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COMPUTATIONAL INSIGHTS INTO PROTEIN-LIGAND INTERACTIONS OF SEMI-SYNTHETIC DERIVATIVES OBTAINED FROM HERBAL PLANTS

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Abstract:
Natural or Herbal products have long been used, especially in developed countries, to cure a wide range of illnesses. In developed countries, the most natural product-based drug development initiatives employ crude extracts in in-vitro or in-vivo tests. Isolating active principles for structural elucidation investigations is a limited effort. It is well known that the process of finding and developing a new medicine is difficult and requires a significant investment of time and money. The production of herbal pharmaceuticals has been too difficult thus far due to the complex and multi-targeted components found in herbal medicinal resources, as well as their bio-active chemical base and modes of action. These issues require thorough, methodical investigation. To pinpoint the precise target of the medication or drugs, in-silico research is conducted. which locates a medication for the specific binding site; to get a conforming outcome, animal testing can be conducted at the end of the process. Structural data is essential in the modern era of drug development and discovery. By using molecular docking or structural information of molecules, we can identify their safety, efficacy or potency.

KEYWORDS: Herbal products, In-vitro, In-vivo, Bio-active chemical, In-silico research, Specific binding site, Drug development, Drug discovery.

Introduction:

The approval of a new drug in the market takes approximately 10-12 years and costs about 1.3 Billion or more per drug. So there is a need for a method that helps to develop a new drug as soon as possible. Molecular docking is a technique that helps to reduce the time and costs of new drug design. Many methods are available for molecular docking. [14] The method is structure-based and needs a high-resolution three-dimensional image of the target protein, which can be generated using methods such as Cryo-Electron Microscopy, Nuclear Magnetic Resonance Spectroscopy, or X-ray crystallography. [15] Pharmaceutical firms' interest in natural products waned for a while, but the unfulfilled promise of combinatorial chemistry has piqued interest once again in natural compounds for lead discovery. [1,2,3] Natural product scientists search for empirical data to support traditional applications of different medicinal plant species, particularly in developing countries where herbal remedies are most popular. [1] Based on conventional uses, plant crude extracts are usually examined in in-vitro or in-vivo disease models for certain disease situations. [4,5,6,7,8,9] Natural product scientists in developing countries continue to have difficulties with compound scale-up to enable comprehensive biological research, in

addition to a lack of the necessary tools and access to natural product databases to assist attempts at structural elucidation. [10] Compounds in different databases can be molecularly docked to virtually screen a large number of small molecules in an attempt to find possible hits. [11] These forecasts provide distinctive molecular scaffolds to the discovery process while also saving money and time. [12] Thus, the purpose of this study is to examine molecular docking techniques in drug development programs based on natural products. Modern technology is required to assess the appropriate therapeutic value or clinical efficacy of the multicomponent/polyherbal formulations. By pinpointing the precise cell, gene, or protein that is impacted and identifying the active protein among them, bioinformatics plays a crucial role in medical science. [13]

Database: Some databases have important data on the phytochemicals taken from different plants; these databases are useful for researching the functional and structural characteristics of a wide range of compounds isolated from plants. The majority of the databases include data such as:

1. Local/biological name of herbal plants
2. Phytochemicals obtained from different herbal plants
3. chemical structure and other information about their phytoconstituents
4. Pharmacological actions of herbal plants
5. if any phytoconstituent gives toxicity, these are mentioned in the database.

