Molecular Docking In Nutraceutical Research; Unveiling Molecular Targets for Disease Management

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Abstract: In recent years, there has been a significant rise in interest regarding nutraceuticals, which are bioactive substances derived from food that can have beneficial effects on health. These compounds serve both medicinal and preventive purposes. As the demand for innovative and effective neutraceuticals grows, molecular docking has become a valuable computational technique for examining the intricate interactions between these bioactive compounds and their target proteins. This article provides a comprehensive overview of the current applications of molecular docking in neutraceutical research and emphasizes its essential role in understanding the complex relationships between neutraceuticals and their biological targets. By offering insights into the field through the perspective of molecular docking, this review aims to enhance knowledge and support the creation of new neutraceutical interventions to promote human health.

Keyword: Molecular Docking, Nutraceuticals, Bioactive Compounds, Molecular Modelling, Computational Biology.

1.0 INTRODUCTION

Molecular Docking has become an essential aspect of in-silico drug development in recent years. This technique involves predicting the interaction between a small molecule and a protein at the atomic level.[1] This enables researchers to study the behavior of small molecules, such as nutraceuticals, within the binding site of a target protein and understand the fundamental biochemical process underlying this interaction.[2] The technique is structure-based and requires a high-resolution 3D representation of the target protein obtained through techniques like X-ray crystallography, Nuclear Magnetic Resonance Spectroscopy, or Cryo-Electron Microscopy.[3]

There are several computational tools and algorithms available for molecular docking techniques, both commercial and free-of-charge. These programs and tools have been developed and are currently being used in drug research and academic fields[4].AutoDock Vina, Discovery Studio, Surflex, AutoDock GOLD, Glide, MCDock, MOE-Dock, FlexX, DOCK, LeDock, rDock, ICM, Cdcker, LigandFit, FRED, and UCSF Dock. Among these programs, AutoDockVina, Glide, and AutoDock GOLD have been identified as top-ranking choices with the best scores.[5] The utility of Molecular Docking in drug discovery and design has been well-established[6].

2.0 MOLECULAR DOCKING

Molecular docking aims to predict the ligand-receptor complex through computer-based methods.[11] The process of docking involves two main steps which include sampling the ligand and utilizing a scoring function.[12] Sampling algorithms help to identify the most energetically favorable conformations of the ligand within the protein's active site, taking into account their binding mode. These confirmations are then ranked using a scoring function.[13]

Molecular docking is the most common computational structure-based drug desing (SBDD) method and has been widely used ever since the early 1980. It is the tool of choice when the three-dimensional(3D) structure of the protein target is available. Molecular docking popularity has been facilitated by the dramatic growth in availability nd power of computers, and the increasing number of and ease of access to small molecular and protein structures.

3.0 TYPES OF DOCKING

A technique for creating, characterizing, and altering compound topologies and interactions as well as the properties of these molecules that depend on their threedimensional geometries is molecular modeling .[14]. During the last 20 years, the development of molecular simulation (MS) technology has exhibited significant progress, especially since the 2013 Nobel Prize in Chemistry was awarded. As of right now, free energy calculation, molecular docking, homology modeling, and molecular dynamics simulation are all included in MS technology. The most popular approach among these in molecular modeling research is molecular docking .[15]

(a) target and ligand as rigid bodies;
(b) ligand as a flexible body and target as a rigid substance; and
(c) both target and ligand as flexible body.

4.0 METHODS IN MOLECULAR DOCKING

Molecular docking turned out to be a powerful tool in drug discovery. The first molecular docking algorithm was introduced in the 1980s and later methods in molecular docking have evolved drastically. Now, it is possible to analyze important molecular events such as binding conformations of the ligand and its interactions with the receptor that alleviate the ligand-receptor complex. Modern molecular docking algorithms exhibit the potential to quantitatively envisage binding energetics to categorize the docked ligands based on the binding energies of their complexes with the receptors. This section will introduce different existing molecular docking methods.

