IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Review On Molecular Docking In Nutraceutical Research; Unveiling Molecular Targets For Disease Management

Miss. Apurva S. Rupnar[1], Dr. Laxmikant N. Barde[2], Miss. Bhagyashali V. Pawar[3], Miss. Prajakta S. Paikrao[4], Mr. Ashish H. Umak[5]

Jagadambha Institute Of Pharmacy & Research, Kalamb, Maharashtra 445401, India[1-3]

ABSTRACT:

Recent years have seen a huge increase in interest in nutraceuticals, which are bioactive substances produced from food sources that may have positive effects on health. These compounds have both medicinal and preventative uses. Molecular docking has become a potent computational method to investigate the complex interactions between bioactive compounds and their target proteins as the market for novel and efficient nutraceuticals grows. An extensive summary of the state of molecular docking applications in nutraceutical research is given in this article. This review also highlights the pivotal role of molecular docking in unraveling the complex interactions between nutraceutical compounds and their biological targets. By providing insights into the current landscape of nutraceutical research through the lens of molecular docking. This review aims to contributeto the advancement of knowledge in the field and foster the development of novel and effective nutraceutical interventions for promoting human health.

Keywords:

Molecular Docking, Nutraceuticals, Bioactive Compounds, Molecular Modelling,Computational Biology

INTRODUCTION

In recent years, molecular docking has emerged as a crucial component of in-silico drug development. This method entails forecasting the atomic-level interactions between a tiny chemical and a protein.[1] A technique for examining how a ligand, or tiny molecule, interacts with a target molecule is called molecular docking. By identifying the preferred orientation of minimum free binding, it predicts the binding affinity of the ligand to form a stable complex with the protein.[2] This helps to untangle the crucial metabolic processes involved in this interaction and allows researchers to examine the behavior of tiny compounds, such nutraceuticals, within the binding region of a target protein. A vast array of important molecular targets with therapeutic value have been revealed by the wealth of structural data on proteins and protein-ligand complexes that have been collected through chemical synthesis, purification, X-ray crystallography, and Nuclear Magnetic Resonance Spectroscopy (NMR). [3] Drug research and academic fields actively use a variety of computational tools and algorithms for molecular docking techniques that have been created. These alternatives include both free and paid options.[4–7] Among the many popular docking applications available, AutoDock Vina, Glide, and AutoDock GOLD stand out as excellent options. These programs include Discovery Studio, Surfex, MCDock, MOE, FlexX, DOCK, LeDock, rDock, ICM, Cdcker, Ligand Fit, FRED, and UCSF Dock, based on their exceptional performance and high scores.[8,9,10] Contemporary docking programs still face a challenge when it comes to accommodating flexible receptor docking, particularly regarding the flexibility of the receptor backbone.[11]

Docking studies provide a way to assess, filter, and forecast the ligand-receptor complex's computational electrostatics. Predicting the shape, position, and orientation (pose) of the ligand—usually a small molecule—within the protein binding site is the first of the two basic steps in the molecular docking process. Second, applying a grading system to assess the pose's quality. The experimental binding mode should ideally be faithfully replicated by the sampling process, and it should be ranked highest among all generated poses by the scorin g function. [2] When comparing dry lab to in vivo laboratory experiments, there is a clear advantage in terms of time and resource efficiency.[12]The use of molecular docking in drug discovery and design has been well-established[13, 14]. The use of molecular docking in food science has garnered a lot of attention recently. Molecular docking is specifically being used by researchers to verify the molecular targets of nutraceuticals for the management of disease. [15] Food items, extracts, or derivatives such as vitamins, minerals, amino acids, herbs, and enzymes are referred to as nutraceuticals. These compounds are nutritionally valuable and may also have pharmacological benefits.[16]Nutraceuticals are naturally occurring substances that come from food and have health-promoting properties.[17] The popularity of these compounds has increased recently due to their potential to prevent and manage chronic illnesses such as diabetes, cancer, cardiovascular problems, and neurological disorders. [18,19] Molecular docking analyses are essential for nutraceutical research before in vitro investigations are conducted. The objective of this review is to explore the key molecular docking applications aimed at evaluating the potential health-promoting effects of nutraceuticals.[20]

MOLECULAR DOCKING

Overview:

Among these techniques, molecular docking is the most widely used approach in computational structure-based drug design (SBDD), having been used since the early 1980s.[21] The molecular docking approach involves several processes, such as ligand preparation, protein-ligand complex binding energy estimation, protein 3-D structure preparation, and analysis.[22] Docking is often used to forecast the affinity and activity of tiny medicinal drugs by predicting how they will align with their protein targets.[23] This interaction includes hydrophobic, van der Waals, ionic, and hydrogen bonds, among other non-covalent connections. Protein-protein, protein-ligand, and protein-nucleotide interactions can all be investigated using molecular docking experiments. [24]

Types of docking:

The basic methodology of molecular docking can be categorized into three ways:

Induced fit docking:

Both the receptor and the ligand are flexible. By adaptably attaching to the receptor's active region, the ligand maximizes the bonding forces between the two molecules. The concept of complementary interactions between ligand and protein is embodied in this process.

Lock and key docking:

The Lock and Key theory states that tight binding is demonstrated by the rigidity of the ligand and receptor. The foundational idea of three-dimensional complimentary is established by this theory.[25]

Ensemble docking:

This method clarifies the intricate and versatile conformational states of proteins. A collection of protein structures is used in concert to bind with the ligand.[26,27]

Common search Algorithms:

Docking is essential to the logical design of pharmaceuticals. Considering the importance of docking studies in pharmacology and biology, a lot of work has gone into improving docking prediction algorithms. The ideal orientation of molecules when they are united to form a stable complex is predicted mathematically.[28] Finding every possible route and shape for the protein to take when interacting with the ligand is the main objective of the search method.[29]