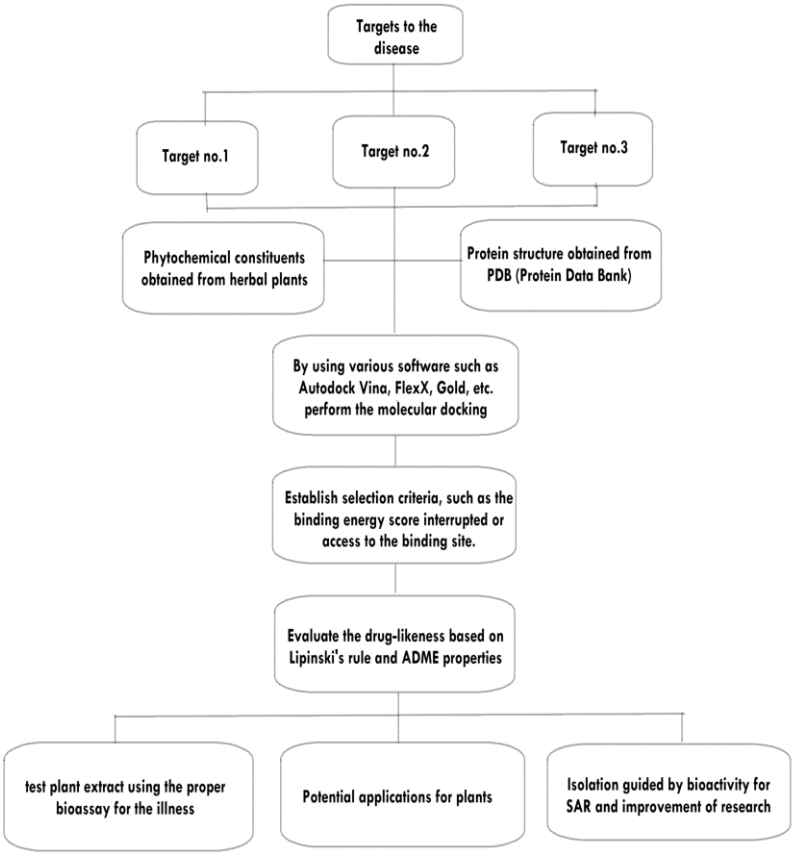
The database also provides the 3D or three-dimensional structure of molecules. There are varieties of databases that are available now such as (1) Traditional Chinese medicine integrated database [33], (2) Medicinal plant database for drug discovery [34], (3) Indian Medicinal Plants, Phytochemistry And Therapeutics (IMPPAT) [35] (4) PubChem Substance Database [36] (5) KNApSAcK Core DB [37] (6) Phytochemica [38] (7) Herbalog [39]

There are **two types of molecular docking** such as (A) Rigid body docking: In rigid docking, If we assume that the molecules are rigid, we are searching for a conversion of one of the molecules in three dimensions that will enable it to fit the other molecules as closely as possible within the constraints of a scoring function. B) Flexible docking: We consider the flexibility of molecules in addition to transformation, and our goal is to find the confirmations of the ligand and receptor molecules as they arise in the complex. [29,30] This review aims to analyse the state-of-the-art molecular docking approaches in medicinal chemistry and drug discovery, highlighting developments in the field and the function of combining ligand- and structure-based approaches. [31] The ligand and receptor conformations are free to alter during the flexible docking computation. Because this type of docking simulation is more accurate and most like the actual docking scenario. [32]

There are many **steps involved in molecular docking** such as the preparation of protein, active site prediction, preparation of ligand and docking.

In preparation of protein, Preparation of protein, Select a 3D structure of a protein molecule according to the requirement. Then the structure will be forwarded for the pre-processing. After that, remove the molecules of water, stabilize the charges and form side chains. [30] After that select a prepared protein molecule, and predict the active site of the protein for docking. Receptor possesses lots of active sites but we need only one site that is more active from other sites. Then Ligands may be obtained from a variety of sources, including Pub Chem and ZNIC, or they can be drawn using a sketch tool. The LIPINSKY'S RULE OF 5 should be applied while choosing the ligand. The Lipinsky Rule: (1) A lower concentration of five hydrogen bond donors; (2) A lower concentration of ten hydrogen bond acceptors; (3)A molecular mass of less than 500 Da; (4) Strong lipophilicity; (5) A molecular refractivity of 40–130. [30] An in-silico technique called "molecular docking" forecasts where tiny molecules or ligands will end up in the target protein's (receptor's) active region. [40] The protein and ligand are docked together, and the interactions are examined. The equation provides a physics-based scoring function (Escore) that combines the energy components for ligand desolvation (lig_desol), electrostatic (ES), and VDW to assess ligand postures. [41] The key objectives of the molecular docking approach are bio-affinity, virtual screening, and binding posture prediction. These objectives are interrelated. The fundamental instruments of the molecular docking approach are scoring functions and search algorithms for ligand conformation creation and analysis. [42]

$$E_{score} = E_{VDW} + E_{ES} + E_{lig\_desol} \quad \text{----------(1)}$$ [41,43,44]



Advantages of Molecular docking:

I.Molecular docking allows us to decrease the amount of artificial and biological testing that is done. [45]

II.It produces the most promising therapeutic candidate by using in silico filters to exclude molecules with unfavourable qualities (low effectiveness, weak ADMET, etc.). [46]

III.It's an automated, quick, efficient, and economical approach.

IV.It allows us to understand the pattern of drug-receptor interaction.

