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A perspective on molecular docking approaches in the discovery and development of natural-based functional foods

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ABSTRACT

Backgrounds and Aims: Molecular docking represents a cutting-edge approach in the exploration and development of functional foods, also known as nutraceuticals. These innovative foods are enriched with bioactive components that, when consumed at safe and effective concentrations, have the potential to enhance health and prevent diseases. These bioactive constituents encompass a range of elements, including nutrients, dietary fibers, phytochemicals, probiotics, and other compounds. A food product earns the label "functional" when its consumption goes beyond mere nutrition, exerting positive effects on specific physiological processes, contributing to overall health, and mitigating chronic disease risk. In light of this, this article seeks to present a comprehensive exploration of the potential of molecular docking as a valuable approach in the discovery and development of functional foods.

Results and Conclusions: Molecular docking represents a powerful computational approach within the realm of functional food research. This methodology enables the virtual screening of bioactive compounds found in food items. By employing molecular docking, researchers can simulate and assess the interactions between these bioactive compounds and specific molecular targets, negating the need for extensive laboratory experimentation. This innovative approach facilitates the identification of bioactive compounds within foods, shedding light on their mechanisms of action and their potential health benefits. Notably, this technology remains at the forefront of research, garnering significant attention and continual progress. Moreover, the intersection of technology and functional foods holds immense promise. The integration of technological advancements with functional foods has the potential to enhance consumer experiences and health outcomes. This synergy can be realized through digital platforms that offer personalized recommendations, enable health parameter tracking, and empower individuals to make informed dietary choices while monitoring their progress. In conclusion, the application of molecular docking simulations offers a forward-thinking strategy to accelerate the discovery and development of functional foods, providing valuable insights into their bioactive constituents' potential interactions and health-promoting effects. The evolving landscape of technology integration further enhances the potential of functional foods to positively impact public health and well-being

KEYWORDS

Functional Food, Molecular Docking, *In Silico* Study, Natural Product, Nutraceutical Developments, Biological Activity of Functional Food.

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INTRODUCTION

Molecular docking, a powerful computational technique, is poised to revolutionize the landscape of functional food research and development. Functional foods, often referred to as nutraceuticals, are a category of innovative foods enriched with substances or live microorganisms that have the potential to enhance health and prevent diseases, provided their concentrations remain within safe and effective limits. These bioactive components span a spectrum, encompassing nutrients, dietary fiber, phytochemicals, probiotics, and various other compounds. Nevertheless, it is crucial to acknowledge that functional meals are not designed to serve as substitutes for medical interventions or address nutritional inadequacies. In contrast, these substances acquire their classification as "functional" by exhibiting beneficial impacts on distinct physiological mechanisms, surpassing their basic nutritional attributes to enhance general health and mitigate the development of chronic ailments. Examples of functional foods abound, ranging from tomatoes enriched with lycopene, margarine infused with omega-3 fatty acids, to calcium-fortified orange juice, all designed to impart health benefits to consumers[1]. These products have not only permeated global markets but have also become integral components of modern diets, offering the potential to enhance both physical and mental health, thereby improving overall quality of life. In an era marked by environmental pollution, heightened stress levels, socioeconomic challenges, and evolving health concerns, functional foods serve as a critical resource for addressing contemporary consumer health risks. The primary drivers behind the widespread adoption of functional foods are their recognized health benefits and the motivation to incorporate them into daily dietary practices[2].

Recent scientific advancements, particularly in next-generation sequencing technology, have profoundly influenced both plant breeding and food science. These advancements hold immense promise for enhancing the nutritional quality and productivity-related attributes of crops and unlocking the potential of bioactive compounds with health advantages. Omics technologies, encompassing genomics, transcriptomics, proteomics, and metabolomics, offer a comprehensive systems biology approach to investigating and improving crop characteristics. This integrated omics technology approach has far-reaching implications for enhancing the nutritional potential of various crops and, consequently, the nutritional safety of the foods derived from them[2].

