**Reverse Pharmacognosy: Exploration of Lead in Drug Discovery**

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**Abstract:**

Life expectancy has significantly grown in developed nations, particularly during the last few decades. There are several prospects for the creation of bioactive substances that support health and wellness. Reverse pharmacognosy combines the traditional use of plants with cutting-edge methods like HTS, virtual screening, and knowledge databases. Numerous in vitro active and selective hits were found through the use of combinatorial chemistry and high throughput screening (HTS). Finding in vivo active medications is still a difficulty, even though many communities across the world have found traditional medical treatments made of natural ingredients to be effective. Due to significant disparities in how other cultures see sickness, these vast and scattered bodies of information are occasionally overlooked in Western studies. Including reverse pharmacognosy and pharmacognosy in the research process gave researchers a quick and effective technique for finding new natural drugs.

**Keywords:**

Reverse Pharmacognosy, Throughput Screening, Combinatorial Chemistry, Virtual Screening Tools

**Introduction:**

Chemicals created by living things including plants, the mushrooms, animals, and microorganisms are known as "natural products." Pharmacognosy, or the study of medications with natural sources, is a crucial area of study in the pharmaceutical sciences. Pharmacognosy is defined as the systematic study of the morphological, chemical in nature, and biological qualities, as well as the history, cultivation, collection, the extraction process, a state of isolation Bio assaying, quality control, and manufacture of crude pharmaceuticals with natural origins. [1]. Since using plants as medication to treat life-threatening illnesses is the earliest human medical practise, it is still common to use plants to find novel drug possibilities. Natural health remedies made from botanicals are becoming more and more popular worldwide. It is well known that about 80% of people in underdeveloped nations use traditional medicine, which consists primarily of herbal prescriptions [2].

Consequently, scientists continue to pay close attention to natural products or chemicals. While some compounds are synthesised to closely resemble a natural plant compound, others are directly extracted from plant extracts and employed as active substances. As a result, natural substances might serve as useful models for creating new therapeutic molecules. Modifying or modelling is a crucial step for the pharmaceutical sector. Because natural materials occasionally exert little or no activity by themselves, yet powerful medications can be made by modifying them and employing chemical or biological processes[3-6]. In this view, natural chemicals are unquestionably valuable leads for the discovery of new medications, and the contemporary significance of drugs derived from nature is undisputed.

**Areas Affecting Pharmacognosy**

It is vital to identify the fields that pharmacognosy encompasses, either fully or partially, in order to evaluate its current viability as an academic (educational) and practical field:

**A. Subjects in biology**

Pharmacognosy in the strict sense (basic verification techniques, macroscopy, and microscopy), Pharmacobotany (ethnobotany, physiology, and biochemistry of secondary metabolites), Genetics (creation of chemical varieties by gene recombination for field production), Biotechnology (microbiology, production of substances, by various cell types in vitro, utilisation of recombinantDNA technologies, enzymes fixed to a carrier), and Pharmacology.

**B. Chemistry-related fields**

Analytical phytochemistry (the best method for obtaining active ingredients), Preparative organic chemistry (the preparation of derivatives and structure modification of isolated compounds), Structural analysis techniques, and Isolation phytochemistry are all examples of phytochemistry.

**C. Manufacturing of raw materials**

Technology of natural pharmaceuticals (processing of biogenic raw materials, substances isolation on an industrial scale) and Production of biogenic material (agrotechnics, fieldproduction).

**D. Technical disciplines**

It includes cataloguing and classifying natural raw materials as well as computer methods (chemical docking).It is impossible to pick one of these disciplines—the majority of which are preparatory—out of the many that together make up pharmacognosy. This is amply supported by data from the literature on the subject of pharmacognosy, which includes forensic, ecological, as well as molecular pharmacognosy as new fields of study [7]; this is a reaction to the ongoing procedure of unambiguous verification of pharmaceuticals based on their genetic profile (DNA), and then the metabolome [8, 9]. It also provides computer-aided methods for monitoring the metabolites of renewable resources as well as the use of molecular tools to assess the level of biogenic material [10,11]. Conventional pharmacognostical techniques are constantly being improved upon because they produce good findings when used properly [12].