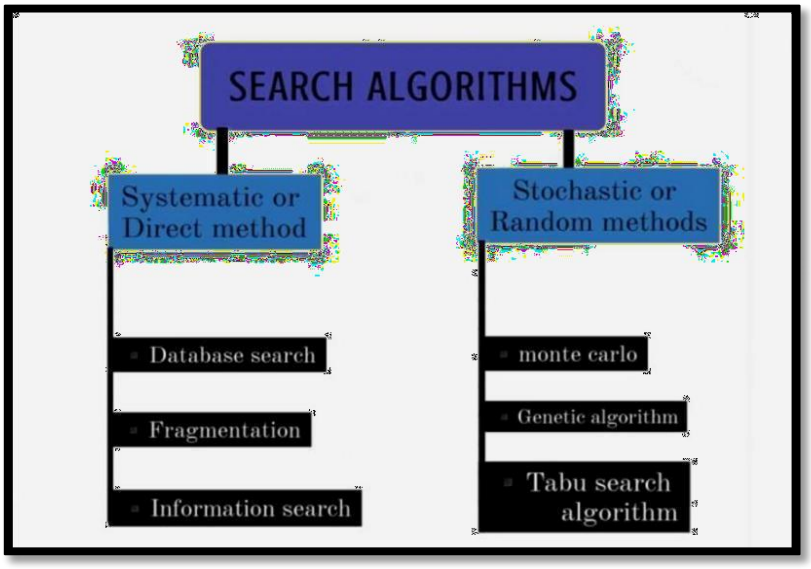

Figure 1: Classes of search algorithm mechanisms

A. Systematic or direct method

There are three subtypes of systematic methods as follows:

i. **Conformational search:**
The structural parameters of the ligand undergo gradual changes in torsional (dihedral), translational, and rotational degrees of freedom.[30,31]

ii. **Fragmentation:** In the molecular docking process, several fragments can dock together to form connections. Alternatively, each fragment might be anchored separately, starting with the first one to be docked and then adding pieces outward in successive steps from that initial bound point. For this, tools like Flex XTM, DOCK, LUDI, etc., are used.

iii. **Database Search:** With this method, it is possible to produce many reasonable conformations for every small molecule that is already registered in the database and then dock them as stiff bodies. One example of the tools used in this process is FLOG.

B. Stochastic methods or Random methods

Stochastic methods carry out the conformational search by randomly modifying the structural parameters of the ligands.[32] There are also three subtypes of stochastic method which are;

i. **Monte Carlo:**
This method entails placing ligands randomly in the receptor binding site, scoring the arrangement, and subsequently generating a new configuration. Instruments like MCDOCK, ICM, etc., are utilized in this process.

ii. **Genetic algorithm:**
The procedure starts with a population of poses, where the "gene" is the configuration and location with respect to the receptor, and the "fitness" is the score. The fittest individuals undergo transformations, hybridization, and other operations to create the next generation, and this cycle is repeated.[37, 38] It employs applications like as AutoDock, GOLD, and others.[33,34]

iii. **Tabu search:**
A tabu search algorithm's basic idea is to take into account previously investigated conformational space regions. The root mean square difference between the present molecular coordinates and each molecule's previously recorded conformations is calculated to determine whether a molecular conformation is acceptable. One tool that makes use of a tabu search algorithm is PRO_LEADS.[35, 36]

Scoring functions:

In structure-based virtual screening, ligand conformation expectations are evaluated and prioritized. The success of computations depends on the ability to differentiate between proper and erroneous poses and identify "true" ligands, even in the case of accurate predictions of binding conformations. Thus, it is essentially essential to establish trustworthy scoring systems and schemes. Protein–ligand interactions may now be quantitatively modeled and binding affinity can be predicted thanks to the development of free-energy simulation tools. [37, 38]

a) Force field-based approach:

In order to determine the binding affinity, it takes into account the impact of non-bonded interactions such torsional deviation, hydrogen bonding, and van der Waals forces in addition to bond-like angle bonding. In this case, tools such as AutoDock, DOCK, GoldScore, etc., are used.[39]

b) In an empirical function approach:

It is based on repeated linear regression analysis of a set of carefully chosen complex structures—a set of protein–ligand complexes with known binding affinities that include certain functional groups and interaction types. Examples include the stacking of aromatic rings, the N–O hydrogen connection, the O–O hydrogen bond, and the salt scaffold. Technologies like AutoDock scoring, ChemScore, LUDI score, and so forth [40]

c) In a knowledge-based approach:

It statistically evaluates a set of complex structures, offering insights into elements, atoms, and functional groups that can be potentially segregated into pairings. Instruments like PMF and Drug Score are employed.[41]

d) The consensus approach combines:

The assessment or ranking obtained from multiple evaluation methods in various configurations.[29]

