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Computer aided drug designing in development of herbal drug

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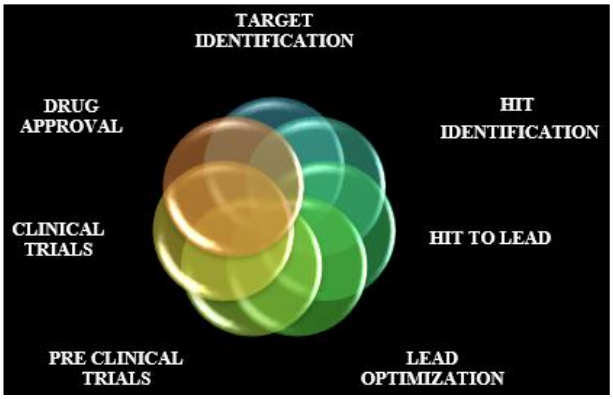
Abstract
Natural products have been an essential component of sustaining civilizations due to their medicinal properties. Serendipitous past discoveries of bioactive natural products have served as a model for the creation of analogs with desired physicochemical features. There are many bioactive natural compounds with medicinal potential in nature, some of which are inaccessible to standard techniques of study. In the case of natural products, the value of computational techniques as flexible instruments for aiding drug discovery and development has been acknowledged for decades without exception. The importance of computer-aided drug design of phyto-components and how researchers still rely on these computational tools for the quick discovery of attractive drug candidate molecules. We also discussed molecular docking phytochemicals like flavonoids, alkaloids and terpenoids. The identification of preclinical drug candidate molecules and the structural elucidation of pharmacological drug targets have hastened the development of both structure-based and ligand-based drugs.

Keywords: Natural products, molecular docking, phytochemicals, computer-aided drug design

Introduction
Far-reaching impacts of natural products on human being have been noted for centuries in the realms of home remedies and medicines. Historical evidence of the first natural products was revealed through paleoanthropological studies in which pollen deposits were found in the grave of Shanidar in present-day Iraq, which is estimated to date back to more than 60,000 years ago [1]. The importance of natural products to civilizations can be attributed to their diverse pharmacological properties. Medical records on the use of natural products as therapeutics have been documented across regions. Furthermore, a clay tablet depicting information regarding medicinal extracts (i.e., resins, oils and juices from approximately 1,000 plants) was discovered in Mesopotamia and dates back to 2600 B.C [2]. The Ebers Papyrus, an Egyptian medical text contained information on plant-based remedies for various diseases [3]. The first known Chinese text on this subject was called Wu Shi Er Bing Fang (containing 52 prescriptions), followed by Shennong Herbal (containing 365 drugs) and Tang Herbal (containing 850 drugs) [4]. As for western countries, historical evidence for the use of natural products was identified in monasteries of England, Ireland, Germany and France during the dark and middle ages. Furthermore, it should not be overlooked that Avicenna, the Persian pharmacist, made significant contributions to the field of pharmacy through his work "Canon Medicinae" [4]. Historical records identified medicinal plants, fungi and algae as rich sources of bioactive natural products [5]. The use of medicinal plants originated with respect to the human instinct for survival, i.e., searching for food and seeking to avoid death [6]. Native Americans, used ashes of the plant genus Salvia to aid childbirth and protect infants from respiratory diseases [7]. The ancient Europeans used Parmelia omphalodes extracts to cure burns and cuts due to its anti-inflammatory properties [8]. Fungi have been used as food (mushrooms), raw materials for perfumes and cosmetics, and ingredients for preparing alcohol and medicine since the early Chinese and Egyptian civilizations [9]. Fungi in the Anthozoans species, i.e., Chondrus crispus, were widely used for the treatment of chest infections [10]. Parmelia omphalodes (Linnaeus) Acharius were widely used in the British Isles as a dye and in Ireland as an anti-inflammatory agent to cure burns and cuts [11]. Among algae, the juice of the red alga Porphyra umbilicalis (Linnaeus) Kützing has been noted for its anticancer properties, particularly with respect to breast cancer [12].

