ISSN: 2455-3751

Contents lists available at http://www.albertscience.com

ASIO Journal of Microbiology, Food Science & Biotechnological Innovations (ASIO-JMFSBI)

Volume 5, Issue 1; 2020; 06-15

RECENT ADVANCES IN MOLECULAR DOCKING TECHNOLOGY APPLIED IN MEDICINES AND FOOD SCIENCE

Nikita Shamsundar Deshmukh

Department of Pharmaceutical Chemistry, Swami Ramanand Teerth Marathwada University, Nanded431606

ARTICLE INFO

Review Article History
Received: 15th May, 2020
Accepted: 5th June, 2020

Corresponding Author:

† N. S. Deshmukh

E-mail:
deshmukhnik07@gmail.com

† Department of Pharmaceutical Chemistry, Swami Ramanand Teerth Marathwada University, Nanded-431606

ABSTRACT

Molecular docking has been accrued and ameliorating for many years, but its ability to bring a medicine to the drug market influentially is still generally questioned. It is nothing but a theoretical transcript method based on bioinformatics, which studies the interaction between molecules [ie, ligands and receptors], and predicts their binding modes and affinity via a computer platform. Here we introduce several successful cases including drugs for treatment of prevalent diseases. An eminent advantage of molecular docking such as predicting experiments are arresting increasing attention for its application potential in various fields. It shows us with confidence that the docking will be extensively employed in the industry and basic research. Moreover, they can actively apply molecular docking and related technology to create new therapies for disease. This review presents the theory and software development of molecular docking, and emphasizes its application in the field of medicines, food science, including nutritional components and food safety.

Keywords: Molecular docking, food, interaction, mechanism, computational drug design.