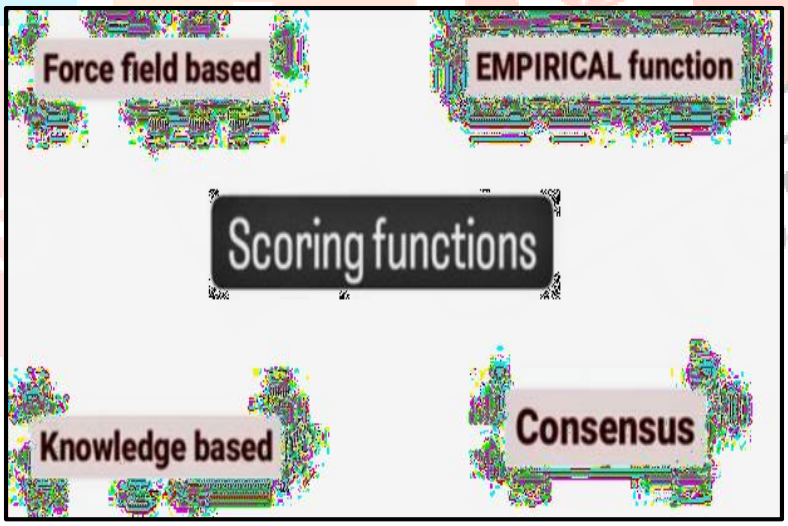

Figure 2: Classes of scoring function mechanisms

S.No.	Software tools	Algorithm	Scoring term	Advantages
1.	Glide (Grid-based Ligand Docking with Energetics)	Monte Carlo	Glide score	Lead discovery and lead optimization
2.	AutoDock	Lamarkian genetic algorithm	Empirical free energy function	Adaptability to user defined input
3.	GOLD (Genetic Optimization for Ligand Docking)	Genetic algorithm	GoldScore, ChemScore, ASP (Astex Statistical Potential), CHEMPLP (Piecewise Linear Potential), User defined	Allows atomic overlapping between protein and ligand
4.	Surflex	Surflex-Dock search algorithm	Bohm's scoring function	High accuracy level by extending force-fields
5.	FlexX	Incremental reconstruction	Modified Bohm scoring function	Provides large number of conformations
6.	ICM (Internal Coordinate Modelling)	Monte Carlo minimization	Virtual library screening scoring function	Allows side chain flexibility to find parallel arrangement of two rigid helixes
7.	MVD (Molegro Virtual Docker)	Evolutionary algorithm	MolDock score	High accuracy level of predicting binding mode
8.	Fred (Fast Rigid Exhaustive Docking)	Exhaustive search algorithm	Gaussian scoring function	Nonstochastic approach to examine all possible poses within protein active site
9.	LigandFit	Monte Carlo method	LigScore, Piecewise Linear Potential (PLP), Potential of Mean Force (PMF)	Generates good hit rates based on LigScore
10.	FITTED (Flexibility Induced Through Targeted Evolutionary Description)	Genetic algorithm	Potential of Mean Force (PMF), Drug Score	Analyzes effect of water molecules on protein-ligand complexes
11.	GlamDock	Monte Carlo method	ChillScore	Provides provision of two-dimensional analysis to screen ligands by targeting protein
12.	vLifeDock	Genetic algorithm	PLP score, XCscore	Facilitates batch docking
14.	iGEMDOCK	Genetic algorithm	Empirical scoring function	Highly significant in post-screening analysis

Figure 3. List of software tools for docking and their algorithms. [42]

Molecular docking software.

In drug discovery, developing a molecular docking tool is crucial, especially when it comes to virtually evaluating phytochemicals or nutraceuticals as possible therapeutic agents.5. The first docking program was created by Irwin Kuntz of the University of California in the middle of the 1980s, and attempts are still being made to enhance docking computations. New developments in docking techniques seek to assess an enzyme's potential and forecast its natural substrates.[43] Modern docking techniques anticipate an enzyme's activity by identifying its natural substrates. Finding the protein's superfamily helps to focus the search for potential substrates and reaction types, which makes it possible to forecast protein complexes with accuracy. [44]

Methodologies of ranking docked molecules.

The docked molecules are meticulously rated through a range of methods and frameworks. This section emphasizes the often used. The idea behind DOCK 3.5.x is that by restricting the transition state that the substrate prefers, enzymes catalyze processes. Furthermore, the protein's stiffness is preserved by hydrolysis mechanisms related to the amidohydrolase superfamily. As a result, compared to docking substrates, docking molecules that line up with transition states should yield a stronger signal.[46] Glide's program narrows down possible substrates by identifying enzymes within a particular subgroup of the enolase superfamily. By fine-tuning and rescoring the docked complex with an advanced physics-based scoring system, positional precision is improved. For increased accuracy, this method also allows the mobility of receptor side chains.[46]

Highlights of molecular docking software.

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

Dock: The UCSF Chimera team developed a molecular docking program called Dock that allows tiny compounds to be easily deposited into receptor-binding sites. It evaluates the ligand-receptor binding affinity using a grid-based method and adds scoring systems to score the resulting poses. The application is easy to use and supports a number of input file formats, including SDF, MOL2, and PDB. Through UCSF, one can gain access to Dock. http://dock.compbio.ucsf.edu/.

Autodock: The Scripps Research Institute's AutoDock molecular docking program is extensively used and open-source. It uses a Lamarckian genetic method to optimize ligand placement in a receptor binding site, enabling both rigid and flexible docking. The program accepts many input file formats, including PDB, MOL2, and SDF, and includes multiple scoring methods for determining the affinity of ligand-receptor binding. You can get AutoDock through the Scripps Research Institute. http://autodock.scripps.edu

GOLDTM *(Genetic Optimization for Ligand Docking):* It is a software for protein-ligand docking with unique features. It uses computations that integrate spine and side chain adaptability, enabling the usage of user-defined scoring systems that can change as circumstances change. Both conformational and non-reinforced contact information serve as the foundation for the energy functions. GOLD offers a range of docking options, including the ability to automatically handle metal atoms when they are correctly set up in the protein data file and remove crystallographic water molecules from the ligand binding site. Gold 5.2 for protein-ligand docking, Hermes 1.6 for thorough protein visualization, and Gold Mine 1.5 for effective docking result analysis are all included in the most recent version of GOLD Suite 5.2.
Access to this software is available at http://www.ccdc.cam.ac.uk/ products/lifesciences/gold

Representation of molecular docking:

Generally, the Docking process can be represented in a flowchart as shown in the Fig.4

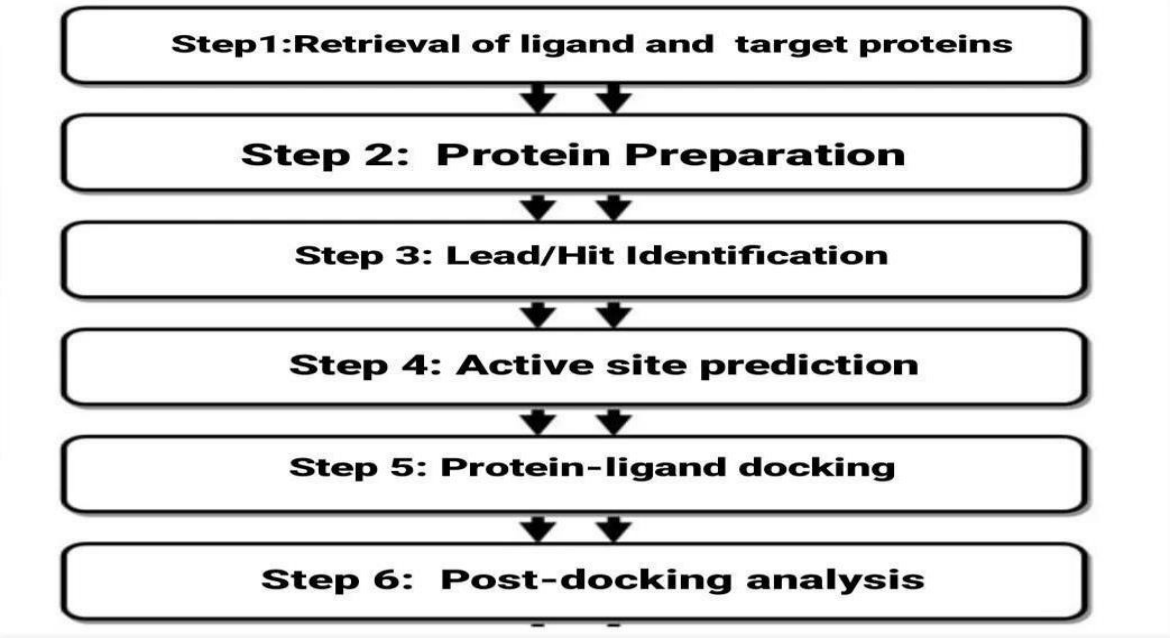

Figure 4. A prototype flow chart of a molecular docking study.