4.1 1 .Conformational search methodsThe basic goal of conformational search methods is to recognize the energetically favorable binding conformations of the ligand-receptor complex.

4.2 2 .Systematic methodsSystemic methods tend to perform an exhaustive and ordered search for the conformational landscape of the ligand by systematically varying its degrees of freedom. This method identifies all the combinations of structural constraints.

4.3 3. Stochastic\random methodsGenetic algorithm (GA) is an exciting application of stochastic search algorithm where conformational optimization is carried out through the process of natural selection and genetics.

5.0 SEARCH ALGORITHMS

The principal target of the search algorithm is to locate every single imaginable direction and conformation of the protein combined with the ligand[13].

The search algorithms are classified as shown in Fig. 1.

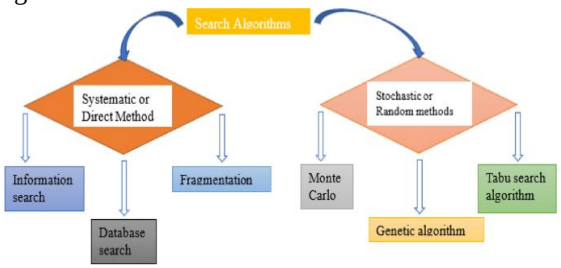

Figure 1: Classes of search algorithm mechanisms.

6.0 SCORING FUNCTION

By applying virtual screening, ligands are evaluated according to their binding affinity, which aids in the evaluation of which ligand structure and rotation is most advantageous concerning the receptor (protein).[19]

According to Fig. 2, four main groupings make up the scoring function.

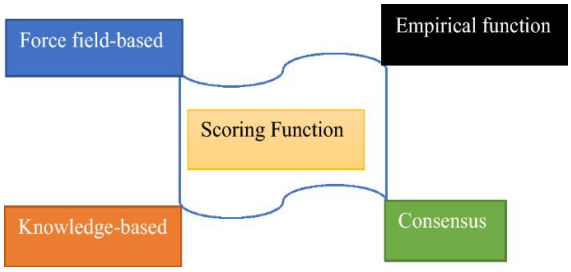

Figure 2 Classes of scoring function mechanisms

7.0 MOLECULAR DOCKING SOFTWARE

In many drug discovery initiatives, molecular docking has become crucial, especially for the virtual screening of phytochemicals or nutraceuticals as possible therapeutic compounds. Irwin Kuntz of the University of California created the first docking program in the middle of the 1980s, and efforts are constantly being made to enhance docking computations. Current developments in docking techniques identify an enzyme's natural substrates to forecast its capacity.[23]

8.0 HIGHLIGHTS OF MOLECULAR DOCKING SOFTWARE

Many programs are available for docking, and some of the most popular ones are discussed in this section.

8.1 Dock

Dock is a molecular docking software developed by the UCSF Chimera team. It is a user-friendly tool that can be used to dock small molecules into a receptor-binding site. Dock uses a grid-based method to evaluate the binding affinity of ligands to the receptor.

8.2 Autodock

Autodock is a widely used molecular docking software developed by the Scripps Research Institute. It is a free, open-source software that can perform both rigid and flexible docking. Autodock uses a Lamarckian genetic algorithm to optimize the placement of ligands within a receptor binding site

9.0 GENETIC OPTIMIZATION FOR LIGAND DOCKING (GOLDTM)

GOLD is a protein–ligand docking software that offers several key features. It allows for the inclusion of spine and side chain adaptability in computations and uses user-defined scoring functions that can adapt accordingly.

10.0 REPRESENTATION OF MOLECULAR DOCKING

Generally, the Docking process can be represented in a flowchart as shown in Fig. 3.