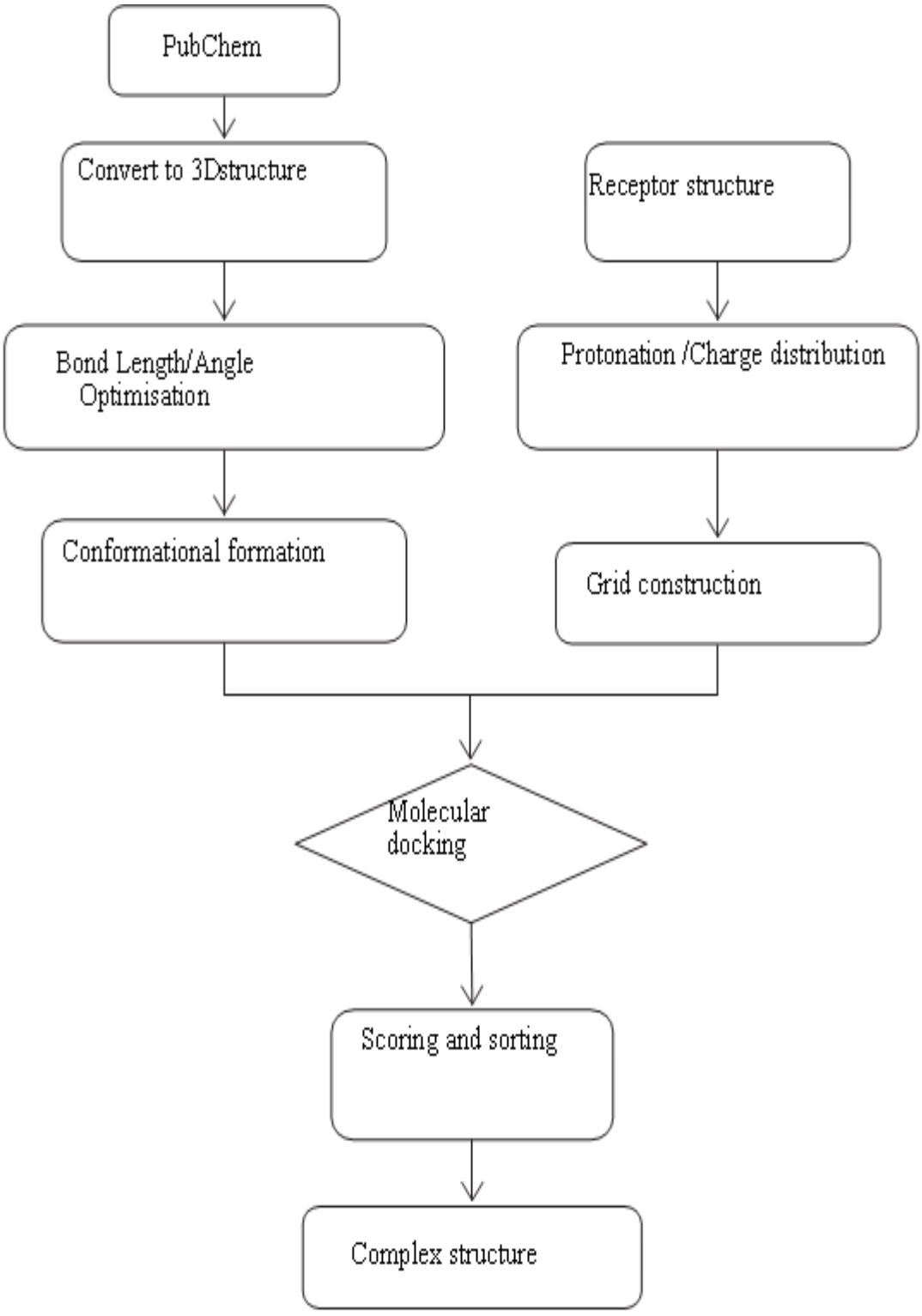
INTRODUCTION

Molecular docking is the most widely used one in molecular modeling research. It can predict binding sites and elucidate the mechanism of molecular recognition by simulating the spontaneous binding process of ligands to receptors [1]. Therefore, it is commonly used in drug design studies [2]. Moreover, it can provide a reference for characterizing the thermodynamic and dynamic changes of inter-molecular interactions, which not only verifies the experimental results at the molecular level but also guides the actual experiment. Considering that the food matrices are usually complex and the reactions are diverse, molecular docking shows a great potential in predicting the action mode and facilitating cost reduction of experiments, which justifies extensive application of this method in food science. Since food provides the human body with essential nutrients, such as proteins, lipids, carbohydrates and vitamins, molecular docking can be widely applied in these particular areas. Moreover, food safety issue concerning with drug residues, biotoxins and foodborne pathogens is one of the utmost importances in the food research, which is increasingly involved with molecule level study [3]. It should be noted that the applications of molecular docking related to food have been growing rapidly in the last few years. Therefore, this review aims to summaries more than 100 articles published in the recent 5 years of molecular docking applications in food science. Molecular docking is a method for predicting the position and affinity of a ligand (small molecule) at a receptor (macromolecule) binding site [4]. Scheme 1 presents the common flow chart of molecular docking.

BASIC THEORY

The numerous interactive processes between receptors and ligands include hydrogen bonding, electrostatic interaction, Van Der Waals forces and hydrophobic interaction.

Doi: 10.2016-53692176; DOI Link :: http://doi-ds.org/doilink/06.2020-22786874/



Scheme 1: The flow chart of molecular docking

Doi: 10.2016-53692176; DOI Link :: http://doi-ds.org/doilink/06.2020-22786874/

Table 1: The comparison of molecular docking software

Software	Algorithm	Evaluation method	Accuracy (%)	Type	Speed	Cost
AutoDock	Lamarckian Genetic	Semi-empirical free energy	49	Semi-flexible docking	Average	Free
DOCK	algorithm (LGA) Geometric matching	The molecular force field	–	Semi-flexible docking	Fast	Free
GOLD	Genetic	Semi-empirical free energy	78	Flexible docking	Fast	Pay
FlexX	Incremental construction	Semi-empirical free energy	58	Semi-flexible docking	Fast	Pay
AutoDock Vina ICM	Broyden– Fletcher–Goldfarb–Shanno Stochastic global Optimization.	Semi-empirical free energy Semi-empirical free energy	78 –	Semi-flexible docking Flexible docking	Fast Fast	Free Pay
Glide	Systematic search	Semi-empirical free energy	82	Semi-flexible docking	Average	Pay
Surflex	Surface-based	Semi-empirical free energy/the	75	Flexible docking	Fast	Pay
Affinity	molecular similarity Monte Carlo (MC)	molecular force field The molecular force field	–	Flexible docking	Slow	Pay
LigandFit	Monte Carlo (MC)	The molecular force field	46	Semi-flexible docking	Fast	Free
Discovery Studio	Molecular Dynamics (MD)	The molecular force field	–	Flexible docking	Slow	Free

Doi: 10.2016-53692176; DOI Link :: http://doi-ds.org/doilink/06.2020-22786874/

IDENTIFICATION OF MEDICINE FOR PREVALENT DISEASES

Influenza

Influenza, commonly referred to as the flu, is a viral infection that can be mild or severe, depending on the strain, and the host it infects. Due to the rapidly mutating nature of the influenza virus, new vaccines must be made and administered annually. There are two types of antiviral drugs that have been used to treat influenza. Specifically Amantadine and Rimantadine were the first marketed influenza antivirals Adamantanes [Fig. 1 A, B]. Adamantanes function by blocking the M2 proton channel [5]. This class of drugs was effective against influenza type A, but drug resistance developed rapidly [6]. Hayden et al. conducted a study in which 17 Rimantadine-resistant influenza strains were recovered from 13 patients [7]. The M2 coding sequences of 17 resistant strains were then compared to 8 drug sensitive strains, and it was determined that all resistant strains had a nonsynonymous substitution in RNA segment 7. I n 14 separate isolates, the most common mutation was f o u n d a s S31N. The other mutations found were A30V, A30T, and V27A. By 2009, all strains of influenza A had become resistant to Adamantanes [8].

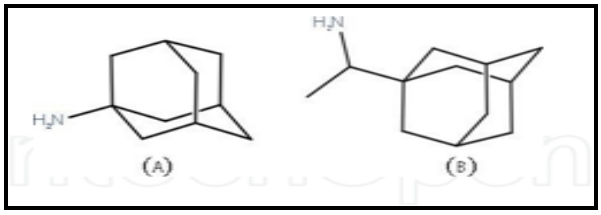


Fig. 1: Two dimensional structures of the Adamantanes, (A) amantadine [SMILES: NC13CC2CC(CC(C1)C2)C3] and (B) Rimantadin [SMILES: NC(C)C13CC2CC(CC(C1)C2)C3].

Malaria

Malaria is an infectious disease caused by a parasitic protist and spread by mosquitoes. There are several different species of this parasite; the most deadly, and most prevalent is *Plasmodium falciparum*. This disease can cause flulike symptoms, and can be fatal if left untreated [9]. Malaria is typically treated with quinine drugs such as Chloroquine, Hydroxy chloroquine, or Amodiaquine (Fig.2 A, B), which function by interfering with heme polymerization [10]. Interference with this function leads to increased levels of hemoglobin and ferri proto porphyrin IX (FPIX), which can be toxic to the parasite. *P. falciparum* has developed resistance to chloroquine (and similar drugs); in resistant cells, quinine drugs are actively transported out of the parasitic vacuole [11]. This form of resistance has become widespread, resulting in a need for new antimalarial drugs.