1. **Retrieval of protein and ligand structure:** Docking requires the identification of workable target proteins and ligands. Finding appropriate target proteins and ligands is essential for conducting docking successfully. Verify whether the target protein is present in the Protein Data Bank (PDB) (http://pdb.org) or Swiss UniProt (http://expasy.org/sprot) databases. If not, utilize tools for homology modeling such as I-TASSER or the Swiss Model Repository (http://swissmodel.expasy.org/repository/). Use the Zinc (http://blaster.docking.org/zinc/), ChmBl, or PubChem databases to find ligands. Consider creating the desired ligand from scratch with ChemDraw or ChemSketch if it cannot be found. [47]

2. **Protein Preparation:** Preparing proteins is essential for accurate docking simulations. Get the structure from PDB or programs such as SWISS MODELLER, finish it by adding atoms, and then minimize energy to reduce structural limitations. Establish the protonation states of ionizable residues for precise electrostatic interactions. To simplify the system, eliminate superfluous ligands and water molecules. In order to optimize and refine the protein structure for effective molecular docking studies, supply the appropriate force field parameters at the end.[48]

3. **Lead or hit identification:** Chemical variety, known biological activity, and drug development potential are taken into account while choosing ligands for docking. Charges are allocated, conformers are created, and shape is optimized in order to get ligands ready for docking. By taking these precautions, ligands are fully represented and docking simulation accuracy is improved. [49]

4. **Active site prediction**: It is important to concentrate on the pertinent place of interest when predicting the active site of a protein after processing. Water molecules and heteroatoms are generally ignored in this process because it's possible that they don't directly affect the binding interactions with possible medication compounds. Eliminating these extraneous components aids in improving the analysis to pinpoint the actual active spot for more research.[50,51]

As highlighted below:

i. Site-directed docking- Here, first, identify the protein–ligand binding site and then dock theligand.
ii. Blind docking- Here, the docked ligand is directly onto the complete receptor structurewithout prior knowledge of the binding site [52]
iii. Docking with a standard- Here, you dock the protein with the test ligands and/orstandard small molecule(s). The standard ligand facilitates the prediction of the relevant binding pocket.[53]

Although it's not always required, calculating the inhibition constant evaluates the inhibitory potential and ligand-protein binding affinity. The study objectives, experimental methodology, and research topic all influence its applicability. The scoring function in protein-ligand docking helps with interaction analysis and gives information about the strength of the binding by giving a score to the best-docked ligand complex. Protein-ligand interaction. Precisely, the necessity of computing the inhibition constant differs according to the objectives of the research. The scoring function in protein-ligand docking assesses and ranks the best-docked ligand complex, providing information about the strength of the contact and facilitating the study of binding kinetics.[54] In post-docking analysis, ligand-protein interactions are assessed. Predicted interaction energy is used to compute ligand binding affinity, and ligands are ranked based on this calculation. Examination of docked structures identifies key interactions like hydrogen bonds and hydrophobic interactions, offering insights into ligand mechanisms. This information guides further structural optimization for promising candidates in drug development.[55]

General application of molecular docking:

i. **Hit Identification:** In hit identification docking, a scoring function evaluates potential drug molecules for their likelihood to bind to a target protein. This in silico screening helps identify molecules with high binding affinity. [56]

ii. **Lead Optimization:** Docking helps determine the specific location and orientation (binding mode or pose) in which a ligand binds to a protein. This information can then be utilized to design more powerful and selective analogs for drug development.[57]

iii. **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. [58]

iv. **Molecular dynamics simulation:** Combining molecular docking with molecular dynamic simulations allows for an exploration of the dynamic aspects of protein-ligand interactions. These simulations provide insights into conformational changes triggered by ligand binding and assess the stability of the resulting complexes.[59] Several software tools combine molecular docking and dynamics simulation. These include frequently used software like AutoDock, Vina, Glide, and GOLD. In addition to molecular docking, they provide capabilities for conducting molecular dynamics simulations, allowing for the exploration of protein–ligand interactions over time and the analysis of their dynamic behaviour.

v. **Structure elucidation:** Molecular docking is handy for revealing the structure of unknown proteins. It predicts how small molecules bind, creating a preliminary model. This model is refined with experimental data to get an accurate representation of the protein's structure.[2]

NUTRACEUTICALS:

In 1989, Dr. Stephen DeFelice, the organizer behind the Establishment for Advancement in Medication, authored the term "nutraceutical" by joining "sustenance" and "pharmaceutical."[60] A combination of "sustenance" and "drug," the term alludes to food or food items conveying medical advantages, incorporating infection counteraction and therapy. This incorporates different structures like detached supplements, dietary enhancements, explicit weight control plans, hereditarily designed food varieties, homegrown items, and handled things like oats, soups, and beverages.[61] Food varieties and supplements are significant for the body's ordinary working, adding to overall wellbeing and reducing the risk of illness. Nutraceuticals, thought about as restorative food varieties, assume a key role in safeguarding prosperity, further developing wellbeing, impacting resistance, and forestalling/treating explicit illnesses. Logical proof from research articles upholds the viability of nutraceuticals in overseeing different medical issues, making them a huge part of advancing individual health.[62]While they have contrasts, nutraceuticals and utilitarian food sources are at times utilized reciprocally. The two terms portray food items that give extra medical advantages beyond essential nutrition.[63,64] Individual inclinations and mastery fundamentally impact the idea of nutraceuticals. For instance, cardiologists could focus on dietary enhancements related to lessening risk factors for heart illnesses, like those decidedly influencing hypertension, hypercholesterolemia, and the decrease of free extremists or platelet-subordinate thrombotic action. Cardiologists track down specific significance in phytosterols, N-3 unsaturated fats, quercetin, and grape flavonoids.[19] Alternately, oncologists might underscore nutraceuticals with anticarcinogenic impacts, including those that support cell reinforcement and microsomal detoxification frameworks or restrain the development of existing cancer.[65]

CLASSIFICATION OF NEUTRACEUTICALS

Several authors used different methods to classify nutraceuticals. The review, however, examines nutraceutical classification through the lens of the Bairagi and Patel food availability framework.