Furthermore, numerous factors can influence the nutritional content and potential health benefits of foods. These factors include genetics, growing conditions, storage conditions, post-harvest treatments, food formulation, and processing methods, all of which can impact the concentration of bioactive components in foods and dietary supplements, ultimately affecting human health and well-being. For example, post-harvest processing is essential for imparting specific qualities to cereal grains, enhancing their cooking properties, organoleptic characteristics, and edibility, while also extending their shelf life, stability, and flavor. A range of cooking methods, including thermal processes like microwave heating, roasting, frying, steaming, autoclaving, boiling, extruding, and baking, play pivotal roles in enhancing palatability and bio-functionality[3].

In light of these dynamic considerations, this paper endeavors to provide insights grounded in the latest evidence, focusing on the utilization of molecular docking. This computational approach holds immense potential in the discovery and development of functional foods, promising to reshape the way we understand, assess, and optimize the bioactive components within these innovative food products.

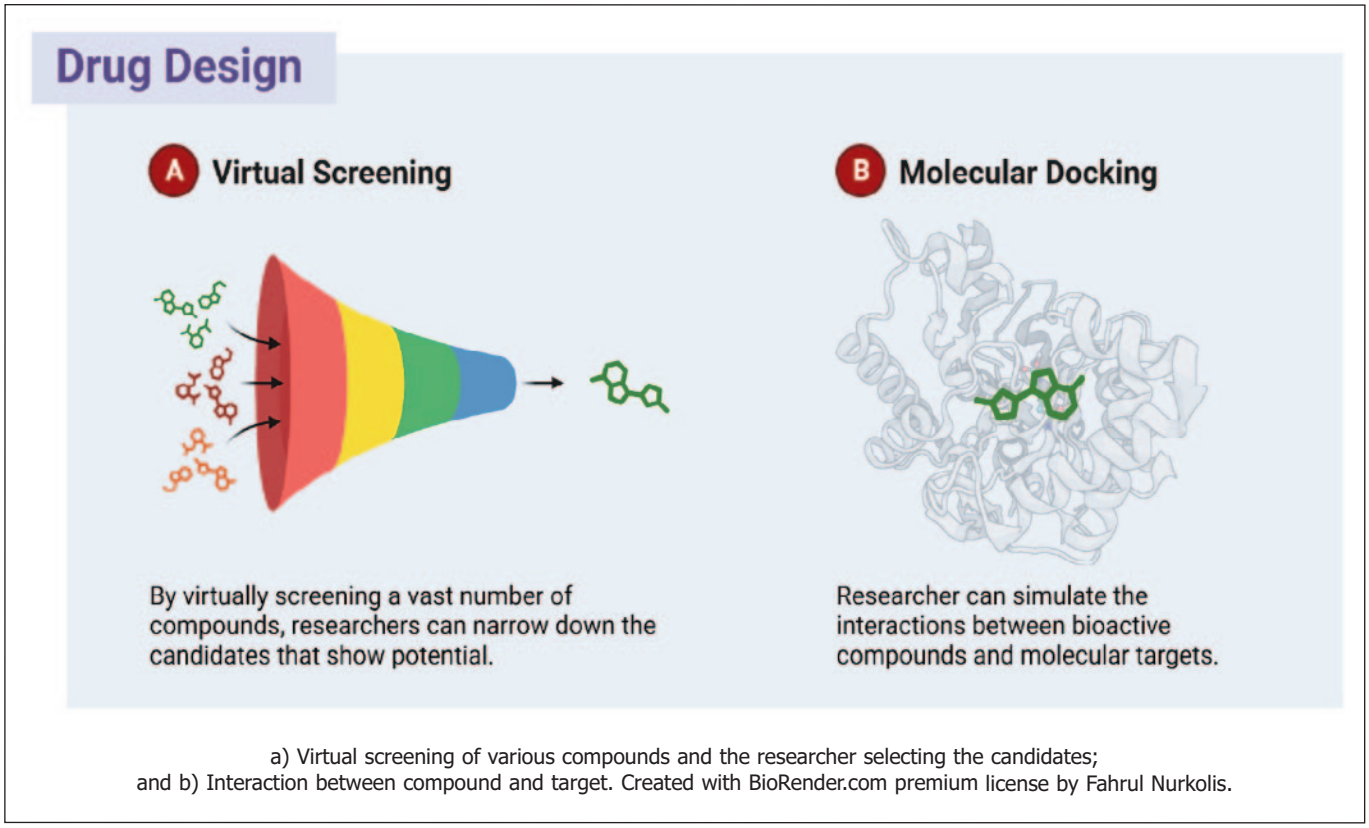
METHODS AND SEARCH STRATEGY

This study constitutes a comprehensive literature review. The search strategy employed primary keywords, including "Functional Food" and "Molecular Docking," alongside pertinent related keywords. Recent scholarly literature published within the past decade (2013–2023) was retrieved from the Medical Literature Analyses and Retrieval System Online (MEDLINE), Science Direct (SCOPUS), and Google Scholar databases. No additional inclusion or exclusion criteria were applied during the literature selection process.

