmaceuticals typically spans a duration of around 10 to 12 years and involves a substantial financial commitment [25]. Within these procedures, it is imperative to first establish and confirm treatment objectives, explore and enhance potential therapeutic alternatives, and conduct pre-clinical and clinical studies prior to the introduction of a new medication into the market [26].

Computer simulation offers a significant benefit in terms of reducing the time required for designing a new medicine and facilitating the precise planning of future in vitro and/or in vivo research, serving as an initial reference. It is feasible to expedite development and concurrently collaborate in reducing the utilisation of animal models and research expenses [27].

The need to organise information regarding therapeutic targets has found support from several sources, such as open access targeting platforms like the Open Targets Platform (OTP). The OTP's objective is to provide scientific evidence on targets and aid in scientific decision-making [24]. However, in order to carry out a bioinformatics study that evaluates the interaction between a novel drug and a particular target, it is necessary to first determine the theoretical and experimental structures of both the substance and the target.

The number of in silico structures that have been elucidated has been increasing in recent years. These structures are being studied to identify and comprehend how these new chemicals interact with certain targets [28, 29]. Therefore, it is essential to carry out comprehensive review investigations that not only provide information on the presence of the target but also facilitate the implementation of computer simulation studies of superior quality.

The pharmaceutical industry currently utilises bioinformatics approaches, such as virtual screening tools, to search through extensive compound libraries. These techniques aid in the research and development of new medications for many comorbidities, including obesity and diabetes [30, 31]. Structure-based drug design (SBDD) and ligand-based drug design (LBDD) are two broad categories of computer-aided drug design (CADD) methods. These approaches involve

analysing the structural and physicochemical properties of ligands and/or targets to gain insights into their potential effectiveness, prior to conducting in vitro testing [30]. The most often used methods in structure-based drug design (SBDD) include structure-based virtual screening (SBVS), molecular docking, and molecular dynamics (MD) simulations [11–13].

Synthetic peptides exemplify the utilisation of bioinformatics approaches, wherein the refinement of these techniques can be employed to optimise the interaction between the substances and the selected targets. Tirzepatide (LY3298176), a recently licenced synthetic peptide, has shown great promise in treating DM. Its clinical trials have demonstrated its effectiveness in combating obesity and diabetes [32].

Several drawbacks can be identified in the studies used to produce the reviews, including the inclusion of low-quality original works and the presence of three-

There are several three-dimensional molecular structures that are accessible, which require the usage of different tools. However, there is a lack of detailed data for the *in silico* study. Although there are limitations, the systematic protocol aims to provide the most commonly utilised molecular targets in computational research, together with their corresponding molecular structures. This will enhance the quality of future studies.

Therefore, the procedure will provide instructions for the creation of the initial comprehensive evaluations that collect the treatment objectives for obesity or diabetes utilised in computer simulation research. The results of systematic reviews should thereafter inform the development of future research conducted using computer simulations, aid in the selection of potential molecular targets, and assist in choosing the most suitable three-dimensional structures to be utilised. Hence, facilitating the exploration and advancement of research involving molecules, chemicals, or substances that have a high likelihood of becoming effective in future therapeutics for obesity or diabetes.

References

1. Wells JCK. The diabesity epidemic in the light of evolution: insights from the capacity–load model. Dia- betologia. 2019; 62: 1740–1750.
2. Ng ACT, Delgado V, Borlaug BA, Bax JJ. Diabesity: the combined burden of obesity and diabetes on heart disease and the role of imaging. Nature Reviews Cardiology. 2021; 18: 291–304.
3. Okunogbe A, Nugent R, Spencer G, Ralston J, Wilding J. Economic impacts of overweight and obesity: current and future estimates for eight countries. BMJ Global Health. 2021; 6: 1–15.
4. Sociedade Brasileira de Diabetes (SBD). Diretriz da Sociedade Brasileira de Diabetes. SBD. 2019; 1:1–491.
5. Associac¸ão Brasileira para o estudo da obesidade e da s´ındrome metabo´lica (ABESO). Posiciona- mento sobre o tratamento nutricional do sobrepeso e da obesidade. 2022; 1: 1–260.
6. International Diabetes Federation (IDF). IDF Diabetes Atlas. IDF. 2021; 10: 1–141.
7. World Health Organization [Internet]. Obesity and overweight; 2021.
8. Mu M, Xu L-F, Hu D, Wu J, Bai M-J. Dietary Patterns and Overweight/Obesity: A Review Article. Iran Journal Public Health. 2017; 46 (7): 869–876.
9. Dragano NRV, Fernø J, Die´guez C, Lo´pez M, Milbank E. Reprint of: Recent Updates on Obesity Treat- ments: Available Drugs and Future Directions. Neuroscience. 2020; 447: 191–215.
10. Lage O, Ramos M, Calisto R, Almeida E, Vasconcelos V, Vicente F. Current Screening Methodologies in Drug Discovery for Selected Human Diseases. Mar Drugs. 2018; 16 (8): 279.