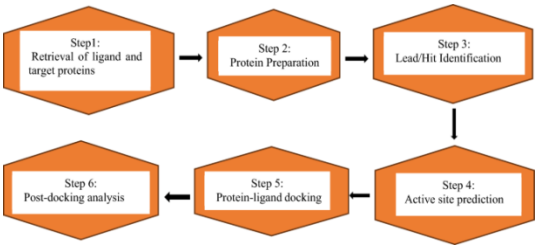

Figure 3:A prototype flow chart of a molecular docking study.

11.0 GENERAL APPLICATION OF MOLECULAR DOCKING

11.1 Hit identification/virtual screening:Molecular docking is widely used in hit identification in drug discovery. It helps in identifying potential drug candidates by predicting the binding affinity of small molecules to a protein or receptor of interest. Docking can be used to screen a large database of small molecules to identify those that can bind to a protein of interest with high affinity32.

11.2 Lead optimization:Once a hit compound is identified, molecular docking can be used to optimize the lead compound's structure to improve its binding affinity and selectivity. Docking can also be used to design new analogs by predicting the binding modes of modified structures.33

11.3 Bioremediation:Molecular docking is used in bioremediation to predict the binding affinity of small molecules to enzymes involved in the degradation of environmental pollutants. Docking can help in designing inhibitors or activators of these enzymes to enhance bioremediation efficiency[34].

12.0 NEUTRACEUTICAL

In 1989, a term called “nutraceutical” was coined by DeFelice and the Foundation for Innovation in Medicine, combining the words “nutrition” and “pharmaceutical”[37]. A press release in 1994 defined nutraceuticals as substances that provide medical or health benefits and can be considered food or a component of food, including disease prevention and treatment[38]. As further explained by Raj et al.nutraceuticals can include a wide range of substances, such as isolated nutrients, dietary supplements, diets, herbal products, genetically engineered designer foods, and processed foods like cereals, soups, and beverages.

13.0 CLASSIFICATIONS OF NUTRACEUTICALS

Several authors used different methods to classify nutraceuticals. However, this seminar considers the food availability framework according to Bairagi and Patel.

Therefore, nutraceuticals are classified as shown in Fig. 4.

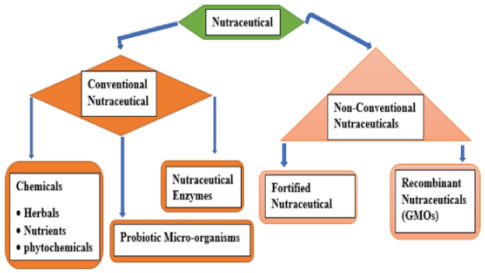

Figure 4 Classification of nutraceuticals.

14.0 INDUSTRIAL DYNAMICS OF NUTRACEUTICALS

The popularity of cannabis together with its byproducts in nutraceuticals is on the rise, as they are believed to offer a wide range of health benefits

Nutraceuticals containing cannabidiol, the active ingredient derived from cannabis or hemp, are becoming increasingly popular. As cannabis becomes legal in more countries, further research is being conducted to determine the potential benefits and risks of cannabis-based products. It is expected that the trend toward cannabis-based nutraceuticals will continue to grow as more consumers become aware of their potential health benefits.[43]

15.0 NUTRICOSMETICS

According to Bairagi and Patel, nutricosmetics are supplements aimed at enhancing the health and appearance of the hair, skin, and nails. As consumers increasingly prioritize natural and holistic approaches to augment their physical appearance, the demand for

nutricosmetics is expected to surge. Taeymans et al. suggest that this trend will continue to gain momentum as consumers become more health-conscious and seek multifaceted benefits from the products they purchase.44

15.1 Sports nutrition space As interest in fitness and sports-related activities increases, so too does the demand for products that can improve athletic performance and overall health. Accordingly, Bairagi and Patel .7 noted that this trend has led to rapid growth in the sports nutrition market, with no signs of slowing down.