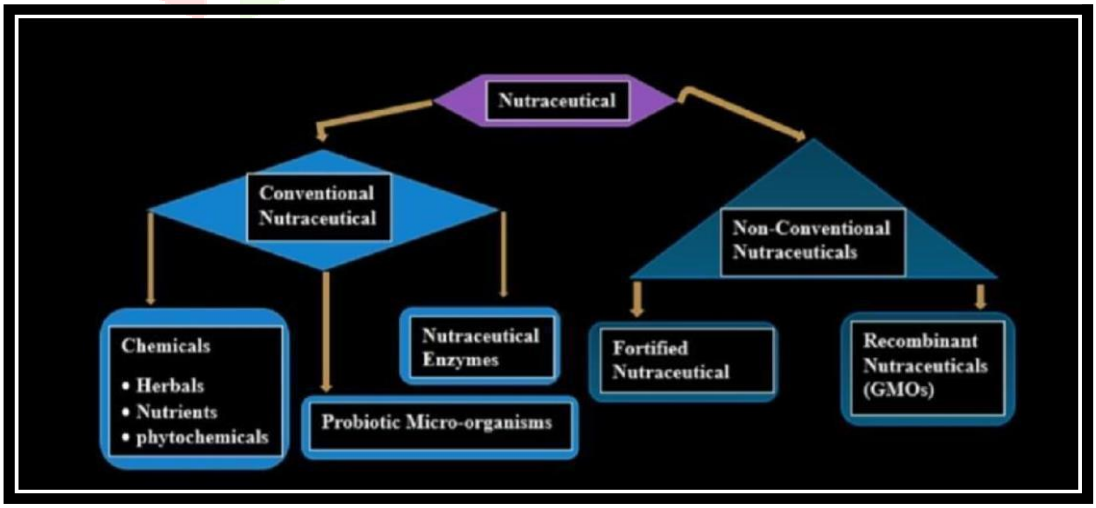

Figure 5. Classification of Nutraceutical [17]

1. Conventional nutraceuticals:

Herbal extracts, vitamins, minerals, and plant-based supplements are examples of traditional nutraceuticals with a long history of therapeutic use dating back millennia. Their health benefits are well-established and readily available in the market, backed by a wealth of studies.Traditional nutraceuticals have gained widespread acceptance, including probiotics, omega-3 fatty acids, vitamin C, and vitamin D.[17,66]

a) Chemicals:
These materials fall into three primary categories: phytocompounds, herbals, and nutrients. Like vitamins and minerals, nutrients are essential to maintaining regular body functions.[79] Herbs, which are derived from plants and include things like ginseng, ginger, and turmeric, are thought to provide a variety of health benefits. Conversely, phytocompounds refer to bioactive plant compounds such as polyphenols, flavonoids, and carotenoids that are believed to have medicinal qualities.[67]

b) Probiotic micro-organisms:
Probiotics are live bacteria that can be found in fermented foods like yogurt, kefir, and sauerkraut. Consuming probiotics may have health advantages. It is thought that these microbes improve gut health by preserving the equilibrium of good bacteria in the gut microbiome. They might also help strengthen the immune system by giving it the energy it needs to lower inflammation.[17]

c) Nutraceutical enzyme:
Nutraceutical enzymes are specialized proteins that speed up chemical reactions in the body and can be used therapeutically when taken as supplements. Digestive enzymes can improve food digestion, while proteolytic enzymes, for instance, may assist lower inflammation.[65]

2. Non-Conventional nutraceuticals :
Nutraceuticals of unusual origins, such as fungi, algae, and animal byproducts, are becoming more and more popular. This include novel proteins, unusual fruits, and unique bioactive substances. Despite growing interest in these nutraceuticals, studies are currently being conducted to determine their efficacy, safety, and health benefits. Examples include the recently-recognized spirulina, chlorella, mushroom extracts, and insect-based proteins.[68]

a) Fortification Nutraceuticals:
Fortified nutraceuticals are products that have been enhanced with additional vitamins, minerals, and nutrients to increase their nutritional value. This method seeks to provide health advantages over their inherent makeup. Fortified nutraceuticals, as defined by Rajasekaran and Kalaivani62, are foods or food items that have been supplemented with extra nutrients to provide health benefits beyond their usual nutritional composition. These include, for instance.[69]
i) Fruit juices that have been fortified are enhanced with extra vitamins and minerals to improve their nutritious content. For instance, to promote bone health, calcium and vitamin D may be added to orange juice.
ii) Breakfast cereals that have been fortified with extra vitamins and minerals are known as fortified cereals. For instance, iron deficiency anemia may be avoided by fortifying specific foods.
iii) Vitamin D is added to fortified milk to improve bone health and make calcium absorption easier.
iv) Enhanced energy beverages Energy drinks may contain vitamin and mineral supplements to improve energy metabolism.

b) Recombinant Nutraceuticals:
Novel nutraceuticals are recently developed products made from genetically modified organisms (GMOs) that are intended to yield certain nutrients or bioactive substances. Compared to their natural counterparts, these innovative products are intended to offer extra health benefits.[70]
Here are some examples of cutting-edge nutraceuticals:
i) Antibodies produced using recombinant DNA technology are referred to as recombinant antibodies. Recombinant monoclonal antibodies, for example, are used to treat autoimmune diseases and cancer.
ii) The process of making recombinant vitamins involves using recombinant DNA technology. For example, vitamin B12 deficiency is treated using recombinant vitamin B12.
iii) Human insulin is one example of a recombinant protein that is produced by using recombinant DNA technology and is vital for the management of diabetes.
iv) Recombinant enzymes, such as lactase, which is necessary for the digestion of lactose in people with lactose intolerance, are created by using recombinant DNA technology.