Molecular Docking Meets Functional Food

Molecular docking is a computational method used to predict interactions between various molecules, such as proteins and ligands, by modeling and analyzing these interactions. Molecular docking aims to understand and predict how molecules interact, thereby aiding in drug design, drug discovery, and understanding the molecular mechanisms involved in biological processes. In molecular docking, the three-dimensional structure of the target protein and ligand is used as input. The target protein refers to the protein molecule whose interactions with the ligand are to be identified. The ligand is a small molecule that binds to the target protein and can potentially be a drug. The docking method then searches for the best conformation of the most suitable ligand for the target protein, considering various interaction forces such as electrostatic interactions, hydrophobic interactions, and Van der Waals interactions[4].

This method is widely used to discover and design new drugs by identifying potential compounds that bind to the target protein (Figure 1). Molecular docking allows researchers to predict the molecular interactions between drug compounds and the target protein and identify drugs that have the potential for high affinity and activity against specific targets. It can also accelerate the drug discovery process by efficiently filtering out compounds that do not bind to the target protein. Researchers can modify the drug molecules to



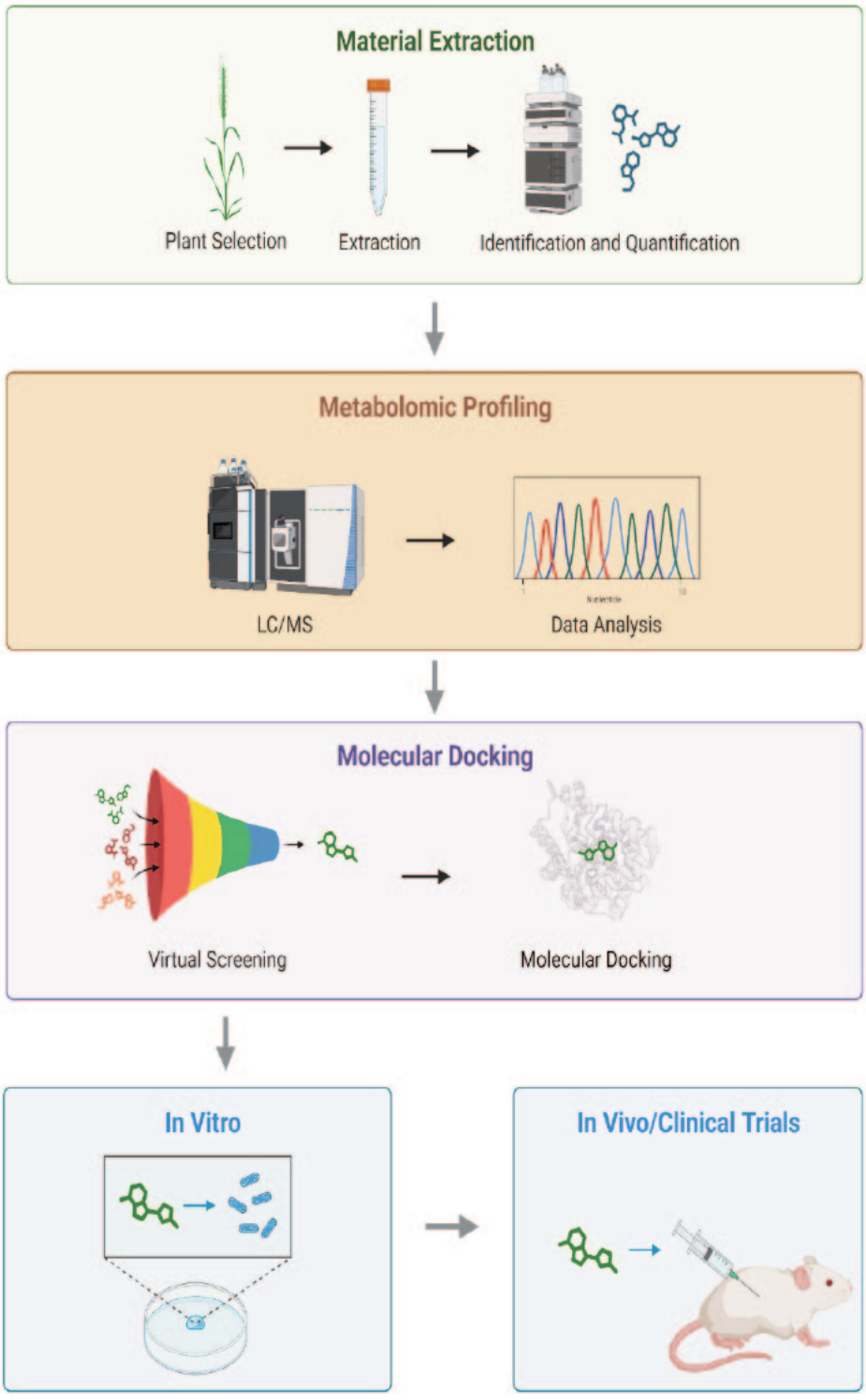
a) Virtual screening of various compounds and the researcher selecting the candidates; and b) Interaction between compound and target. Created with BioRender.com premium license by Fahrul Nurkolis.