The importance of natural products in medicine has been indicated by the continual use of classical natural products. One of the classic examples of a natural product is Papaver somniferum, the opium poppy, which contains naturally occurring alkaloids as bioactive compounds [13]. From theEgyptian to Chinese civilizations, opium was cultivated and used for several purposes. Ancient physicians used it as an anesthetic agent to perform medical surgery [14]. Likewise, they were used as painkillers during the American Civil War. In addition, they were used as recreational drugs in ancient China. The Chinese and Indians are considered to be the pioneers of herbal medicine, and their formulae have had great impacts on the traditional medicine of many countries worldwide [15]. The knowledge of the Chinese and Indians has been exchanged for a long time through the silkroad [16] Ayurveda is an Indian traditional medicine that defines the body in terms of three main constitutions (dosha), and the dynamic equilibrium of these dosha is essential for normal bodily function [17]. In contrast, the disturbance of these dosha is believed to be the root causes of diseases [18]. Similarly, Traditional Chinese Medicine (TCM) defines yin, yang and qi as the three main biological forces in the human body. The balanced equilibrium of yin and yang is essential for being healthy, and qi is required as the energy that circulates and nourishes the entire body [19, 20]. Traditional Chinese medicine is considered to be the prototype of Japanese traditional medicine (kampo medicine) [21] and Korean traditional medicine or Sasang constitution medicine (SCM) [22], to which the original formulae have been adapted. The Chinese and Ayurvedic traditional medicine systems have had great impacts on traditional medicine in Asian countries, including Thailand. The history of utilizing natural products for medicinal purposes has been noted since the Ayutthaya period (1350–1767 A.D.) [23] Both Ayurveda and TCM are herbal medicine systems in which herb formulae that contain various medicinal herbs are prescribed to provide synergistic effects and reduce adverse effects [24]. Despite having distinct formulae, the traditional medicines of India and China are based on the same belief that an individual's physical constitution plays a major role in susceptibility to diseases and its response to treatment [25]. The prescribed formulae can be adjusted according to the patient's condition [24]. A similar basis of different body constitutions that lead to differential responses to herbs is also implied SCM [26]. The unique characteristics of these traditional medicines are in agreement with modern individualized medicine [27]. Furthermore, recent studies have revealed the relationships between traditional medicine systems (i.e., Ayurveda [28, 29], Chinese [30, 31], Japanese [32, 33] and Korean [34-36] and genomic differences of individuals [27], which renders these systems thought-provoking alternative personalized treatment strategies in the post-genomic era [27]. The great importance of natural products in human being has been documented. Approximately 11% of drugs in the WHO's essential medicines list are exclusively derived from plants, and 25% of the drugs prescribed worldwide are plantderived products [37]. Most of the African and Asian populations rely on traditional medicine for their primary healthcare [38] because of limited access to healthcare facilities and healthcare professionals [39], affordability and belief of safety [40]. In addition, the ancient use of natural products has formed the basis of later clinical, pharmacological and chemical studies [5], which can be identified from the discovery and development of many currently used drugs, e.g., aspirin, morphine, digitoxin, quinine and pilocarpine [41]. Currently, the botanical statuses of countries differ because of distinct features of advancement in science and technology, regulations within the country, culture and society [42]. In the Europe Union (EU) and the United States of America (USA), herbal extracts are used as active compositions in herbal medicinal products, dietary supplements (in the USA) and food supplements (in the EU). In Asian countries, natural products from plants are widely used as drugs for therapeutic purposes in traditional medicine and are used as health foods for the prevention of diseases and promotion of good health [42].



(Hits = Compounds that can bind to a target, Leads = Hits with preferable potency, QSAR = Quantitative structure-activity relationships, QSPR = Quantitative structure properties relationships).

Fig 1: Conceptual framework of drug discovery and development and the roles of computational approaches.

Computer Aided Drug Design

It is computer-based technique used in the computational chemistry to discover, enhance or study of drug and related biologically active molecule is called as (CADD) Computer Aided Drug Design.