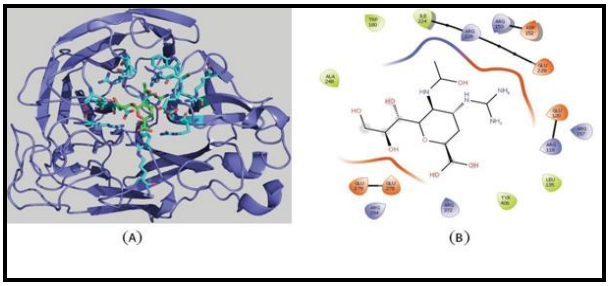


Fig. 2: (A) (PDB ID: 5 L17) this structure shows Zanamivir bound to influenza a neuraminidase. Zanamivir, shown with green carbons, interacts with R119, E120, L135, D152, R153, W180, I224, R226, E229, E278, E279, R294, R372, and Y406 (cyan carbons). (B) Ligand interaction diagram showing a closer look at how these residues interact with the ligand.

In *P.* falciparum, M18 aspartyl aminopeptidase (*Pf*M18AAP) and its interactions with mem- brane proteins are essential for parasite survival, making it an attractive antimalarial drug target. Using molecular docking and other computational methods, Kumari *et al.* determined structural requirements for *Pf*M18AAP inhibitors using GOLD v5.2 and the Schrödinger Mae- stro 9.1 GLIDE program [12]. This study selected and screened just fewer than 30,000 compounds for binding activity. From the results, it was concluded that the best inhibitors had one hydrogen donor, one hydrophobic group, and two aromatic rings. Molecular docking and pharmacophore modeling have been used to search for novel inhibitors using those criteria.

Tuberculosis

Tuberculosis (TB) and infectious disease caused by *Mycobacterium tuberculosis*. Human infection with TB dates back all the way to ancient Egypt, India, and China [13]. TB is spread through the air, usually by a cough or sneeze from an infected person. TB kills nearly 2 million people each year, mostly in Africa [14]. The most effective treatments for non-resistant TB are Isoniazid and Rifampin. Unfortunately, TB drug resistance has become extensive [15]. There are three categories of resistant TB strains: multidrug resistant (MDR), extensively drug- resistant (XDR), and totally drug-resistant (TDR). In order to be classified as MDR TB, the strain must be resistant to both Isoniazid and Rifampin. A TB strain is classified as XDR if it is resistant to Isoniazid, Rifampin, and “is also

resistant to three or more of the six classes of second line TB drugs,". TDR strains are resistant to all known TB drug [16]. Dramatic increases of drug resistance have prompted researchers to seek new drug targets; in order to reduce research costs and get results as quickly as possible, many are turning to docking simulations for preliminary trials. In *M. tuberculosis, a* protein [i.e, Shikimate kinase] is involved in an amino acid biosynthesis pathway [17]. Interruption of this pathway prevents synthesis of essential amino acids, leading to incomplete proteins, which leads to cell death. Vianna and de Azevedo used docking simulations (MOLDOCK) to identify novel SK inhibitors; these compounds were compared to staurosporine, which has demonstrated SK inhibition *in vitro* [18]. The novel inhibitors were docked to a number of structures for *Mt*SK (PDB: 2DFN, 1U8A, 1WE2, 1ZYU, 2G1K, 2IYQ, 2IYR, 2IYS, 2IYX, 2IYY, 2IYZ, and 3BAF).Another response to drug resistance is drug repurposing. The advantage of drug repurposing is that potential drugs have already been shown not to have severe side effects, which speeds up the process and saves money. Studies of this nature often utilize molecular docking and other computational methods to save even more time and money by screening more potential drugs in a shorter time frame.

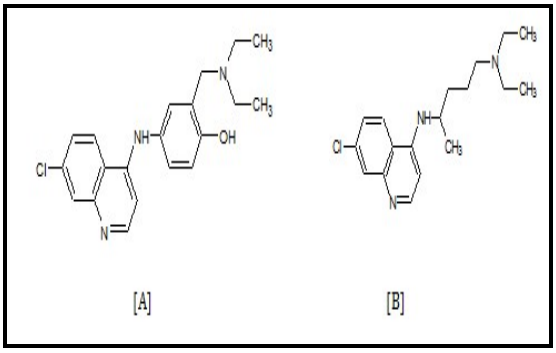


Fig. 3: Two-dimensional structures of the common quinine drugs, (A) Amodiaquine [SMILES: Clc1cc2nccc(c2cc1)Nc3cc(c(O)cc3)CN(CC)CC] and (B) Chloroquine [SMILES: Clc1cc2nccc(c2cc1)NC(C)CCCN(CC)CC].

Zika

The Zika virus (ZIKV), named for the Ugandan forest in which it was originally found, was first isolated in monkeys [19]. ZIKV belongs to a genus of viruses known as flaviviruses; other viruses belonging to this genus are dengue fever, yellow fever, hepatitis, and West Nile. ZIKV can be transmitted by mosquitoes or sexual contact. Symptoms of the virus include fever, joint pain, and rash for up to 7 days. ZIKV has also been associated with Guillain-Barre syndrome [20], an autoimmune disease. The virus can also be transmitted from mother to fetus, which can result in severe birth defects. From 2007 to 2014, several small outbreaks of the virus were reported [20–22]. The first ZIKV epidemic began in Brazil in 2015. As outbreaks become more and more severe, it is becoming increasingly urgent to find a drug to treat ZIKV.