Figure 1. Molecular docking utilization

enhance their effectiveness, selectivity, and pharmacological properties by performing redocking between existing drugs and the target protein. Molecular docking can also investigate unknown protein structures by performing docking between homologous protein structures and known ligands. This method helps predict potential protein structures and assists in determining more accurate three-dimensional structures[5,6]. Molecular docking simulations can leverage big data and data mining techniques to extract valuable information from data related to compounds, protein structures, and bioactivity (Figure 1). Molecular docking simulations can utilize these databases and apply data mining techniques to extract relevant information. By analyzing this data, researchers can identify potential drug candidates with desirable properties, such as high binding affinity and selectivity to specific targets. Data mining can also help identify structure-activity relationships, optimizing compounds for improved drug efficacy and reduced side effects[7].

Molecular docking simulations are computer-based methods that eliminate the need for time-consuming and costly experimental procedures and offer a faster and more efficient way to screen and analyze molecules. In the pharmaceutical field, molecular docking simulations enable the virtual screening of large compound libraries (Figure 1). Instead of physically testing each compound in the lab, researchers can use computational models to predict how these compounds interact with specific target proteins. By virtually screening many compounds, researchers can narrow down the candidates with potential for further development. This approach saves significant time and resources by focusing experimental efforts on the most promising compounds, accelerating drug discovery[8]. In functional food research, the computer-based approach allows for the virtual screening of bioactive compounds in foods. Instead of performing extensive laboratory experiments, researchers can simulate the interactions between bioactive compounds and molecular targets using molecular docking simulations. This virtual screening process helps identify bioactive compounds in foods that have the potential to interact with specific targets, providing insights into their mechanisms of action and potential health benefits[9].