15.2 Seed oil as nutraceutical deposit Seed oils, such as flaxseed oil as well as chia seed oil are becoming popular as a source of essential fatty acids and other nutrients.45 these oils are being incorporated into a wide range of nutraceutical products, including supplements and functional foods. The trend toward using seed oils as a nutraceutical deposit is expected to continue as consumers seek out more plant-based sources of nutrients46.

16.0 MOLECULAR DOCKING VALIDATIONS OF NUTRACEUTICALS TARGETS IN DISEASES

Molecular docking validation is a computational approach that is increasingly being used in the field of nutraceutical research to identify potential targets for the management of various diseases. Nutraceuticals are naturally occurring compounds that have potential health benefits and are found in food sources such as fruits, vegetables, and herbs.46 With the rise of chronic diseases such as diabetes, cardiovascular disease, and cancer, there is a growing interest in the use of nutraceuticals as a complementary approach to conventional medical treatments.7 Molecular docking validation can help researchers identify potential nutraceutical targets for disease management, providing a more efficient and cost-effective way to screen potential treatments before proceeding with costly clinical trials. This method makes drug discovery more ethical since it lessens the need for animal testing throughout the development of novel medicines.47

17.0 MOLECULAR DOCKING DISCOVERY OF NUTRACEUTICALS TARGETS

Molecular docking is a computational technique used to predict the interactions between small molecules, such as nutraceuticals, and larger biomolecules, such as enzymes, receptors, RNA, DNA, and other proteins. The technique involves the simulation of the molecular interactions between the small molecule and the target biomolecule, which can provide insights into the binding affinity, binding site, and possible mechanism of action.

CONCLUSION

Molecular docking proves valuable in pinpointing molecular targets for nutraceuticals in treating illnesses. It predicts binding affinity and conformation, aiding in the identification of potential treatment targets. The accessibility of databases and advancements in computational tools elevates molecular docking's significance in drug discovery. Its application enhances the efficiency and effectiveness of the drug discovery process, reducing time and costs associated with traditional experimental methods. Consequently, incorporating molecular docking in dietarysupplement research holds significant promise for discovering novel therapeutic targets and developing safe and effective supplements for disease treatment.

REFERENCE

[1] Sahoo, R. N., Pattanaik, S., Pattnaik, G., Mallick, S. &Mohapatra, R. Review on the use of molecular docking as the first line tool in drug discovery and development. Indian J. Pharm. Sci. 84(5), 1334–1337 (2022).

[2] Meng, X. Y., Zhang, H. X., Mezei, M. & Cui, M. Molecular docking: A powerful approach for structure-based drug discovery. Curr. Comput. Aided Drug Des. 7, 146–157 (2011).

[3] Smyth, M. S. & Martin, J. H. X-ray crystallography. Mol. Pathol. 53, 8–14 (2000).

[4] Jorgensen, W. L. The many roles of computation in drug discovery. Science 303(5665), 1813–1818 (2004).

[5] Potluri, H., Prasanth, D. S. &Atmakuri, L. R. In vivo antinociceptive effect of methanolicextract of Ipomoea marginata Desr. in rodents as well as in silico molecular docking of some phytoconstituents from the plant. Indian J. Pharm. Sci. 83(4), 732–741 (2021).

[6] Pinzi, L. &Rastelli, G. Molecular docking: Shifting paradigms in drug discovery. Int. J. Mol. Sci. 20, 4331 (2019).

[7] Bairagi, G. R. & Patel, V. P. Nutraceutical a review on basic need, classification, recent

trends in industry and delivery systems. J. Emerg. Technol. Innov. Res. (JETIR) 8(5), c183–c199 (2021).

[8] Heyland, D. K. In search of the magic nutraceutical: Problems with current approaches. J. Nutr. 131(9), 2591S-2595S (2001).