Industrial dynamics of nutraceuticals

Nutraceuticals' dynamic action—a combination of nutritional and medicinal—has made them more popular than medications among the general public and healthcare professionals. The spike in growth of the nutraceuticals sector can be ascribed to three factors: a rise in healthcare indicators, a greater awareness of nutritional advantages, and higher demand.[71]

Nutricosmetics:

Demand for nutricosmetics, which are products made to enhance the appearance and health of skin, hair, and nails, is rising. Nutraccosmetics is expected to become more popular as people place a larger importance on holistic and natural ways to improve their physical beauty. According to Taeymans et al., this trend is expected to continue because consumers are becoming more health-conscious and looking for a variety of benefits from the products they buy.[72]

Sports nutrition space:

The increase in popularity of sports and fitness-related activities is matched by a rise in the market for goods designed to improve general health and athletic performance. This tendency, as Bairagi and Patel point out, has led to the sports nutrition market's explosive growth, which shows no signs of slowing down.[16]

Seed oil as nutraceutical deposit:

Flaxseed oil and chia seed oil are two prominent seed oils that are rich in numerous minerals and vital fatty acids.[73] These oils are finding their way into a wider range of nutraceutical goods, including functional foods and supplements. Given customer preferences for plant-based nutrient sources, it is expected that seed oils will continue to be used as a nutraceutical resource.[74]Due to customers' increased health consciousness and preference for natural solutions over conventional medications, the nutraceuticals industry is expanding significantly. Innovative delivery techniques, customized nutrition, and the incorporation of blockchain and artificial intelligence for product traceability and quality control are some of the major trends in the business. Notably, there's a rise in the use of nutraceuticals for mental health that's been matched by an increased demand for plant-derived components sourced sustainably. In the evolving landscape, companies emphasizing innovation and sustainability are poised for significant success.[75]

Molecular docking validations of nutraceuticals targets in diseases:

Molecular docking validation is a computer technique that is increasingly being used in nutraceutical research to find possible targets for various disease management. Nutraceuticals are naturally occurring substances that may be beneficial to one's health and are often found in foods such fruits, vegetables, and herbs.[88] Interest in using nutraceuticals as an adjunctive approach to traditional medical treatments has grown due to the rising incidence of chronic illnesses like diabetes, heart disease, and cancer.[76] Molecular docking validation provides a more effective and economical way to evaluate possible treatments prior to investing in costly clinical trials by helping researchers identify potential targets for nutraceuticals in disease management.[77] This method lessens the need for animal experimentation while developing novel medications, which advances ethical drug discovery. [78]

Moleculer docking discovery of nutraceutical targets:

Sub-atomic docking is a PC-based technique for determining collaborations between little particles (like nutraceuticals) and bigger biomolecules like chemicals, receptors, RNA, DNA, and proteins. It incorporates mimicking these atomic connections to acquire experiences about restricting proclivity, restricting sites, and possible components of activity.

Enzyme: Catalysts, crucial for body responses, are impacted by nutraceuticals like curcumin, resveratrol, quercetin, and hesperidin. Curcumin, for example, represses COX-2, an irritation-related catalyst. Atomic docking predicts restricting and communication strength, supporting grasping instruments, and restorative potential.

Receptors: Receptors, proteins restricting particles like chemicals, synapses, and medications, trigger cell reactions. Nutraceuticals additionally impact receptors; for example, resveratrol initiates sirtuin proteins connected with cell digestion and maturation.

Epigenetic markers: As indicated by late examinations. Epigenetic adjustments, fit for altering quality articulation without DNA succession changes, are key concentrations for nutraceuticals. Atomic docking predicts communications with proteins like HDACs, DNMTs, and receptors like estrogen and androgen receptors, impacting transgenerational impacts through epigenetic adjustments.

Other proteins: Nutraceuticals can possibly influence different proteins like carriers, particle channels, and primary proteins. A model is hesperidin, which has been shown to hinder alpha-glucosidase, a chemical responsible for carb breakdown.[88,101] To grasp how nutraceuticals work and their likely remedial impacts, sub-atomic docking predicts where the nutraceutical ties are and the strength of their association with the protein target.[79]

Application of molecular docking in nutraceutical for disease management:

1. ***Identification of Bioactive Compounds:*** Molecular docking aids in identifying bioactive compounds within nutraceuticals that can interact with specific disease-related targets, paving the way for targeted dietary interventions.[80]
2. ***Inhibition of Disease-Related Enzymes*:** Docking studies help predict how bioactive compounds in nutraceuticals may inhibit disease-related enzymes, such as those involved in inflammation or metabolic disorders.[81]
3. ***Anti-Inflammatory Effects:*** Molecular docking contributes to understanding how anti-inflammatory compounds in nutraceuticals interact with mediators and receptors associated with inflammation, aiding in disease management.[82]
4. ***Antioxidant Activity: Antioxidant Activity:*** Docking studies assist in elucidating how antioxidants in nutraceuticals interact with free radicals and oxidative stress-related biomolecules, relevant for diseases associated with oxidative damage.[83]
5. ***Modulation of Immune Response:*** Docking helps in understanding how bioactive compounds modulate immune responses, contributing to the development of nutraceuticals for conditions where immune dysregulationis implicated.[84]
6. ***Metabolic Syndrome Management:*** Molecular docking aids in identifying nutraceutical compounds that interact with targets associated with metabolic syndrome, offering potential dietary strategies for managing conditions like diabetes and obesity.**[85]**
7. ***Cancer Prevention and Treatment:*** Docking studies contribute to identifying bioactive compounds in nutraceuticals with potential anticancer properties, aiding in the development of dietary strategies for cancer prevention and adjunctive treatment.[86]
8. ***Neuroprotective Effects:*** Molecular docking helps understand how nutraceutical compounds may exhibit neuroprotective effects by interacting with receptors involved in neurodegenerative diseases.[87]
9. ***Cardiometabolic Health:*** Docking studies contribute to identifying nutraceutical compounds that positively impact cardiovascular health, influencing targets related to blood pressure regulation, cholesterol metabolism, and vascular function.[88]

LIMITATION OF MOLECULAR DOCKING:

Overall, scoring capabilities in sub-atomic docking face difficulties in precisely foreseeing complex associations like solvation impacts and entropy changes, making it vital to mindfully decipher results. Propels in refining these forecasts could altogether improve the dependability of sub-atomic docking studies. Positively, scoring capabilities frequently ignore specific urgent intermolecular collaborations like halogen holding, which exploration has displayed to assume a critical role in protein-ligand restricting fondness. Perceiving and integrating such collaborations can refine the exactness of computational docking forecasts. Precisely dealing with water particles in the limiting pocket during docking remains a difficult errand for two primary reasons. X-beam gems, first and foremost, require exact hydrogen organization, prompting hardships in distinguishing water atoms that might connect among ligands and receptors. Besides, there's an absence of solid hypothetical ways to deal with foreseeing what ligands mean for water particles and the related hydrogen holding organization, making it difficult to expect the dislodging of water atoms by possible ligands. This issue requires huge consideration and headway sooner rather than later. Totally, managing unbending receptors in docking represents a critical test as proteins can display different compliances in view of the ligands they tie. Docking with an unbending receptor frequently catches just a solitary compliance, possibly bringing about bogus negatives. This restriction arises from dismissing the unique idea of proteins that can move between various states with comparative energies. Recognizing and tending to this conformational adaptability is urgent for working on the precision of docking expectations. Precisely, the effect on askew proteins is trying to anticipate in computational screens and is generally surveyed through creature and human preliminaries for a more exact understanding.[89]