By avoiding the need for extensive laboratory testing, this approach offers a more efficient and cost-effective way to analyze the bioactive components of functional foods (Figure 2). Overall, the computer-based approach in molecular docking simulations revolutionizes the screening and analysis of molecules in pharmaceutical and functional food fields (Figure 2). It eliminates the need for time-consuming and expensive experimental procedures, allowing for the virtual screening of compound libraries and bioactive compounds. This approach significantly accelerates the research process, enabling researchers to focus their



The procedure starts with material extraction, continues with metabolomic profiling, and identification of the compound through molecular docking. The identified compound has been used on *in vitro* or *in vivo* experimental studies.
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Figure 2. The process of making functional food

resources on the most promising candidates and facilitating the development of novel drugs and functional food products (Figure 2). Molecular docking simulations provide a rapid and cost-effective approach for screening and prioritizing potential compounds or bioactive molecules. These simulations help focus experimental efforts on the most promising candidates, saving time and resources in both pharmaceutical and functional food research[9,10].

DISCUSSION

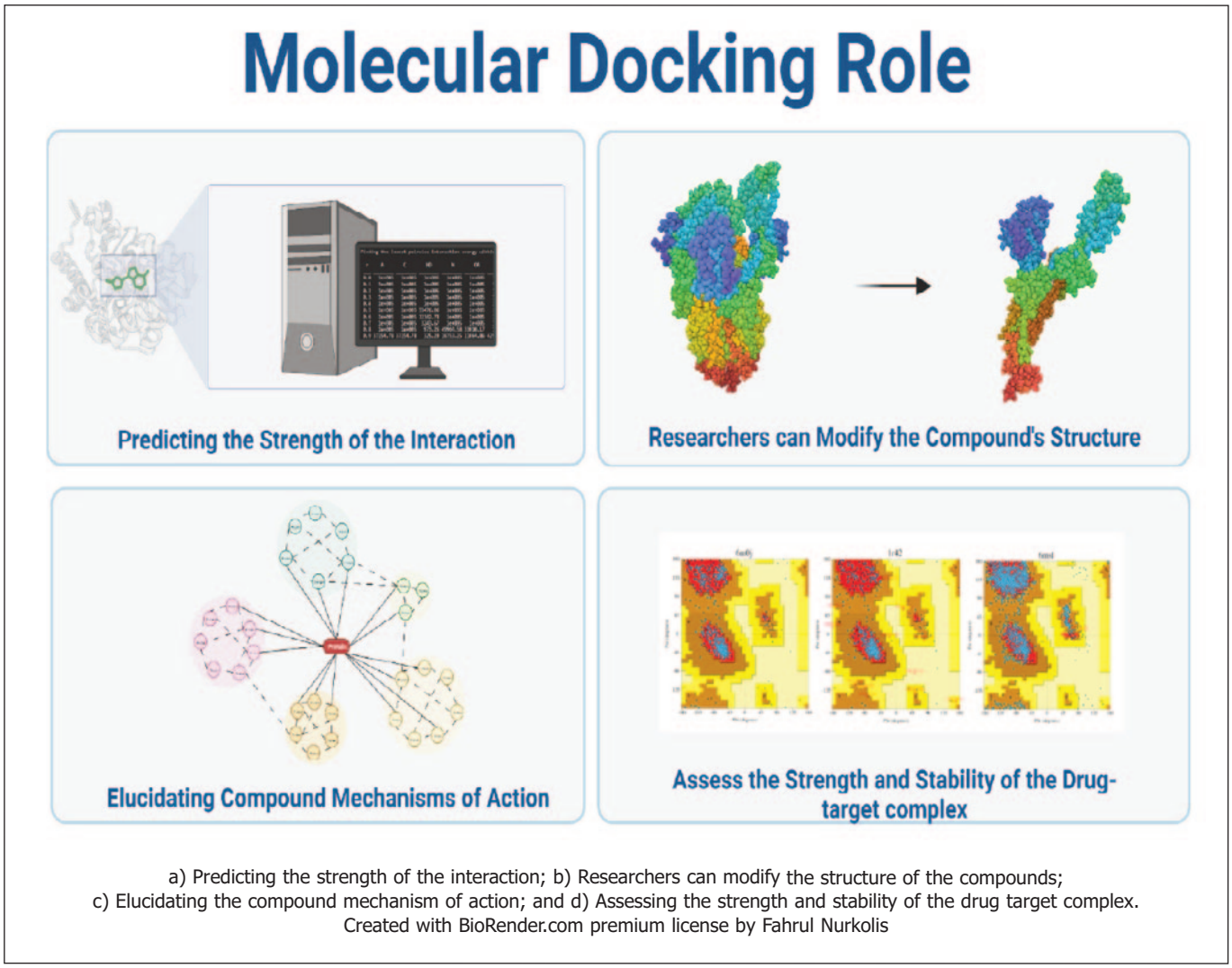
By considering its health effects on the human body, the discovery of optimal functional food must go through several research methods to identify and understand the interactions of its components on the human physiology system. With technological advances in the field of functional foods that have increased rapidly in recent years, solutions using in silico or molecular docking research can facilitate and optimize functional food discoveries by predicting the strength of the interaction of protein molecules and other bioactive components with the desired receptor targets so that nutraceutical effects are achieved[8]. In several studies related to chronic diseases that require the primary management of a patient's diet, such as type 2 diabetes mellitus and atherosclerosis, the discovery of functional food through molecular docking research as a solution to these diseases is considered very good because it can optimize the bioactive activity in food consumed[11,12]. Researchers can modify the compound's structure to enhance interactions and affinity with the target by redocking bioactive compounds with related target proteins, thereby increasing the desired biological effects[13]. In the pharmaceutical field, these simulations help in screening and designing potential food candidates by thoroughly identifying metabolites that are likely to bind to their receptors. This enables the selection of promising drug candidates for further development and testing, saving time and resources compared to traditional experimental methods[5].