11. Hollingsworth SA, Dror RO. Molecular Dynamics Simulation for All. Neuron. 2018; 99 (6): 1129–1143.
12. Dong D, Xu Z, Zhong W, Peng S. Parallelization of Molecular Docking: A Review. Current Topics in Medicinal Chemistry. 2018; 18 (12): 1015–1028.
13. Brogi S, Ramalho TC, Kuca K, Medina-Franco JL, Valko M. Editorial: In silico Methods for Drug Design and Discovery. Frontiers in Chemistry. 2020; 8 (612): 1–5.
14. Singh J. The national centre for the replacement, refinement, and reduction of animals in research. J Pharmacol Pharmacother. 2012; 3 (1): 87–9.
15. Pollock A, Berge E. How to do a systematic review. International Journal of Stroke. 2018; 13 (2): 138– 156.
16. Timo GO, Reis RSSV dos, Melo AF de, Costa TVL, Magalhães PO, Homem-de-Mello M. Predictive Power of In Silico Approach to Evaluate Chemicals against M. tuberculosis: A Systematic Review. Phar- maceuticals. 2019; 12 (3): 1–23.
17. Fadlalla M, Ahmed M, Ali M, Elshiekh AA, Yousef BA. Molecular Docking as a Potential Approach in Repurposing Drugs Against COVID-19: a Systematic Review and Novel Pharmacophore Models. Cur- rent Pharmacology Reports. 2022; 8 (3): 212–226.
18. Taldaev A, Terekhov R, Nikitin I, Zhevlakova A, Selivanova I. Insights into the Pharmacological Effects of Flavonoids: The Systematic Review of Computer Modeling. International Journal of Molecular Sci- ences. 2022; 23 (11): 1–18.
19. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015; 349: 1–25.
20. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Systematic Reviews. 2016; 5: 1–10.
21. Zaugg H, Tateishi I, Randall DL, West RE. Mendeley: Creating Communities of Scholarly Inquiry Through Research Collaboration. Tech Trends. 2011; 55 (1): 32–36.
22. Monks T, Currie CSM, Onggo BS, Robinson S, Kunc M, Taylor SJE. Strengthening the reporting of empirical simulation studies: Introducing the STRESS guidelines. Journal of Simulation. 2019; 13: 55–67.
23. Sheldon TA, Wright J. Twin epidemics of covid-19 and non-communicable disease. BMJ. 2020; 369– 370.
24. Ochoa D, Hercules A, Carmona M, Suveges D, Gonzalez-Uriarte A, Malangone C, et al. Open Targets Platform: supporting systematic drug–target identification and prioritisation. Nucleic Acids Research. 2021; 49 (1): 1302–1310.
25. Spedding M. New directions for drug discovery. Dialogues in Clinical Neuroscience. 2006; 8 (3): 295– 301.
26. Shaker B, Ahmad S, Lee J, Jung C, Na D. In silico methods and tools for drug discovery. Computers in Biology and Medicine. 2021; 137: 104851.
27. Maia EHB, Assis LC, de Oliveira TA, Silva AM, Taranto AG. Structure-Based Virtual Screening: From Classical to Artificial Intelligence. Frontiers in Chemistry. 2020; 8: 343.
28. Goodsell DS, Zardecki C, di Costanzo L, Duarte JM, Hudson BP, Persikova I, et al. RCSB Protein Data Bank: Enabling biomedical research and drug discovery. Protein Science. 2020; 29 (1): 52–65.
29. Rifaioglu AS, Atas H, Martin MJ, Cetin-Atalay R, Atalay V, Doğan T. Recent applications of deep learn- ing and machine intelligence on in silico drug discovery: methods, tools and databases. Briefings in Bio-informatics. 2019; 20 (5): 1878–1912.

30. Va´zquez J, Lo´pez M, Gibert E, Herrero E, Luque FJ. Merging Ligand-Based and Structure-Based Meth- ods in Drug Discovery: An Overview of Combined Virtual Screening Approaches. Molecules. 2020; 25 (20): 4723.