**Challenges in Pharmacognosy**

The analysis of the amount of pharmaceuticals containing these ingredients and drugs produced from natural formulas that are listed in the World Health Organization's List of Basic Medical Products shows the significance of herbal remedies in therapy. The 13th revision contains about 300 different medications that are deemed necessary for medical practise, including about 210 small-molecule medications [13]. These include over 70 synthetic medications derived from pharmaceuticals comprising natural ingredients or synthetically modified natural structures, as well as 44 unmodified natural items, 25 semi-synthetic derivatives of natural goods, and 25 semi-synthetic derivatives of natural products. According to their argument, the definition of the genesis of substances from nature adheres to the Newman, Crag, and Snader convention [14].

Pharmacognosy currently faces three new challenges that have not been applied in practise before:

* The first is the evaluation of traditional medicines used by ethnic groups, which are based on cultural tradition and are used in pharmaceutical products (principles of traditional Chinese medicine [yin-yang], traditional Indian medicine [Ayurveda], traditional Japanese medicine [Kampo], and traditional Mongolian medicine [Dom]).
* The examination of biogenic materials (extracts and pure chemicals), in addition to preparations that lack the legally binding nature of drugs but are nutraceuticals, dietary supplements, or innovative foods, present the second issue. Despite the fact that they are unique foods in which no medical indication is required, they are nonetheless significant for therapy and need to be evaluated. The products have a significant positive economic influence on pharmacies as well as a positive practical impact because nutraceuticals are frequently employed in regulated therapy and occasionally even in self-medication as the therapeutic agent. Although various procedures are in progress at the EU level, the problem is still complicated and ought to be handled by law. Even if they're considered foods, the issue of nutraceuticals needs to be treated in accordance with current knowledge.
* The pharmaceutical knowledge of marine creatures is the third problem. The first reference of their use was made 50 years ago, and their deeper development occurred around 40 years ago (for example, in Sweden) [15,16,17]. Many articles demonstrate the depth of this field of Pharmacognosy [18,19]. In order to succeed in isolating macromolecular drugs with unexpected effects, pharmacist-pharmacologists have to be professionally prepared in their research as part of their academic training; the main focus of pharmacognosy continues to be on small-molecule drugs, which are much simpler to work with.

In such case Reverse pharmacognosy is crucial component of contemporary pharmacognosy because they concentrate on identifying resources from nature that contain active molecules and targets for natural chemicals through virtual or actual screening. High-throughput screening (HTS), virtual screening, as well as databases with information on conventional plant usage are among the methods used.

**Reverse Pharmacognosy**

Reverse pharmacognosy is a novel idea that involves first identifying new biological targets from chemical compounds with structurally comparable properties, and then identifying the natural sources of the naturally occurring substance that contains them. Pharmacologists from India claim that the system of quality control should be affected by a reevaluation and expanded involvement of practitioners of traditional medicinal knowledge. Currently, Western technological and analytical viewpoints were used to independently design quality standards.

Reverse pharmacognosy employs natural metabolites to identify potentially novel medicinal qualities of natural material while classical pharmacognosy utilises plants to identify new bioactive chemicals. For the quick and efficient discovery of new medicines, pharmaceutical knowledge and reverse pharmacognosy can be included into the research process. Target-based Drug Discovery (TDD), also known as reverse pharmacology, is based on two procedures: first, it is hypothesised that altering the activity of a particular protein target will have positive therapeutic effects. Investigations in small-molecule chemical archives are then employed to find substances that have a strong affinity for the target [20].

The findings of this screening serve as a springboard for the identification of potential medication candidates. This technique has gained popularity for sequencing the genome of humans, making it possible to quickly create vast quantities of purified proteins. It is now the most used in the area of drug development. The action of in vivo found active compounds is anticipated by the reverse technique, as opposed to classical pharmacology, typically only in the last stages of discovering drugs with a reversed pharmacological strategy. Additionally, it is crucial for evaluating natural compounds [20].

Every therapeutic system has its own unique epistemology, presumptions, theories, and techniques. When it comes to the creation of objective and verifiable criteria for conventional medicines or medications, they had not yet formed their own quality norms and limits. Each traditional herbal medicine system eventually creates its own internal quality standards for things like collecting and processing, planting and harvesting dates, and so on. This also contains attributes that are expressed in other (subjective) ways, such as flavours and scents as well as the traditional humoral categories of hot and cold, centripetal or centrifugal action, and so forth.

Experts in the therapeutic tradition must be included in the identification of a traditional plant utilised, not only a biologist or systematist. One illustration (among many) is the fact that the Sanskrit word for "plant" (Brahmi) may refer to two different botanical taxa, namely Centella asiatica (L.) Urban and Bacopa monneri (L.) Pennell (also known as Neer Brahmi and Manduka Parni, respectively).In certain traditional systems, a plant that is referenced in old scriptures may occasionally be substituted by another.The other plant, which is botanically different but contains very comparable compounds, may frequently be found. A HPLC profile relating Aconitum heterophyllum Wall. (Ranunculaceae) and Cyperus rotundus L. (Cyperaceae) provided evidence of this in one instance.