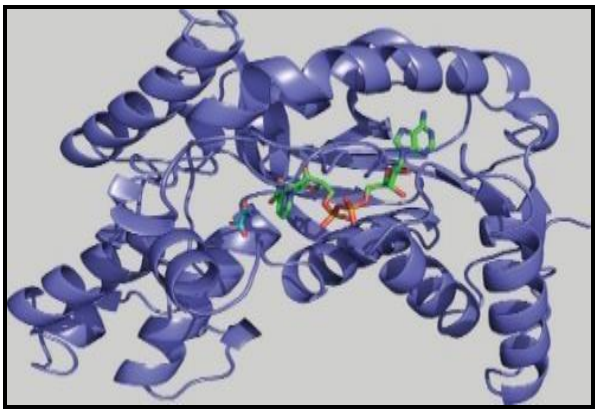


Fig. 4: Structure of plasmodium falciparum lactate dehydrogenase in complex with Oxamate and NADH.
NADH[SMILES:O=C(N)c1ccc[n+](c1)[C@@H]2O[C@@H]([C@@](O)[C@H]2O)COP([O])(=O)OP(=O)(O)OC[C@H]5O[C@@H](n4cnc3c(ncnc34)N)[C@H](O)[C@@H]5O];Oxamate [SMILES: C(=O)(C(=O)O)N].

Non-structural protein 5 methyl transferase (NS5 MTase) is crucial for the maintained stability of a flaviviral genome, and the ability to evade immune response [23] which makes it an attractive target for antiviral activity. Zhang et al. used docking simulations (AutoDock 4.2) to determine potential designs for novel NS5 MTase inhibitors and binding sites [24]; the authors of this study found that dengue virus inhibitor compound 10 found by Lim et al. (PDB: 3P8Z) may bind to ZIKV NS5MTase. Preliminary methods included homology modeling, binding site prediction, and pharmacophore modeling. Out of 31 compounds subjected to docking studies, 3 were chosen for the next step, molecular dynamic simulation. It was concluded that two of their compounds showed "substantial stability in complex with the target enzyme (ZIKV NS5)," [25]. Hepatitis C is commonly treated with polymerase inhibitors (Ribavirin and Sofosbuvir). Sacramento et al. used docking simu- lations (MODELER 9.16) to model binding between Hepatitis C polymerase inhibitors and Zika RNA polymerase (PDB: 4WTG) [26].

MOLECULAR DOCKING APPLICATIONS IN FOOD SCIENCE

Protein

Protein does not function in isolation and requires the identification of other molecules to successfully fulfil its intended role [27]. Consequently, molecular docking methods are increasingly employed to study the binding state of proteins and ligands and are widely utilised in food science. The main proteins studied in the food industry include protease and human serum albumin (HSA). The molecular docking technology was adopted to study the relationship between enzyme activity and substrates. The contact between protease and substrates includes hydrogen bonding and hydrophobic interaction, while the hydrophobic cavity of the enzyme denotes the main binding site [28]. The substrate interacts with the amino acid residues of the protease to occupy the active site and inhibit the activity of the enzyme [29]. In addition, the binding of food ingredients to enzymes triggers the structure and conformation of the enzyme to change, which can reduce its activity [30]. Moreover, the study found that the binding capacity of catechin gallate (EGCG) exceeded that of the other three catechin isomers (epicatechin gallate (ECG), epicatechin [EC] and epigallocatechin (EGC)) that were docked with trypsin. As show in **Fig. 5**, s1 pocket of trypsin was occupied by EGCG, which inhibited the trypsin activity.

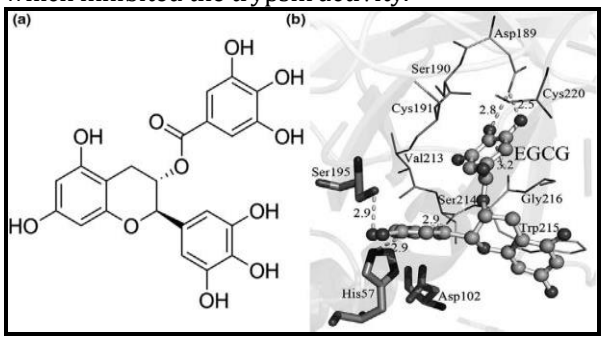


Fig.5: The structures of the catechin and trypsin–catechin complexes. (a) The 2D structure of EGCG. (b) The structure of theEGCG–trypsin complex. A ball-stick model represents EGCG, while a stick model denotes the interaction residue. The dashed line represents hydrophobic action [31].

Bioactive Peptide

Bioactive peptides (BAPS) derived from food protein are composed of 3–20 amino acids [32]. Its biological activities are closely related to human diseases and include many beneficial properties such as antimicrobial activity, antiinflammatory, as well as anti-diabetic qualities [33]. Therefore, the preparation of novel BAPS for oral drugs or as functional food additives to prepare various health foods is of great significance to human health. Based on computer simulation, bioinformatics then represented a new method for discovering BAPS [34]. Where after, a new tripeptide WCW was successfully screened out from 8000 tripep- tide libraries constructed by GOLD software, and its IC_{50} value was 49 lM [35].