[9] Carpio, L. E., Sanz, Y., Gozalbes, R. &Barigye, S. J. Computational strategies for the discovery of biological functions of health foods, nutraceuticals, and cosmeceuticals: A review. Mol. Divers. 25, 1425–1438 (2021)

[10] .LengauerT,Rarey M. et al. Computation method for biomolecular docking. Current Opinion in Structural biology. 1986; (3):402-406. Jain, A. N. Virtual screening in lead discovery and optimization. Curr. Opin. Drug Discov. Devel. 7(4), 396–403 (2004).

[11] Jain, A. N. Virtual screening in lead discovery and optimization. Curr. Opin. Drug Discov. Devel. 7(4), 396–403 (2004).

[12] Das, D. R., Kumar, D., Kumar, P. & Dash, B. P. Molecular docking and its application in search of antisickling agent from Carica papaya. J. Appl. Biol. Biotechnol. 8(01), 105–116 (2020). Kitchen, D. B., Decornez, H., Furr, J. R. &Bajorath, J. Docking and scoring in virtual screening for drug discovery: Methods and applications. Natl. Rev. Drug Discov. 3(11), 935–949 (2004).

[13] Kitchen, D. B., Decornez, H., Furr, J. R. &Bajorath, J. Docking and scoring in virtual screening for drug discovery: Methods and applications. Natl. Rev. Drug Discov. 3(11), 935–949 (2004).

[14] Raval K, Ganatra T. Basics, types and applications of molecular docking: A review. IP International Journal of Comprehensive and Advanced Pharmacology. 2022;7(1):12-16. DOI: 10.18231/j.ijcaap.2022.003.

[15] Tao X, Huang Y, Wang C, Chen F, Yang L, Ling L, et al. Recent developments in molecular docking technology applied in food science: A review. International Journal of Food Science & Technology. 2020;55(1):33-45. DOI: 10.1111/ijfs.14325.

[16] Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules. 2015;20(7):13384-13421. DOI: 10.3390/molecules200713384.

[17] Williams, P. A. et al. Crystal structure of human cytochrome P450 2C9 with bound warfarin. Nature 424(6947), 464–468 (2003).

[18] Halperin, I., Ma, B., Wolfson, H. &Nussinov, R. Principles of docking: An overview of search algorithms and a guide to scoring functions. Proteins 47, 409–443 (2002).

[19] Brooijmans, N. & Kuntz, I. D. Molecular recognition and docking algorithms. Annu. Rev. Biophys. Biomol. Struct. 32, 335–373 (2003).

[20] Burnett, R. M. & Taylor, J. S. DARWIN: A program for docking flexible molecules. Proteins 41, 173–191 (2000).

[21] Li, Y., Zhang, X. & Cao, D. The role of shape complementarity in the protein-protein interactions. Sci. Replication 3, 3271 (2013).

[22] Hari, K. V. &Bhaskar, D. A novel volumetric criterion for optimal shape matching of surfaces for protein-protein docking. J. Comput. Des. Eng. 5(2), 180–190 (2018).

[23] Gohlke, H. &Klebe, G. Approaches to the description and prediction of the binding affinity of small-molecule ligands to macromolecular receptors. Angew. Chem. Int. Ed. 41, 2644–2676 (2002).

[24] Noureldeen, A. F. H. et al. Molecular design, spectrosco pic, DFT, pharmacological, and molecular docking studies of novel ruthenium(III)–Schiff base complex: An inhibitor of progression in HepG2 cells. Int. J. Environ. Res. Public Health 19, 13624 (2022).

[25] Xing, D. et al. Insights into protein-ligand interactions: Mechanisms, models, and methods. Int. J. Mol. Sci. 17(2), 144 (2016).

[26] Venhorst, J. et al. Homology modeling of rat and human cytochrome P450 2D (CYP2D) isoforms and computational rationalization of experimental ligand-binding specificities. J. Med. Chem. 46(1), 74–86 (2003).