Turmeric (Curcuma longa L.) harvest periods were another intriguing discovery. It has always been customary to pick the plant at night.A generic test for pharmacological activity known as the brine shrimp bioassay can be used to determine the quantity of the active component. According to the results of this test, the extract from roots that were gathered at night was 1.5 times more bioactive than roots that were harvested during the day. The traditional ayurvedic preparation of Piper longum L., cooked in milk, was 27 times more active than the same potent preparation in water, according to the same bioassay.

The majority of recognised standards for herbal products, including the British Herbal Pharmacopoeia, WHO monographs, and even the Indian Ayurvedic Pharmacopoeia, lack intercultural considerations, according to the researchers.These researchers recommend that databases of conventional quality standards be built globally and that new technologies be created for the aforementioned non-analytical components. Some characteristics of the warm-cold categorization of herbs in TCM seem to be connected to a pattern in their photon emission [21,22,23].

**PARTS OF REVERSE PHARMACOGNOSY**

**Structural database for natural compounds**

The structural database, also known as the Virtual Chemical Database (VCDB), is composed of natural chemicals that are mentioned in published literature and compounds identified in commercial databases. These substances can be found in many places, and typically the process used to extract them is also detailed.

**Target database**

The target database is made up of 3D protein structures that have been established using homology modelling or X-ray crystallography. Although it also incorporates proteins from other sources, the majority of the structures are made from human tissue.

**Virtual screening tools**

Virtual screening's main objective is to narrow down the vast virtual chemical pool of tiny organic molecules into a manageable set of compounds that have the best possibility of developing into therapeutic candidates before synthesising and screening against a particular target protein. Virtual screening can be done using one of two approaches: either screening based on ligand properties, such as physical and chemical characteristics (one-dimensional data), fragment descriptions (two-dimensional data), or pharmacophores (3D data), which are techniques of quantitative structure-activity relationship (QSAR), or screening based on target properties, which necessitates knowledge of the 3D structures of the target and the ligand and are techniques of de NoVo design and docking process, which involve creative thinking[5-9]

**Ethnopharmacological database (ETPHDB)**

ETPHDB has been created in order to generate botanic data, organic chemical structures, and physiological tastings of extract and compounds. This database includes the family, genus, organisms, common names, and aliases of the plants. The database expedites the search for bioactive components, such as anti-inflammatory chemicals. The ETPHDB's botanical data on plant and their traditional applications, as well as phytochemistry information related to the biological functions of plants, make it possible to establish a connection between molecules in plants and activity.

While the bold, black arrows correlate to the processflow, the simple arrows show the flow of information. When 'knowledge validation' is used to turn virtual hits into genuine hits and to locate the origins of compounds, data from an ethnopharmacological database (ETPHDB) are used.Internal biological tests and/or information obtained from scientific publications are both used in the experimental validation procedure. The verified accuracy of the target models is made possible by genuine finds or real inactive candidates.

**Comparison of Pharmacognosy and Reverse Pharmacognosy**

Raw plants chosen based on their biodiversity or historic applications are the basis for pharmacognosy. Plant extracts are produced, and those that are active are tested using biological tests. Iterative bio-guided fractionation distinguishes the active compounds. Pharmaceutical knowledge therefore begins with plants and ends with molecules. It is possible to do reverse pharmacognosy with or without a virtual component. Chemical variety influences the selection of molecules. They undergo many biological testing for screening. Then, plants that contain bioactive compounds may be identified with the use of a chemical source database. Software for docking and inverse-docking can be used before biological testing.

Finding ligand/target couples through this process allows for a significant reduction in the number of chemicals that must be assessed and the number of biological experiments. The compoundsource database is then used to identify the natural sources. Reverse pharmacognosy starts with molecules to obtain bioactive plants, and then their biological activity is molecularly characterised. A digital repository for traditional knowledge (TKDL): The Government of India has started an ambitious endeavour to develop a Traditional Medicine in order to stop the award of patents based on Indian Traditional Knowledge.