Amino acids

There are 20 kinds of amino acids in nature, and eight types of essential amino acids are found in the human body. They are the essential components of proteins and present various positive effects. Acylation of amino acids is one of the most common reactions, [36] confirmed the exclusivity of Llysine e-amino acylation at the molecular level via flexible dock- ing simulation and interaction energy calculation. The study on the interaction mechanism between hydrophobic amino acids and b-cyclodextrin provided molecular basis for removing the bitterness of bioactive peptides composed of hydrophobic amino acids [37]. Amino acids are capable of both activating and inhibiting enzyme activity. For example, the mycosporine-like amino acids isolated from marine sources occupied the binding sites of proline and glycine in collagenase, thus causing competitive inhibition [38]. However, the application of molecular docking in human Angiotensin-converting enzyme (ACE) inhibitory peptides are extensively used in the treatment of hypertension. They employed molecular docking technology to screen short hypotensive peptides from 113 kinds of peptides and docked them with ACE using Discovery Studio 3.5 software. The use of molecular docking technology for the virtual screening of bioactive peptides provides a directive reference and saves costs for the screening process. Molecular docking is also widely used in identifying BAPS [39] and evaluating their biological activities [40]. The novel ACE inhibitory peptide YLVR was purified from wild hazelnuts, and it displayed a significantly higher inhibitory effect due to cationpion interaction [41]. Absorption of amino acids has yet to be subjected to a comprehensive research.

Carbohydrates

Carbohydrates consist of polyhydroxy aldehydes or polyhydroxyl ketones, as well as their condensates and Derivatives. Carbohydrates in foods include glucose, sucrose, lactose, maltose, starch and cellulose. They play a crucial role in the physical activities of living beings and are the primary source

Doi: 10.2016-53692176; DOI Link :: http://doi-ds.org/doilink/06.2020-22786874/

of energy for all living organisms to maintain vitality. The docking methods of polysaccharides and pro- teins are constantly updated. A novel docking method was proposed, which was dominated by the geometric constraints of carbohydratearomatic interactions. The results showed that GLP did not interact with the hydrophobic cavity of BSA, but with five sites on its surface. Residues from 67 amino acids were involved in the binding process, and the main forces included hydrogen bonding and van der Waals forces. The binding of carbohydrates to enzymes can modulate its catalytic activity. The participation of residues of a-glucosideH⁺ transporters in the transport of AGT1 permease was studied, which provided theoretical basis for the transport mechanism of the same type of sugar transporters [42]. Levansucrase catalysed the conversion of sucrose to levan, and its residues 327 and 154 played an important role in regulating the transfructosylation and hydrolysis activities,[43] Levansucrase binding to sucrose was beneficial to its activity in a wide range of pH [44]. In addition, simulating the binding of sweeteners and their receptors provided an alternative direction for the design of new sweeteners [45]. Pentagalloyl-glucose (PGG) inhibited the activity of alpha-amylase and can be used as a food additive to maintain normal glycaemic levels [46].

Lipids

Lipids are nutritionally crucial for the human body to function efficiently, which include simple lipids, compound lipids and derivative lipids in food. Pancreatic lipase is the most important enzyme to hydrolyse dietary fat and is closely related to the digestion and absorption of fat. Its activity is affected by other substances in the environment. As shown in Fig. 6. astaxanthin and p-NPB binded to pancreatic lipase, but there was no competition between them. And astaxanthin acted with the adjacent residues of the catalytic site to change the conformation of pancreatic lipase, thereby inhibiting its activity. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are crucial lipid derivatives in human body. Molecular docking technology has been broadly studied in the synthesis and function of EPA and DHA. The interaction of EPA and DHA with coenzyme Q10 (CoQ10) improved its permeability, which was helpful to determine the best carrier of CoQ10 [47]. It was reported that amyloid-b (Ab) can cause Alzheimer's disease (AD) [48]. Studies have shown that oleic acid (OA) and DHA have direct inhibitory effects on Ab. Polyunsaturated fatty significant attention following clenbuterol acids as dietary supplements have far- reaching significance in the treatment of AD.[49] The body can also use linoleic acid and a-linolenic acid to synthesise EPA and DHA, which are regulated by various enzymes[50] docked n-3 desaturase with substrates (linolenic acid and arachidonic acid) by using PyMOL software (Schro€dinger, New York, USA), and then found the molecular structure and binding domain of n-3 desaturase , which provided guidance for better application of n-3 desaturase to convert n-6 polyunsaturated fatty acid into n-3 polyunsaturated fatty acid. Ceramide could also affect the interaction between Hsd17b4 and Pex5 enzymes and indirectly regulate the production of DHA [51].

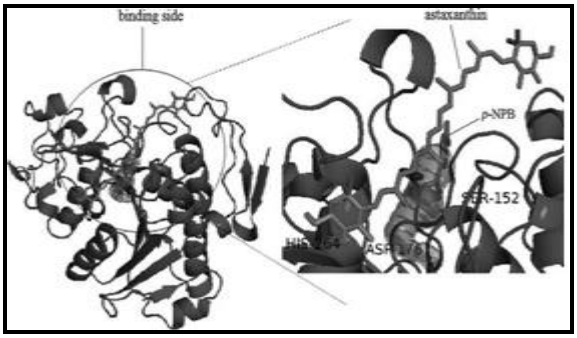


Fig. 6: The docking of p-NPB and astax-anthin to pancreatic lipase using AutoDock 4.2

Vitamins

Vitamins are tracing organic substances that cannot be synthesized by human body and must be obtained from food. They play an important role in the growth, metabolism and development of the human body [52] studied the inhibitory effects of vitamin B2 and D3 on xanthine oxidase (XO), between which was a synergistic effect. The docking revealed that the main interaction forces included hydrogen bonding, hydrophobic interaction and van der Waals force. And the results provided the possibility of reducing the risk of hyperuricaemia and preventing gout through diet. Subramanian [53] proposed that the interaction sites between vitamins and their receptors are Thr (314), Ile (20), Ser (16), Phe (142), Trp (24) and Asn (315), which are more conducive to intestinal absorption. Ascorbic acid and folic acid, two water-soluble vitamins, inhibit the activity of human pancreatic a-amylase (HPA). Adding vitamins to starch reduced the rate of increase of postprandial blood glucose level. The founding is conducive to the development and design of new foods and drugs for diabetics [54]. Furthermore, the inter- action between vitamin A and b-42 peptide included hydrophobic interaction and hydrogen bonding.