[27] Aja, P. M. et al. Prospect into therapeutic potentials of Moringaoleifera phytocompounds against cancer upsurge: De novo synthesis of test compounds, molecular docking, and ADMET studies. Bull. Natl. Res. Cent. 45, 99 (2021).

[28] Chaudhary, K. K. & Mishra, N. A review on molecular docking: Novel tool for drug discovery. JSM Chem. 4(3), 1029 (2016).

[29] De Azevedo, J. &Filgueira, W. MolDock applied to structure-based virtual

screening. Curr. Drug Targets 11(3), 327–334 (2010).

[30] Pujadas, G. et al. Protein-ligand docking: A review of recent advances and future perspectives. Curr. Pharm. Anal. 4(1), 1–9 (2008).

[31] Torres, P. H. M., Sodero, A. C. R., Jofily, P. & Silva-Jr, F. P. Key topics in molecular docking for drug design. Int. J. Mol. Sci. 20(18), 4574 (2019).

[32] Gaba, M., Gaba, P., Singh, S. & Gupta, G. D. An overview of molecular docking. Int. J. Drug Dev. Res. 2(2), 219–231 (2010).

[33] Eweas, A. F., Maghrabi, I. A. &Namarneh, A. I. Advances in molecular modeling and docking as a tool for modern drug discovery. Deriv. Pharm. Chem. 6, 211–228 (2014).

[34] Suresh, P. S., Kumar, A., Kumar, R. & Singh, V. P. An in silico [correction of insilico] approach to bioremediation: Laccase as a case study. J. Mol. Graph Model 26(5), 845.9 (2008).

[35] Dhanik, A., McMurray, J. S. &Kavraki, L. E. DINC: A new AutoDock-based protocol for docking large ligands. BMC Struct. Biol. 13(1), S11 (2013).

[36] Ferreira, L., dos Santos, R., Oliva, G. &Andricopulo, A. Molecular docking and structure-based drug design strategies. Molecules 20(7), 13384–133421 (2015).

[37] Kalra, E. K. Nutraceutical–definition and introduction. AAPS Pharm. Sci. 5(3), E25 (2003).

[38] Andlauer, W. &Fürst, P. Nutraceuticals: A piece of history, present status, and outlook. Food Res. Int. 35(2–3), 171–176 (2002).

[39] Aronson, J. K. Defining 'nutraceuticals': Neither nutritious nor pharmaceutical. Br. J. Clin. Pharmacol. 83(1), 8–19 (2017).

[40] Verma, G. & Mishra, M. A review on nutraceutical: Classification and its role in various diseases. Int. J. Pharm. Ther. 7(4), 152–160 (2016).

[41] Rajasekaran, A. &Kalaivani, M. Designer foods and their benefits: A review. J. Food Sci. Technol. 50, 1–16 (2013).

[42] Facioni, M. S., Raspini, B., Pivari, F., Dogliotti, E. &Cena, H. Nutritional management of lactose intolerance: The importance of diet and food labeling. J. Transl. Med. 18(1), 260 (2020).

[43] Das, R. Nutraceutical from hemp (Cannabis sativa L.) and functional evaluation (2016).

[44] Taeymans, J., Clary, P. &Barel, A. Use of food supplements as nutricosmetics in health and fitness: A review. Handb. Cosmet. Sci. Technol. 14, 587–596 (2014).

[45] Gunstone, F. D. Oilseeds, vegetable oils, and seed meal: An overview by commodity. Lipid Technol. 20, 96 (2008).

[46] Vergallo, C. Nutraceutical vegetable oil nanoformulations for prevention and management of diseases. Nanomaterials (Basel) 10(6), 1232 (2020)

[47] Chandra, A., Gurjar, V., Qamar, I. & Singh, N. Identification of potential inhibitors of SARS-COV-2 endoribonuclease (EndoU) from FDA approved drugs: A drug repurposing approach to finding therapeutics for COVID-19. J. Biomol. Struct. Dyn. 39(12), 4201–4211 (2021).