- It is most useful in new drug design.
- It provides knowledge about the chemical and biological properties of ligands and targets.
- It is used to find and improve novel drug.
- Discovery of in-silico filters for prediction of undesirable properties like poor activity and poor Pharmacokinetic and Toxicity of drug molecule.
- It is used for the optimization of novel drug targets. CADD is being used to find hits.
- By using chemical scaffolds to find out novel Virtual screening is applied for new drug molecules [43-50].

Structure-Based Drug Design

Structure-based computer aided drug design depend on the knowledge of the target protein structure to calculate interaction energies for all tested compounds [52, 53]. In structural database is crystalized target proteins are available. Structure- based is to design compounds that bind with minimal energy by specifically and tightly to the target [54, 55]. A broader terminology, Virtual high-throughput screening, is a computer-based screening tool that allows screening of a large library of similar chemical compounds for a particular biological activity [56, 57]. Virtual high-throughput screening comes in many forms, including: chemical similarity search, selecting compounds by

predicted biologic activity through quantitative structure activity relationship (QSAR) models or pharmacophore mapping, and virtual docking of compounds against protein target of interest. 66-74 By using computational tools in the lead optimization phase of drug development is significant and cost benefit. Application of computational tools in hit-to-lead optimization while reducing the number of compounds that must be synthesized and tested *In vitro*. 58-65. Fig 2: Computer aided drug design model 66 LIGAND-BASED DRUG DESIGN Ligand-based exploits the knowledge of known active and inactive molecules for chemical similarity searches or quantitative structure activity relation (QSAR). Ligand-based, is ideal where the 3D structure of the target proteins are not available.

Structural-Based Computer Aided Drug Design: Steps includes:

1. For docking Preparation of the target protein and compound library.
2. Determining a Proper binding pose for each compound.
3. Ranking the docked structures of molecules.

To predicts the orientations or conformations of a receptor-ligand complex by using the Molecular docking and it is a structural based computer simulation procedure and used to predict the binding affinity between the molecules in the complex [67].

Types of Molecular Docking

1 Search Algorithm: The experimentation method determines the binding modes and number of configurations creates. For docking analysis, the Monte Carlo method, fragment and genetic based, systemic searches is applied.

A. Rigid Docking
B. Flexible Docking
C. **Rigid Docking:** In this docking the receptor and ligand molecule both are fixed. Docking is performed [68].
D. **Flexible Docking:** In this docking the ligand and the receptor both are movable. It is conformation ally flexible. Each rotation the energy is calculated. Each conformation surface cell occupancy is calculated. After that the most optimum binding pose is selected [69].

2. Scoring Function: The binding affinity directly corresponding to the binding score. The best binders are best scoring ligands. It can be experimental, knowledge and molecular mechanics based. Docking Scoring is play important role in designing of drug: a) Knowledge-based and b) Energy component methods [70, 71].

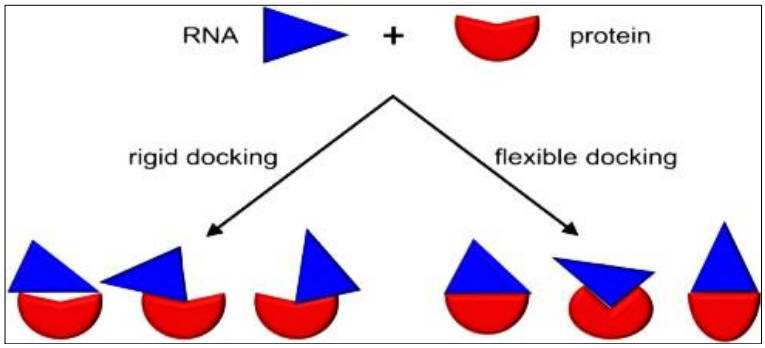


Fig 2: Flexible Docking [81]

Molecular Docking Mechanics Steps

In-Silico method studied the intermolecular interaction between 2 drug molecules. The protein receptor is Macromolecule. It acted as an inhibitor. The following steps involved in docking process areas.