In some research on patients with atherosclerosis and stroke, nutritional recommendations to reduce levels of low-density lipoproteins (LDL) and triglycerides in their diet will be recommended as one of the supportive therapies. This has led researchers to focus on functional food discovery targeting phytosterols or stanols (e.g., β-sitosterol) and/or polyunsaturated fatty acids (e.g., omega 3)][12,14]. Molecular docking could enhance the process of characterizing the bioactive components of functional foods and elucidating their mechanisms of action, thus contributing to the development of evidence-based functional food products (Figure 3). By simulating the binding process on each of the metabolite components found in these functional foods, researchers can assess the strength and stability of the drug-target complex, as well as identify critical interactions and binding sites, which also optimizes the drug candidate's structure and properties to enhance its efficacy and reduce potential side effects (Figure 3)[15].

The main components in molecular docking are the conformational search algorithm and the scoring function (Figure 3). The search scoring function is the biggest challenge in molecular docking related to predicting binding affinity. The binding affinity of a complex molecular bond between the receptor and the ligand can have a different value in other tests[16]. In recent years, the accuracy of molecular docking has been a matter of debate among researchers, including in predicting the energy interaction between two molecules. The programs used for molecular docking have an average identification accuracy of 60 – 75% in determining correct processes. Two major approaches are used in terms of molecular docking accuracy, namely ensemble and consensus docking. Ensemble docking performs docking simulations on different protein conformations with an approach to protein flexibility. Accuracy in the docking ensemble is 78%. Ensemble docking successfully identified interactions between proteins, GPCR modeling, characteristics of nuclear receptor modulators, metabolism, and molecule toxicity.

Meanwhile, consensus docking focuses on increasing binding forces and pose selection. The validity of molecular docking needs to be done before simulating protein modeling and selection. This is because docking sources can come from different sources, and there may be redundancy, missing atoms, and residues from the same source. The general steps taken to validate the docking protocol are redocking the reference ligand to test whether the docking algorithm produces a correct pose. Researchers use A common standard measure for validation: the root mean squared deviation (RMSD) by comparing predicted vs. predicted coordinates based on the initial conformation of all atoms from both conformations[17].