Doi: 10.2016-53692176; DOI Link :: http://doi-ds.org/doilink/06.2020-22786874/

FOOD SAFETY HAZARD FACTORS PESTICIDES AND VETERINARY DRUG RESIDUES

The annual output of chemical pesticides in the world totals nearly 2 000 000 tons. And the study focused on the performance of pesticides and their impact on food safety. The production and use of DDT were banned after the 1970s due to its acute toxicity and prolonged presence in the soil. Molecular docking was used to initially validate the QSAR models of DDT, providing a new method for designing high-performance pesticides [55].

Veterinary drug residues have attracted poisoning. The docking results of furan antibiotics nitrofurantoin (NFT) and nitrofurazone (NFZ) with BSA showed that the binding sites were located in the hydrophobic cavity of BSA, while electrostatic and hydrophobic interactions featured prominently during the binding process [56]. The directional mutagenesis of amino acid residues was performed on the anti-sarafloxacin ScFv antibody, and then, the affinity of the mutant antibodies to the drug was evaluated with molecular docking [57].

Biotoxins

Biotoxins are also one of the main sources of food safety problems. Staphylococcal enterotoxin is a kind of protein toxin produced by *Staphylococcus aureus,*[58] and most food poisoning inci- dents are caused by staphylococcal enterotoxin A (SEA). The docking models of SEA with EC, ECG, EGC and EGCG were compared, and the results that the binding ability of SEA with EGCG was the strongest, while the common binding site was located in the A-6 region. The spontaneous combina- tion of EGCG and SEA occupied the active site of SEA, thereby reducing its toxicity.[59] Zearalenone (ZEN) and citrinin (CIT) are con- taminants widely existing in food and beverage.

Food borne pathogens

Food borne pathogens can contaminate food and water sources directly or indirectly, and cause food poisoning, leading to severe food safety problems. In order to prevent food contamination, molecular docking technology has been used to study the toxicological effects of food borne pathogens. They successfully screened the antimicrobial peptide Pep49, and the specific binding of *Salmonella* Typhimurium (LPS) to pep49 was validated by molecular docking. *cholerae* were successfully isolated and identified by molecular docking technology combined with UV, FT-IR and NMR [60].

THE MECHANISMS OF INTERATIONS BETWEEEN MOLECULES

Molecular docking is a technique for exploring the interaction modes between molecules. The acting forces between molecules include hydrogen bonding, van der Waals forces, hydrophobic interaction, electrostatic interaction, p-p stacking and salt bonding [61]. Hydrogen bonding is produced by the covalent bonding of hydrogen atoms with more electronegative atoms, such as oxygen, nitrogen and sulphur [62]. The formation of hydrogen bonding is an inter-atomic interaction and is generally included in all molecular docking. The basic units of proteins and BAPS are amino acids. Since amino acids easily lose electrons, they are generally positively charged. These amino acids can then interact with negatively charged moieties to produce electrostatic inter- action. Moreover, most of the BAPS and proteins have hydrophobic cavities, allowing for effortless hydrophobic interaction [63]. Therefore, electrostatic interaction exists widely in the complex containing proteins or peptides. In addition, the p-p stacking is often formed between aromatic rings of molecules. According to the structures of the molecules, the modes of intermolecular interaction can be predicted and verified by molecular docking.

CONCLUSION, LIMITATIONS AND FUTURE RESEARCH

Molecular docking technology has a good application prospect in food science. However, it is worth noting that molecular docking can be used to verify experimental results and provide guidance for further research, and it does not entirely replace the actual experiment. Many docking procedures are conducted in a vacuum environment. In addition, the important factor to judge the accuracy of docking results is that the receptor and ligand have known stable structures.

Therefore, the proteins in Protein Data Bank (PDB) are often used as research objects, the substances that cannot determine the crystal structure need to be modeled, so there are many limitations. As a result, molecular docking technology should pay more attention to the development of algorithms to ensure the effectiveness of docking results. It is also necessary to design and develop docking software based on the characteristics of the receptor and ligand.

REFERENCES

[1] Brooijmans, N. & Kuntz, I.D. (2003). Molecular recognition and docking algorithms. *Annual Review of Biophysics and Biomolecular Structure*, 32, 335–373.