Step I – Preparation of protein and Ligand: From Research Collaboratory Structural Bioinformatics Protein data bank (PDB) downloading the 3D-structure of the Protein. After that downloaded structure should be pre-processed. From removal of the water molecules, the charges stabilization, missing residues filling, add hydrogen atom side chains generation [72, 73].

Step II –Ligand Preparation: By using different databases such as ZINC, Pub Chem Ligands molecule can be downloaded. It can be draw in Chem sketch tool in mol file. Then utilized lipinsky's rule of 5 for this ligand molecule. It is used for the drug like and unlike molecules. It increases the high chance of success rate and decrease the failure due to drug likeness properties for molecules [74, 75].

Step III-Grid Generation: In this all factors like site, rotatable group, excluded volumes, constraints kept constant. The number of genetic operations performed (crossover, migration, mutation) is the key parameter in determining. Binding Cavity Prediction are to be done [76, 77].

Step IV-Prediction of Active site: The active site of protein molecule should be predicted. After that Preparation of protein, the water molecules and hetero atoms if present they are removed from cavity [78, 79]. Step V-Docking: Ligand and protein interactions are analyzed. Best docking score should be selected [80].

Table 1: Docking software [82-90]

Sr. No.	Program	Docking Approach	Scoring Function	Advantages	Disadvantages	Licence Term
1.	Auto Dock	Genetic algorithm and Simulated	force-field methods	Small cavities opened for hydrophobic ligands	Polar flexible ligand	Free for Academic Use
2.	Dock	Annealing fitting of Shape	Chem Score	Known binding site	Slow speed	Free for Academic Use
3.	Flex X	Construction Increment	Flex X Score,	Small cavities opened for hydrophobic ligands	More flexible ligands	Commercial Free evaluation (6 week)

4.	FRED	fitting of Shape	Piece wise Linear Potential,	High speed, large binding site	Polar ligands	Free for Academic Use
5.	Glide	Sampling of Monte Carlo	Glide Score, Glide Comp	Flexible Hydrophobic ligands	Ranking very slow	Commercial
6.	GOLD	GA Searching	Gold and Chem Score	Small Hydrophobic ligands	Large cavity ligand ranking	Commercial
7.	Ligand Fit	Sampling Monte Carlo	Ligand Score	Known binding site	Slow speed	Commercial

Docking of phytoconstituents

Flavonoids

A. Docking of flavonoids from Ocimum forskolei Benth

Eman Maher *et al.* isolated flavonoids from the dichloromethane fraction which was the most potent; with an ulcer index value of 2.67 ± 2.18*** and % inhibition of ulcer of 97.7%; following a bioassay-guided fractionation. The isolated flavonoids were subjected to molecular docking analysis in an attempt to explain their significant antiulcer potential, and the results revealed that salvitin followed by sideritiflavone were the main active ones acting against M3 and H-2 receptors, respectively [91].

B. Flavonoids Isolated from Daucus carota

Muhammad I *et al.* focuses on in silico approaches were adapted to use a natural product as a source of cancer therapy. For in silico studies, Chemdraw and Molecular Operating Environment were used for structure drawing and molecular docking, respectively. Flavonoids isolated from D. Carota were docked with cancerous proteins. Based on the docking score analysis, They found that compound 7 was the potent inhibitor of both cancerous proteins and can be used as a potent molecule for inhibition of 2N0W and 4JGR interaction with p53 [92].

C. Flavonoid derivatives as potent inhibitors of influenza H1N1 virus neuraminidase

Sadati *et al.* explained based on their antiviral effect, the flavonoids quercetin, catechin, naringenin, luteolin, hispidulin, vitexin, chrysin and kaempferol were selected in the present study and compared alongside oseltamivir on molecular docking, binding energy and active site structure, in order to provide insight on the potential of these compounds as targeted drugs for the control and treatment of influenza type A. The molecular characterization of flavonoids with binding affinity was performed using AutoDock Vina software. The results indicated that these compounds may effectively block the NA active site [93].