FUTURE PERSPECTIVE:

A potent technique for identifying the molecular targets of nutraceuticals in the treatment of diseases is molecular docking. Molecular docking has enormous potential for use in nutraceutical research in the future. We expect increasingly precise predictions of the interactions between bioactive chemicals and molecular

targets as computing power and algorithms improve. This will hasten the process of discovering new nutraceuticals for the treatment of illness. Moreover, the amalgamation of artificial intelligence and big data would facilitate an all-encompassing comprehension of sophisticated biological systems, revealing complex chemical processes. A more individualized approach to illness management and wellbeing is made possible by this changing field, which offers more focused and efficient nutraceutical therapies.

CONCLUSION:

Molecular docking is a useful tool for identifying molecular targets for the therapeutic use of nutraceuticals. It assists in identifying possible therapeutic targets by predicting binding affinity and shape. The importance of molecular docking in drug discovery is increased by the availability of databases and the development of computer tools. By using it, the drug discovery process becomes more successful and efficient while spending less money and time on traditional experimental procedures. Therefore, using molecular docking in dietary supplement research has great potential for identifying new therapeutic targets and creating secure and efficient supplements for the treatment of disease.

REFERENCES:

1. Sahoo, R. N., Pattanaik, S., Pattanaik, 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. Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure- based drug design strategies. Molecules. 2015; 20(7): 13384-13421.

3. Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: a powerful approach for structure-based drug discovery. Curr Compute Aided Drug Des. 2011; 7: 146-157.

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

5. 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).

6. Bajorath, J. Integration of virtual and high-throughput screening. Natl. Rev. Drug Discov. 1(11), 882–894 (2002).

7. Langer, T. & Hofmann, R. D. Virtual screening an effective tool for lead structure discovery. Curr. Pharm. Discov. 7(7), 509–527 (2001).

8. Potluri, H., Prasanth, D. S. & Atmakuri, L. R. In vivo antinociceptive effect of methanolic extract 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).

9. Ghode, P. & Jain, S. K. Structural requirements for some 3-amino-N-substituted-4- (substituted phenyl) butanamides as dipeptidyl peptidase-IV inhibitors using 3D-QSAR and molecular docking approaches. Indian J. Pharm. Sci. 79(6), 974–986 (2018).

10. Tomar, N. R. et al. Molecular docking studies with rabies virus glycoprotein to design viral therapeutics. Indian J. Pharm. Sci.72(4),

11. Bissantz, C., Folkers, G. & Rognan, D. Protein-based virtual screening of chemical databases. 1. Evaluation of different docking/scoring combinations. J.
Med. Chem. 43(25),4759–4767 (2000).

12. Pramanik, A., Sahoo, R. N., Pradhan, S. K. & Mallick, S. Characterization and molecular docking of kaolin-based cellulosic film for extending ophthalmic drug delivery. Indian J. Pharm. Sci. 83(4), 794–807 (2021).

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

14. Tao, X. et al. Recent developments in molecular docking technology applied in food science: A review. Int. J. Food Sci. Technol.55, 33–45 (2020).

15. Aja, P. M. et al. Hesperidin abrogates Bisphenol A endocrine disruption through binding with fibroblast growth factor 21 (FGF21), α-amylase and α-glucosidase: An in silico molecular study. J. Genet. Eng. Biotechnol. 20(1), 84. https://doi.org/10.1186/s43141-022- 00370-z (2022).

16. Santini A, Tenore GC, Novellino E. Nutraceuticals: a paradigm of proactive medicine. Eur J Pharm Sci. 2017;96:53 –61. https://doi.org/10.1016/j.ejps.2016.09.003.

17. Bairagi, G. R. & Patel, V. P. Nutraceutical a review on basic need, classifcation, recent trends in industry and delivery systems. J. Emerg. Technol. Innov. Res. (JETIR) 8(5), c183– c199 (2021)

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

19. Miller, E. G. et al. Emerging trends in dietary components for preventing and combating disease. Food Technol. 5, 114 (2012).

20. 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)

21. Kuntz ID, Blaney JM, Oatley SJ, Langridge R, ein TE. A geometric approach to macromolecule-ligand interactions. J Mol Biol 1982;161(2):269–88.

22. Mukesh B, Rakesh K. Molecular docking: A review. IJRAP. 2011; 2: 1746-1751.

23. GM Morris M Lim-Wilby Molecular dockingMethods Mol Biol .20084433658210.1007/978-1-59745177-2_19

24. Rangaraju A, Rao AV. A review on moleculardocking- Novel tool in drug design and analysis. J Hormo. Res Pharm. 2013; 2: 215-221.

25. Agarwal S, Mehrotra R. An overview of Molecular Docking. JSM Chem. 2016; 4: 1024

26. Lorber DM, Shoichet BK. Flexible ligand docking using conformational ensembles. Protein Sci. 1998; 7: 938-950.

27. Huang SY, Zou X. Ensemble docking of multiple protein structures: considering protein structural variations in molecular docking. Proteins. 2007; 66: 399-421

28. B K Shoichet S L Mcgovern B Wei J Irwin Lead discovery using molecular dockingCurr Opin Chem Biol .2002644398510.1016/s1367-5931(02)00339-3

29. 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).

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

31. Sousa, S. F., Fernandes, P. A. & Ramos, M. J. Protein-ligand docking: Current status and future challenges. Proteins Struct. Funct. Bioinform. 65(1), 15–26 (2006).

32. Gorelik, B.; Goldblum, A. High quality binding modes in docking ligands to proteins. Proteins Struct. Funct. Bioinform. 2008, 71, 1373–1386. [Google Scholar] [CrossRef] [PubMed]

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

34. 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).

35. Westhead, D. R., Clark, D. E. & Murray, C. W. A comparison of heuristic search algorithms for molecular docking. J. Comput. Aided Mol. Des. 11, 209–228(1997)

36. Baxter, C. A., Murray, C. W., Clark, D. E., Westhead, D. R. & Eldridge, M. D. Flexible docking using tabu search and an empirical estimate of binding affinity. Proteins 33, 367– 382 (1998).