Digital Knowledge Library. This project is a collaboration between the Central Council for Research in Ayurveda & Siddha and the Council of Scientific Research. This effort aims to cover around 35,000 formulas found in old Ayurvedic literature and transform them into formats that are compliant with patents. A collaborative team of Ayurveda specialists, IT specialists, and patent examiners has started the task. All information on international patent classification, traditional research classification, Ayurvedic terminology, concepts, definitions, classical formulations, dosages, illness conditions, and document references will be available in the digital library in digital form.[24-29]

**REVERSE PHARMACOGNOSY: TOOLS AND APPLICATIONS**

**1. General Cheminformatics Tools**

They include visualisation, computation of physical-chemical properties, statistical tools, and chemical-focused similarity/diversity selection/searching algorithms, among other things. Some are accessible through open source communities, while others come from for-profit businesses.For instance, free software includes OpenBabel [30], Chemistry Development Kit (CDK) [31], or ScreeningAssistant [32]. They compute physico-chemical descriptors and/or perform searches using various filters (such as substructure, similarity, etc.)[33-34].

**2. Inverse Screening and Target Database**

Inverse screening process is connected to a target database that contains structural and activity data in such a manner that possible target proteins are connected to a specific natural chemical of interest and its activity.

**a. Process of Inverse Screening**

"In "classical" docking, chemicals It is necessary to have three-dimensional protein structures, which can be produced using homology, NMR, or X-ray crystallography. Additionally, a high resolution and the presence of a ligand that has been co-crystallized may improve the accuracy of predictions. It is recommended to compute the three-dimensional structures of the molecules that need to be docked using specialised software like Concord [35-37] or Corina [38]. A scoring function that considers the many physico-chemical factors, such as ionic interactions, steric hindrance, hydrogen bonding, etc., is used to determine the affinities between ligands and proteins. Popular docking software programmes include AutoDock [39], Dock [40], FlexX [41], Glide [42], Gold [43], and Surflex [44]. The process of "classical" screening entails docking many substances into a protein binding site. Finding the protein(s) that can bind a certain drug is the goal of inverse screening. Although there isn't any actual software for inverse screening, there are docking tools designed for the job that are linked to a database of protein targets.

Software for inverse screening varies in terms of desired database size and scoring functionality. The score function, which is calculated for solutions with as many proteins as possible as replies to docking experiments with only a single molecule, is the key factor. Contrast this with "classical" docking problems, in which several newligands are docked into a single receptor or enzyme protein.Ranking the answers to that problem becomes a challenging endeavour. For instance, some active site models get excellent results with any molecule by failing to distinguish between weak and strong binders.

A number of approaches have been proposed to overcome the classical docking

* **Invdock [45-48]**

INVDOCK, one of the earliest inversescreening software programmes, was created by the Bioinformatics and Drug Designgroup at the University of Singapore. It connects to a database of target activities known as TTD and employs a protein structures database from the Protein DataBank (PDB) [55]. INVDOCK was tested against chemicals derived from TCM-relevant organisms.

* **Tarfisdock [48]**

An inverse screening platform called Target Fishing Dock is freely available online at http://www.dddc.ac.cn/tarfisdock. Online users have the option of immediately sending an interest compound to this interactive website. The molecule is docked to proteins taken from the Potential Drug Target Database, a remote database. From PDB and other target databases, PDTD is built. As a result, fresh target candidates are discovered (or fished for) in the PDB pool and subsequently categorised according to their interaction energy score. TarFisDock is a DOCK extension [49]

* **Selnergy [75]**

Greenpharma's internal inverse screening tool is called Selnergy.The foundation is FlexX. It makes use of a verified target database of 7000 therapeutically relevant proteins.

**b. Target Databases**

The databases contain both molecules and their annotations, two different forms of data. The 3D structures of the biomolecules, along with their names and synonyms, EC numbers for enzymes [50] or membership in a protein family, therapeutic classes (such as CNS, dermatology...), applications that may result in modulating the targets, the source organisms from which the proteins are derived, and bibliographic references, are required. Different techniques, such as X-ray crystallography, nuclear magnetic resonance, or homology modelling, can be used to establish the 3D coordinates of a protein. The best methods for obtaining enough resolution are RX and NMR, but homologymodeling structures are less precise.

The absence of crystallised structures for some proteins, especially those belonging to significant families like GPCR and ion channel, is a significant limitation in this regard. When co-crystallized ligands are available, the annotations have to include indications on the active sites that have been seen. These complexes are used as proof in related blind docking scenarios where docked conformations are compared to experimental geometries.In the same way that specific ligands may attach to numerous active sites, certain proteins can bind a variety of ligands. Because proteins are flexible [51], their spatial configurations are subject to alter upon ligand binding. 3D coordinates, however, are static and do not represent dynamic processes in structure files.