D. Docking study of flavonoid compounds for possible matrix metalloproteinase-13 inhibition

Taherkhani A *et al.* studied molecular docking and network analysis using AutoDock and Cytoscape software, respectively. Pharmacokinetic and toxicity characteristics of compounds were predicted using bioinformatics web tools. The results revealed that nine of the studied flavonoids had considerable estimated free energy of binding and inhibition constant: Rutin, nicotiflorin, orientin, vitexin, apigenin-7-glucoside, quercitrin, isoquercitrin, quercitrin-3-rhamnoside, and vicenin-2. Proline-242 was found to be the most important amino acid inhibiting the enzyme [94].

E. Flavonoids for their inhibition pattern against β-catenin for Wnt signaling pathway

Iftikhar H *et al.* done a comparative molecular docking analysis was performed to elucidate the binding mode of experimentally reported and unknown inhibitors. Based on the knowledge of geometry, binding affinity and drug score, we described a subset of novel inhibitors. The binding energy of known inhibitors (isorhamnetin, fisetin, genistein and silibinin) was observed in a range of -5.68 to -4.98 kcal/mol, while novel inhibitors (catechin, luteolin, coumestrol and β-naphthoflavone) exhibited -6.50 to -5.22 kcal/mol. We observed good placement and strong interactions of selected compounds inside the binding pocket of β-catenin. Moreover, flavonoid family members and T cell factors 4 (TCF4) compete for β-catenin binding by sharing common binding residues [95].

F. Molecular docking of citrus flavonoids with some targets related to diabetes

Shen, *et al.* explained the molecular targets, (i.e. glucokinase, glycogen synthase kinases 3 beta, peroxisome proliferator-activated receptor gamma, and dipeptidyl peptidase IV) whose crystallographic structures are available on the PDB database as 1V4S, 1Q4L, 2PRG, 2ONC respectively, were used for the docking analysis using the Autodock tool V 4.2 and ADT v1.5.4 programs. The docking studies of the ligands citrus flavonoids with four different target proteins showed that citrus flavonoids are good molecules which dock well with various targets related to diabetes mellitus [96].

Alkaloids

A. Molecular docking of alkaloid compounds with the matrix metalloproteinase 2

Jayaraman Selvaraj *et al.* finds matrix metalloproteinase protein-2 (MMP-2) is linked to the human oral squamous cell carcinoma. Therefore, it is of interest to design new inhibitors for MMP-2 to combat the disease. Thus, we document the molecular docking features of Aristolochic acid, Cryptopleurine, Epipodophyllotoxin, and Fagaronine with MMP-2 for further consideration [97].

B. Molecular Docking of Isolated Alkaloids for Possible α-Glucosidase Inhibition

Rahman N *et al.* assessed the bonding potential of isolated alkaloids with the targeted protein. For this purpose, the 3D structure of the target protein (α-glucosidase) was reproduced using MODELLER 9.20. The modeled 3D structure was then validated and confirmed by using the RAMPAGE, ERRAT, and Verify3D online servers. The molecular docking of 32 alkaloids reported as α-glucosidase inhibitors, along with reference compounds (acarbose and miglitol), was done through MOE-Dock applied in MOE software to predict the binding modes of these drug-like compounds [98].

C. Docking of the alkaloid geissospermine into acetylcholinesterase

Araújo JQ *et al.* performed comparative automatic molecular docking simulations using the AutoDock and Molegro Virtual Docker (MVD) programs in order to propose a plausible binding mode between GSP and AChE,

which might explain the observed experimental inhibitory activity. A sample of ten crystal structures of the Pacific electric ray (Torpedo californica) TcAChE, in complex with ten diverse active site ligands, was selected as a robust re-docking validation test, and also for GSP docking. The MVD results indicate a preferential binding mode between GSP and AChE, in which GSP functional groups may perform specific interactions with residues in the enzyme active site, according to the ligand-protein contacts detected by the LPC/CSU server. Four hydrogen bonds were detected between GSP and Tyr121, Ser122, Ser200, and His440, in which the last two residues belong to the catalytic triad (Ser200•••His440•••Glu327). Hydrophobic and π-π stacking interactions were also detected between GSP and Phe330 and Trp84, respectively; these are involved in substrate stabilization at the active site [99].