37. Kollman, P. A. Free energy calculations: applications to chemical and biochemical phenomena. Chem. Rev. 93,2395–2417 (1993).Review of the theory of free-energy calculations and their areas of application, including ligand binding.

38. Simonson, T., Archontis, G. & Karplus, M. Free energy simulations come of age: protein– ligand recognition. Acc.Chem. Res.35, 430–437 (2002).

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

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

41. 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)

42. Tripathi A, Misra K (2017) Molecular Docking: A Structure-Based Drug Designing Approach. JSM Chem 5(2): 1042.

43. 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).

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

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

46. 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).

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

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

49. De Azevedo, J. & Filgueira , W. MolDock applied to structure-based virtual screening. Curr. Drug Targets 11(3), 327–334 (2010)

50. McMartin C, Bohacek RS, et al. QXP: Powerful, Rapid Computer Algorithms for Structure- based Drug Design. J Compute Aid. Mol. Des. 1997;11:333-344.15.

51. Schnecke V, Kuhn LA, et al. Virtual Screening with Solvation and Ligandinduced Complementarity, Perspect. Drug Discov. 2000;20:171- 190.16

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

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

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

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

56. https://www.researchgate.net/deref/https%3A%2F%2Fwww.creativebiolabs.com%2Fdrug-discovery%2Ftherapeutics%2Flead-optimization-4.html

57. https://www.researchgate.net/deref/https%3A%2F%2Fwww.creative-biolabs.com%2Fdrugdiscovery%2Ftherapeutics%2Flead-optimization-4.html

58. Suresh PS, Kumar A, Kumar R, Singh VP et al. An in silico [correction of in silico] approach to bioremediation: laccase as a case study. J Mol Graph Model.
2008;26(5): 8459.

59. 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).

60. Brower V. Nutraceuticals: poised for a healthy slice of the healthcare market? Nat Biotechnol. 1998;16:728-731.

61. Biesalski HK. Nutraceuticals: the link between nutrition and medicine. In: Kramer K, Hoppe PP, Packer L, editors. Nutraceuticals in health and disease prevention. New York: Marcel Dekker Inc. 2001;1-26.

62. Rama CS, Shirode AR, Mundada ASand Kadam VJ. Nutraceuticals-an emerging era in the treatment and prevention of cardiovascular diseases. Curr Pharm Biotechnol. 2006;7(10): 1523.

63. Wildman, R. & Kelley, M. Handbook of nutraceuticals and functional foods. In Nutraceuticals and Functional Foods (ed. Wild-man, R.) 1–9 (Taylor & Francis, 2007)

64. Whitman, M. Understanding the perceived need for complementary and alternative nutraceuticals: Lifestyle issues. Clin. J. Oncol. Nurs. 5(5), 190–194 (2001).

65. Aronson, J. K. Defining ‘nutraceuticals’: Neither nutritious nor pharmaceutical. Br. J. Clin. Pharmacol. 83(1), 8–19 (2017).

66. Kumari, M., Jain, S. & Singh, J. Nutraceutical-medicine of future. J. Glob. Biosci. 4(7), 2790– 2794 (2015).

67. Verma, G. & Mishra, M. A review on nutraceutical: Classifcation and its role in various diseases. Int. J. Pharm. Ter. 7(4), 152–160 (2016).
68. Miller, E. G. et al. Emerging trends in dietary components for preventing and combating disease. Food Technol. 5, 114 (2012).25. Madley, W. R. Functional foods. New Prod. 66,125 (2003).

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

70. Zaman, T., Adetunji, H. & Salih, E. Nutraceutical: A slow transition from preventive to curative healthcare and pretition about the physicians and patient—A study of South Delhi India. Int. J. Pharm. Sci. Res. 8(7), 3113–3117 (2017).

71. Elkhalifa, A.E.O.; Alshammari, E.; Adnan, M.; Alcantara, J.C.; Awadelkareem, A.M.; Eltoum, N.E.; Ashraf, S.A. Okra (AbelmoschusEsculentus) as a Potential Dietary Medicine with Nutraceutical Importance for Sustainable Health Applications. Molecules 2021,26, 696.

72. 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).

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

74. Parker, J., Schellenberger, A. N., Roe, A. L., Oketch-Rabah, H. & Calderón, A. I. Therapeutic perspectives on chia seed and its oil: A review. Planta Med. 84(9–10), 606–612 (2018).

75. Vergallo, C. Nutraceutical vegetable oil Nano formulations for prevention and management of diseases. Nanomaterials (Basel)10(6), 1232 (2020).

76. Dash, R., ,, R. N., Nandi, S., Swain, R. & Mallick, S. Sustained release bioadhesive suppository formulation for systemic delivery of ornidazole: In silico docking study. Indian J. Pharm. Educ. Res. 53(4), S580–S586 (2019).

77. Kumar, V., Kancharla, S. & Jena, M. K. In silico virtual screening-based study of nutraceuticals predicts the therapeutic potentials of folic acid and its derivatives against COVID-19. Virus Dis. 32(1), 29–37 (2021).

78. Kirschner, K. M. Reduce, replace, refine-Animal experiments. Acta Physiol. 223(3), e13726 (2021).

79. Agu, P.C., Afiukwa, C.A., Orji, O.U. et al. Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management. Sci Rep 13, 13398 (2023). https://doi.org/10.1038/s41598-023-40160-2

80. Scalbert, A., et al. (2020). The food metabolome: A window over dietary exposure.

81. Manach, C., et al. (2004). Polyphenols: Food sources and bioavailability.

82. Calder, P. C. (2017). Omega-3 fatty acids and inflammatory processes.

83. Pisoschi, A. M., & Pop, A. (2015). The role of antioxidants in the chemistry of oxidative stress: A review.

84. Maggini, S., et al. (2018). Immune function and micronutrient requirements change over the lifecourse.

85. Bays, H. (2011). Abdominal obesity and the metabolic syndrome: Implications for cardiovascularhealth.

86. Liu, R. H. (2004). Potential synergy of phytochemicals in cancer prevention: Mechanism of action.
87. Gómez-Pinilla, F. (2008). Brain foods: The effects of nutrients on brain function.

88. Hu, F. B. (2002). Dietary pattern analysis: A new direction in nutritional epidemiology.
89. Sethi, A., Joshi, K., Sasikala, K., & Alvala, M. (2020). Molecular Docking in Modern Drug Discovery: Principles and Recent Applications. IntechOpen. doi: 10.5772/intechopen.85991