V.Compared to conventional high throughput screening, it provides compounds with high hit rates by scanning vast libraries of compounds in silico. [47]

VI.These methods reduce the likelihood of errors occurring at the last stage.

In-silico studies are very helpful in the treatment of various types of disease by using herbal plants:

(1) In-silico studies in Post-traumatic disease: [16]

A mixture of herbs Free and Simple Wanderer is a treatment for post-traumatic stress disorder that uses antioxidants. Ten components that were chosen from the extract decreased oxidative damage caused by H2O2.

(2) In-silico studies in Cardiovascular disease: [17]

A research on thrombosis, a cardiovascular illness that is brought on by platelet aggregation. 38 substances with a DockScore above 70 show great promise for the development of anti-thrombosis medications.

(3) In-silico studies in Hypertension: [18]
An innovative method for finding new CYP11B2 inhibitors from Traditional Chinese Medicine was made possible by a study on the use of CYP11B2 inhibitors to lower hypertension.
(4) In-silico studies in Infection: [19]
In Chinese medicine, a common anti-infection therapy involves the synergistic combination of medications that include either Gentamicin or Oxacillin.
(5) In-silico studies in Malaria: [20]
One potential new antimalarial drug is artemisinin.
(6) In-silico studies in Cholesterol: [21]
Finally, acetyl coenzyme and ten compounds with anticipated inhibitory effects against ACAT-2 were discovered.
(7) In-silico studies in Insomnia: [22]
Kadsura longipedunculata is used to treat insomnia because of its hypnotic and sedative properties.
(8) In-silico studies in Diabetes mellitus: [23]
Twenty enriched targets were suggested in the in silico study for Cassia auricuata elements implicated in insulin signalling pathways. The absorption of glucose and the expression of glucose transporters are both improved by Cassia auriculata.
(9) In-silico studies in iron deficiency: [24]
According to research on piperine and iron deficiency, conjugating piperine with iron slows down iron metabolism, which means that piperine likely increases the bioavailability of iron.
(10) In-silico studies in Asthama: [25]
The detection of lipoxygenase inhibitory activity using piperine and its derivatives has greater importance for therapeutic uses.
(11) In-silico studies in Cancer: [26]
One ingredient of Artemisia annua L. is scopoletin. One potential lead molecule for a medication development program is scopoletin.
(12) In-silico studies in HIV: [27]
Because 4-thiazolidinone has an antiviral effect, this study examines compounds of this molecule and its derivatives to improve therapy options against AIDS.
(13) In-silico studies in Epilepsy: [28]
To determine the inhibitory activity in epilepsy, this study examines chemicals that are produced from various herbal medications and their quantitative structure-activity connections.

Application of molecular docking:
I.Target fishing and profiling: ligand-receptor complementarity-based target prediction for compounds. [48,49]
II.Virtual screening: Identification and optimisation of molecules that modulate disease-related targets. [50]
III.Ligand-Target binding rationalisation: Identifying the structural characteristics required for effective ligand-receptor binding. [51]
IV.Drug Repositioning: Identification of new therapeutically relevant targets for currently labelled medicines and recognised chemical and natural substances. [52]
V.Polypharmacology: Identifying and optimising drugs that affect a group of targets implicated in the same illness. [53]
VI.Prediction of Adverse Drug Reaction: Predicting and rationalising pharmacological target actions based on ligand-target complementarity. [54]
VII.Ligand optimization: Docking may be used to anticipate binding poses, which can be utilised similarly to confirm ligand-bound structures experimentally. This can guide the optimisation of a ligand's binding affinity and the alteration of other features of the ligand. [55,56]
VIII.Measurement of Pharmacokinetics: Docking is used to measure the pharmacokinetic parameters such as ADME (Absorption, Distribution, Metabolism, Excretion). [57,58]

Conclusion:

The study emphasises how much progress has been achieved in our knowledge of how semi-synthetic compounds from herbal plants interact with protein targets. Molecular docking, virtual screening, and molecular dynamics simulations are examples of computational techniques that have been very helpful in forecasting and clarifying the binding affinities and processes of these derivatives. By combining these methods, it is now possible to gain a better understanding of their possible therapeutic uses, which present encouraging substitutes for traditional medications. When compared to their natural counterparts, the semi-synthetic derivatives frequently show increased binding affinity and selectivity towards target proteins, indicating that deliberate alterations may increase their effectiveness and decrease their adverse effects. The analysis does, however, also highlight the necessity of additional experimental validation in order to validate computer predictions and fully investigate these substances' potential.

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