Doi: 10.2016-53692176; DOI Link :: http://doi-ds.org/doilink/06.2020-22786874/

[2] Ferreira, L.G., dos Santos, R.N., Oliva, G. & Andricopulo, A.D. (2015). Molecular docking and structure-based drug design strate- gies. *Molecules*, 20, 13384–13421.
[3] San-Martin, A., Donoso, V., Leiva, S. *et al*. (2015). *Current Topics in Medicinal Chemistry*, 15, 1743–1749.
[4] Roche, D.B., Brackenridge, D.A. & McGuffin, L.J. (2015). *International Journal of Molecular Sciences*, 16, 29829–29842.
[5] Moorthy NS, Poongavanam V, Pratheepa V. Mini Reviews in Medicinal Chemistry. 2014; 14(10):819-830
[6] Moscona A. Neuraminidase inhibitors for influenza. The New England Journal of Med- icine. 2005; 353(13):1363-1373.
[7] Hayden FG, Belshe RB, Clover RD, Hay AJ, Oakes MG, Soo W. The New England Journal of Medicine. 1989; 321(25):1696-1702.
[8] Alves Galvao MG, Rocha Crispino Santos MA, Alves da Cunha AJ. Cochrane Database Systematic Review. 2014;11. CD002745
[9] Newton CR, Krishna S. Pharmacology & Therapeutics. 1998;79(1):1-53
[10] Wellems TE. Malaria. How chloroquine works. Nature. 1992;355(6356):108-109
[11] Chinappi M, Via A, Marcatili P, Tramontano A. PLoS One. 2010;5(11) .
[12] Kumari M, Chandra S, Tiwari N, Subbarao N. 3D QSAR, pharmacophore and molecular docking studies. BMC Structural Biology. 2016;16(12)
[13] Hershkovitz I, Donoghue HD, Minnikin DE, Besra GS, Lee OY, Gernaey AM, Galili E, Eshed V, Greenblatt CL, Lemma E, et al. Detection and molecular characterization of 9,000-year-old mycobacterium tuberculosis from a Neolithic settlement in the eastern Mediterranean. PLoS One. 2008;3(10):e3426
[14] Keshavjee S, Farmer PE. Tuberculosis, drug resistance, and the history of modern med- icine. The New England Journal of Medicine. 2012; 367(10):931-936
[15] Centers for Disease Control and Prevention. MMWR Recomm Report. 2009; 58(RR-3):1-43
[16] Velayati AA, Masjedi MR, Farnia P, Tabarsi P, Ghanavi J, ZiaZarifi AH, Hoffner SE.. 2009; 136(2): 420-425
[17] Ratledge C, Patel PV, Mundy J. Iron transport in mycobacterium smegmatis: The loca- tion of mycobactin by electron microscopy. Journal of General Microbiology. 1982;128(7): 1559-1565.
[18] Vianna CP, de Azevedo WF, Jr.: Identification of new potential mycobacterium tubercu- losis shikimate kinase inhibitors through molecular docking simulations. Journal of Molecular Modeling. 2012;18(2):755-764.
[19] Sikka V, Chattu VK, Popli RK, Galwankar SC, Kelkar D, Sawicki SG, Stawicki SP, Papadimos TJ. Journal of Global Infectious Disease. 2016;8(1):3-15.
[20] Cao-Lormeau VM, Blake A, Mons S, Lastere S, Roche C, Vanhomwegen J, Dub T, Baudouin L, Teissier A, Larre P, et al. 2016;387(10027): 1531-1539.
[21] Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, Pretrick M, Marfel M, Holzbauer S, Dubray C, et al. The New England Journal of Medicine. 2009;360(24):2536-2543.
[22] Musso D. Zika virus transmission from French Polynesia to Brazil. Emerging Infectious Diseases. 2015;21(10):1887.
[23] Dong HP, Fink K, Zust R, Lim SP, Qin CF, Shi PY. Flavivirus RNA methylation. Journal of General Virology. 2014;95:763-778.
[24] Zhang C, Feng T, Cheng J, Li Y, Yin X, Zeng W, Jin X, Li Y, Guo F, Jin T. Biochemical and Biophysical Research Communications; 2016;7(2)7-12.
[25] Ramharack P, Soliman MES. Journal of Biomolecular Structure & Dynamics. 2017:1-16.
[26] Sacramento CQ, de Melo GR, de Freitas CS, Rocha N, Hoelz LV, Miranda M, Fintelman-Rodrigues N, Marttorelli A, Ferreira AC, BarbosaLima G et al: The clinically approved antiviral drug sofosbuvir inhibits Zika virus replication. Scientific Reports. 2017;7: 40920.
[27] Salmaso, V. & Moro, S. (2018). Bridging molecular docking to molecular dynamics in exploring ligandprotein recognition pro- cess: an overview. *Frontiers in Pharmacology*, 9, 923.
[28] Yue, Y.Y., Zhao, S.F., Liu, J.M., Yan, X.Y. & Sun, Y.Y. (2017a). *Chemosphere*, 185, 1056–1062.
[29] Wang, Y.Q., Zhang, H.M., Kang, Y.J., Gu, Y.L. & Cao, J. (2016b). *Journal of Molecular Structure*, 1107, 91– 98.
[30] Cui et al.,2015. Conformation of the T1R3 receptor, causing the active region to expand, which is beneficial to the combination of umami peptides.
[31] Wang, J., Chan, C., Huang, F.W. *et al*. (2017a). Interaction mecha- nism of pepsin with a natural inhibitor gastrodin studied by spec- troscopic methods and molecular docking. *Medicinal Chemistry Research*, 26, 405–413.
[32] Manikkam, V., Vasiljevic, T., Donkor, O.N. & Mathai, M.L. (2016). *Critical Reviews in Food Science and Nutrition*, 56, 92– 112.
[33] Agyei, D. & Danquah, M.K. (2012). Tu, M.L., Cheng, S.Z., Lu, W.H. & Du, M. (2018). *TracTrends in Analytical Chemistry*, 105, 7–17.
[34] Udenigwe, C.C. (2014). *Trends in Food Science & Technology*, 36, 137–143.
[35] Panyayai, T., Sangsawad, P., Pacharawongsakda, E., Sawatdichaikul, O.,