The challenges in molecular docking related to receptor-ligand flexibility and binding evaluation can be overcome by the following steps based on the shape of the docking bond. First, the protein-ligand docking form is the most common and valuable when modifying multiple ligands. In addition, this form has the characteristics of requiring narrow sampling and induced fit docking. Flexibility in the form of protein-ligand docking bonds can use three methods, namely: 1) Protein Energy Landscape Exploration (PELE), which combines protein and ligand perturbations; 2) docking ensembles; and 3) metadynamics[18]. Second, the form of docking peptides or peptide-like ligands. This form is highly variable and virtually irreproducible because of its high flexibility[19]. Lastly, the form of protein-protein docking with the biggest challenge lies in the backbone's flexibility. Until now, comprehensive computational studies still need to be conducted to solve the problem[20]. Another challenge in molecular docking, as previously mentioned, is binding affinity. In other tests, a complex molecular bond between the receptor and the ligand may have a different binding affinity. The reason is that docking programs can produce one or several poses for each ligand, including rank compounds based on scoring functions.



a) Predicting the strength of the interaction; b) Researchers can modify the structure of the compounds; c) Elucidating the compound mechanism of action; and d) Assessing the strength and stability of the drug target complex. Created with BioRender.com premium license by Fahrul Nurkolis

Figure 3. Molecular docking role

Therefore, to overcome this problem, we use a fourth metric called docking power, ranking power, scoring power, and screening power. Docking power is the ability to identify native poses, ranking power is the ability to rank compounds, scoring power correctly is the ability to predict binding affinity, and screening power is the ability to identify the true binders from a random pool of ligands[13].

The concept of functional food stems from the idea that foods have additional health benefits beyond basic nutrition or can reduce the risk of disease. However, while functional foods may offer certain health benefits, they are not intended to replace medical treatment. In terms of the future development of functional food, here are some trends and developments that may shape the future of functional food: 1) Food is microbiome friendly. The microbiome plays an essential role in health, digestion, and immunity. Functional foods can focus on promoting a healthy gut microbiome by including probiotics, prebiotics, and other bioactive compounds that support beneficial bacteria[21]. 2) Functional drinks. The trend for herbal teas, energy drinks, and fortified drinks with added additives is growing. A future that presents functional drink innovations targeting specific health, such as drinks fortified with vitamins, minerals, adaptogens, or plant extracts[22]. 3) Personalized nutrition. Technological developments such as genomics have allowed functional foods to be adapted to specific genetics to target individual needs. This approach aims to optimize health outcomes and prevent chronic disease[23].

The other future development of functional foods is 4) Nutraceuticals and bioactive compounds. Nutraceuticals are bioactive compounds that have health benefits. For example, polyphenols, antioxidants, omega-3 fatty acids, and plant sterols. Technological developments that are increasingly developing nutraceuticals and bioactive compounds can become more precise formulations and delivery systems to increase

their effectiveness[24]. 5) Vegetable protein and alternatives. Functional foods that utilize protein sources such as nuts, algae, and insects tend to grow rapidly. This can provide nutritional benefits while reducing the environmental impact associated with traditional animal farming. 6) Digital integration. Now the technology field continues to receive significant attention from several researchers so technological progress never goes out. This technological advancement can be integrated between functional food and digital platforms. This platform may contain personalized recommendations, track health parameters, and empower individuals to make informed choices and monitor progress[25]. 7) Innovative delivery system. Food science and technology developments may lead to new delivery systems for functional ingredients. For example, encapsulation techniques can protect easily contaminated compounds. In addition, developing nano-sized particles can facilitate the absorption and mobility of nutrient delivery[26].

In the future of functional food, it is essential to remember that the regulatory framework, consumer acceptance, and scientific advances are the benchmarks that can influence it. However, if this functional food focuses on health and well-being, it can significantly improve well-being and overcome specific health problems.

CONCLUSIONS

The identification of the molecular targets for bioactive compounds in food can be accomplished through the use of molecular docking. It permits the prediction of the binding affinity and conformation of bioactive compounds with target proteins to discover potential health benefits. Molecular docking is now a key technique in the compound development process thanks to the accessibility of databases and the advancement of computational tools. By reducing the time and price required for traditional experimental approaches, the use of this technology has increased the efficiency and effectiveness of bioactive compounds development. In order to identify new therapeutic targets and develop safe and effective dietary supplements for the treatment of disease, molecular docking has a lot of potential for use in research on bioactive compounds.

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