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D. Molecular Docking Study of Certain Plant Alkaloid Derivatives

Ganesh R, *et al*. generates total of 150 derivatives of Curcumin, Bacopaside IV, and Ginkgolide B the ACD ChemSketch software. These files were then converted to the Brookhaven protein data bank file using the OpenBabel software. Preliminary docking studies were then performed using the iGEMDOCK v2.0 software. All the prepared ligands were then tested for drug-likeliness properties using the DruLiTo and admetSAR softwares. Finally, compounds with good fit and drug likeliness were subjected to final docking with the AUTODOCK VINA software. In this study, the ligand with the name 8-(1-fluoro-2-methylpropan-2-yl)-6, 12, 17-trihydroxy-16-methyl-2, 4, 14, 1tetra oxahexa cyclonon adecane-5,15,18-trione is found to be a good inhibitor of 3 well-known drug targets [100].

Terpenoids

A. Molecular docking and ADMET-based mining of terpenoids

In the present study, docking and computational ADME parameters of a few terpenoid ligands isolated from the above-mentioned plant against two control molecules (Sitagliptin, Metformin) were compared. The retrieved docked images indicated the docking sites in the target protein. Out of the five compounds, Digoxigenin monodigitoxoside has shown the best docking result. The LD50 of this compound is very similar to control and lower than others. This in silico study confirmed that terpenoids present in the plant rhizome are a potent drug candidate for the treatment of type-II diabetes [101].

B. Molecular docking based screening of triterpenoids as potential G-quadruplex stabilizing ligands

Compounds selectively binding and stabilizing G-quadruplex structures could inhibit the telomerase or downregulate the oncogenes and may act as anti-cancer agents. Targeting human telomeric G-quadruplex DNA could be one of the mechanisms by which these GLTs exert anti-cancer activity. In this study, 208 GLTs were screened for ligands with high binding affinity and selectively to stabilize the pG4DNA by using the docking tool AutoDock4. The results showed that ganoderic acid A and ganoderic acid Df exhibit high binding affinity and selectively bind to the lateral groove of pG4DNA [102].

C. Molecular Docking and Dynamic Simulation Studies of Terpenoids of I. wightii (Bentham) H. Hara against Acetylcholinesterase and Histone Deacetylase3 Receptors

Ramnath MG, *et al.* focuses on terpenoids such as abietic acid, oleanolic acid, α-amyrin acetate, β-amyrin acetate were docked with AchE and HDAC3 receptors using AutoDock Vina (version 1.1.2). Further, GROMACS 5.1.2 package was used to perform molecular dynamic simulation. *In vitro* apoptosis was tested using hoechst 33258 and acridine orange/ethidium bromide [103].

D. Molecular docking, and dynamics of anticancer terpenoids from *Salvia lachnocalyx*

Hadavand Mirzaei H *et al.* report the effects of three potent anticancer terpenoids previously isolated from Salvia lachnocalyx, including geranyl farnesol (1), sahandinone (2), and 4-dehydrosalvilimbinol (3) on cancer cell cycle

alterations and reactive oxygen species (ROS) production. Interactions of compounds 1-3 with topoisomerase I were also investigated by using molecular docking and dynamics simulation. Accumulation of cells in sub-G1 phase of the cell cycle indicated that all tested compounds induce apoptosis in MOLT-4 cancer cells. Measurement of ROS production demonstrated that this mechanism is not involved in the induction of apoptosis. We suggest topoisomerase I inhibition as the mechanism of cytotoxic activity of compounds 1-3 based on docking and molecular dynamics (MD) calculations [104].

Conclusion

Eco-friendly practises and healthy eating are becoming more popular for the newest generation. Additionally, it is anticipated that the conventional medicine's polypharmacology-based premise would successful outcomes of therapy for complex disorders. This review article will assist researchers and physicians in recognising and creating therapeutic compounds in herbal medicines, therefore maximising the enormous potential of computer-aided drug design.

Acknowledgement

Nil

Conflict of interest

The authors have declared that there is no conflict of interest associated with this publication.

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