Tongsima, S. & Choowongkomon, K. (2018). *Computational Biology and Chemistry*, 77, 207– 213.
[36] Mandal, S.M., Porto, W. *Biochimie*, 95, 1939–1948. *Journal of Food Science and Technology-Mysore*, 53, 1222–1229.
Ouertani, A., Chaabouni, I., Mosbah, A. *et al*. (2018). *Frontiers in Microbiology*, 9, 1148.
[37] Xue, Z.H., Wen, H.C., Zhai, L.J. *et al*. (2015). Antioxidant activity and anti-proliferative effect of a bioactive peptide from chickpea (Cicer arietinum L.). *Food Research International*, 77, 75–81.
[38] Liu, C.L., Fang, L., Min, W.H., Liu, J.S. & Li, H.M. (2018a). *Food Chemistry*, 245, 471–480.
[39] Dettori, L., Jelsch, C., Guiavarc'h, Y., Delaunay, S., Framboisier, X. & Chevalot, I. (2018). *Process Biochemistry*, 74, 50–60.
[40] Liu, Z., Liu, Y., Zeng, G. *et al*. (2018b). Application of molecular docking for the degradation of organic pollutants in the environmental remediation: a review.
Chemosphere, 203, 139–150.
[41] Hartmann, A., Gostner, J., Fuchs, J.E. *et al*. (2015). *Planta Medica*, 81, 813–820.
[42] Trichez, D., Knychala, M.M., Figueiredo, C.M. *et al*. (2019). Key amino acid residues of the AGT1 permease required for mal- totriose consumption and fermentation by Saccharomyces cere- visiae. *Journal of Applied Microbiology*, 126, 580–594.
[43] Xu, W., Ni, D.W., Yu, S.H., Zhang, T. & Mu, W.M. (2018). *International Journal of Biological Macromolecules*, 116, 335–345.
[44] Li, J.Q., Geng, S., Liu, B.G., Wang, H.B. & Liang, G.Z. (2018). Self-assembled mechanism of hydrophobic amino acids and beta- cyclodextrin based on experimental and computational methods. *Food Research International*, 112, 136–142.
[45] Goel, A., Gajula, K., Gupta, R. & Rai, B. (2018). Insilico predic- tion of sweetness using structure-activity relationship models. *Food Chemistry*, 253, 127–131.
[46] Goel, A., Gajula, K., Gupta, R. & Rai, B. (2018). Insilico predic- tion of sweetness using structure-activity relationship models. *Food Chemistry*, 253, 127–131.
[47] Du, X.P., Bai, M.L., Huang, Y. *et al*. (2018). *Journal of Functional Foods*, 48, 551–557.
[48] Zul immuno- suppression caused by Nosema ceranae. *PLoS ONE*, 12, e0187726.
fakar, M.H., Chan, L.M., Rehman, K., Wai, L.K. & Heard,C.M. (2018). *An Official Journal of the American Associ- ation of Pharmaceutical Scientists*, 19, 1116– 1123.
[49] Kotler, S.A., Walsh, P., Brender, J.R. & Ramamoorthy, A. (2014). Differences between amyloidbeta aggregation in solution and on the membrane: insights into elucidation of the mechanistic details of Alzheimer's disease. *Chemical Society Reviews*, 43, 6692– 6700.
[50] Rong, C.C., Chen, H.Q., Tang, X. *et al*. (2019). Characterization and molecular docking of new 17 fatty acid desaturase genes from Rhizophagus irregularis and Octopus bimaculoides. *Rsc Advances*, 9, 6871–6880.
[51] Zhu, Z., Chen, J., Wang, G. *et al*. (2019). Ceramide regulates inter- action of Hsd17b4 with Pex5 and function of peroxisomes. Biochimica et biophysica acta. *Molecular and Cell Biology of Lipids*, 1864(10), 1514– 1524.
[52] Glavinic, U., Stankovic, B., Draskovic, V. *et al*. (2017).Dietary amino acid and vitamin complex protects honey bee from
[53] Subramanian, V.S., Sabui, S., Teafatiller, T., Bohl, J.A. & Said, H.M. (2017). *American Journal of Physiology-Cell Physiology*, 313, C228–C238.
[54] Borah, P.K., Sarkar, A. & Duary, R.K. (2019). Watersoluble vitamins for controlling starch digestion: conformational scrambling and inhibition mechanism of human pancreatic alpha-amylase by ascorbic acid and folic acid. *Food Chemistry*, 288, 395–404.
[55] Saini, V. & Kumar, A. (2014). *Sar and Qsar in Environmental Research*, 25, 777–790.
[56] Zhang, Q.L. & Ni, Y.N. (2017). *Rsc Advances*, 7, 39833–39841.
[57] Wang, J.P., Dong, J., Duan, C.F. *et al*. (2016a). *Journal of Agricultural and Food Chemistry*, 64, 7957– 7965.
[58] Argudin, M.A., Mendoza, M.C. & Rodicio, M.R. (2010). Food poisoning and staphylococcus aureus enterotoxins. *Toxins*, 2, 1751– 1773.
[59] Shimamura, Y., Utsumi, M., Hirai, C. *et al*. (2018). Binding of cate- chins to staphylococcal enterotoxin A. *Molecules*, 23, pii: E1125.
[60] Kar, S., Mishra, R.K., Pathak, A., Dikshit, A. & Rao, G.N. (2018). *Journal of Molecular Structure*, 1156, 433– 440.
[61] Rajarathinam, G. & Dronamraju, S.V.L. (2018). *In vitro* and *in silico* antimicrobial activity of sterol and flavonoid isolated from Tri- anthema decandra L. *Microbial Pathogenesis*, 121, 77–86.
[62] Cleland, W.W. (2010). The low-barrier hydrogen bond in enzymic catalysis. *Advances in Physical Organic Chemistry*, 44(44), 1–17.
[63] Wu, C., Ma, W.C. & Hua, Y.F. (2019a). *International Journal of Food Science and Technology*, 54, 231–239.

Doi: 10.2016-53692176; DOI Link :: http://doi-ds.org/doilink/06.2020-22786874/