The primary reference database for three-dimensional structures in the field of proteins, nucleic acids, and their complexes is the Protein Data Bank [52-54] at the Research ollaboratory for Structural Bioinformatics (RCSB-PDB) in the United States. The website provides analysis and visualisation stools. In ordinary ASCII text files with the dot-PDB extension, which is now commonly used in the research community, structural data are kept.

**The Kyoto Encyclopaedia of Genes and Genomes database** [55]is another sizable data source that offers many search features, links to expert annotations, and processed data focusing on particular topics like genomes, species, mutations, or associated diseases. It contains useful information about proteins and their ligands from chemical structures to biological metabolic pathways. Since its founding in 1995, KEGG has been maintained by the Human Genome Centre at the University of Tokyo and the Bioinformatics Centre at Kyoto University in Japan. Numerous interrelated subdatabases, including KEGG PATHWAY, KEGG GENES, KEGG DISEASE, and KEGG ENZYME, are contained inside the main database [56]. With its 5000 enzymes, the latter is particularly intriguing for RPG. Each enzyme has a collection of annotations related to the coding genes in various species, their function in the connected metabolic pathways, and the products.

**Braunschweig Enzyme Database** is referred to as BRENDA This database is robust due to the amount of data and the complex relational links between the data. [57]. Its primary weakness—a database that is only focused on enzymes and excludes any other proteinfamily—is also its primary asset. It was first published in 1987 as a book, then in 1998 it was transformed into an online database. This database, which is updated by the Institute of Biochemistry and Bioinformatics at the Technical University of Braunschweig, has about 4800 entries for enzymes as well as the data-mining software FRENDA and AMANDA [58].Entries address nomenclature, different enzymatic processes, ligands, IC50 test outcomes, host species, and related bibliographic references.

The enzymatic activity and accompanying therapeutic uses are linked in a section on diseases that also contains a bibliography for target placement and filtering. Therapeutic Target Database (TTD) [59] is a database that is centred on targets having therapeutic uses, similar to BRENDA, but unlike BRENDA, it also includes pharmaceuticals. It was developed in 2001 by Dr. Chen Yuzon of the National University of Singapore's Bioinformatics & Drug Design group (BIDD), a research division of the Department of Computational Science. Here, general scientific literature, pharmacology books, reviews, and original studies serve as the collection's beginning point rather than PDB-based datasets with added annotations; connections to PDB are included at the collection's conclusion. It gives a sizable number of ligands with references and information, such as 2D structures, CAS numbers, targets, or biological features, with a drug-specific focus. Invock [60], a proprietary inverse screening tool created by BIDD, predicts protein-ligand interactions using information from the TTD and organic chemicals found in TCM-relevant plants.

**Potential Drug Target Database** (PDTD) is produced by Shanghai Drug Discovery and Design Centre in 2008 [61-62]. Targets that are part of PDTD are taken from the PDB and chosen from complete, high-resolution structures that have co-crystallized ligands and an active site that is clearly characterised.Though PDTD has many features with TTD, its integration with TarFisDock—which provides some really valuable RPG tools—is the major draw of PDTD.The purpose of this presentation was not to provide a full list of all databases currently in use, but rather to highlight a few that are RPG-compliant and practical: PDB for 3D protein structures, KEGG and BRENDA for accessing biological pathways and relationships, and finally TDT and PDTD because of their comparable approaches with regard to biological pathways and relationships

Additional databases with comprehensive and helpful information on targets and ligands should be added here as well: sc-PDB [63], a processed subset of the PDB with a druggability focus; SuperTarget [64] is a comprehensive drug-target relational database that contains metabolic pathway data for many species. DrugBank [65] for its contents of commercial medications and their targets, which are mostly fed with pharmaceuticals and proteins that have FDA (Food and Drug Administration) approval. They are comparable to those previously mentioned. The reader is directed to the published literature [66] for a comprehensive evaluation of the open compound/activity databases. A resource to study known and anticipated interactions of chemicals and proteins is the data mining programme STITCH [67]. Evidence from tests, databases, and the literature is used to relate chemicals to one another and to proteins [68].

**3. Natural Compounds and Traditional Knowledge Databases**

A fundamental challenge in RPG is (re-) placing an organism into therapeutic or cosmetic indications depending on the molecules present in these sources. It is vital to search for natural chemicals and the species that inhabit them.A traditional knowledge database contains information on how organisms are used by distant communities and in various folk remedies. It may also be used to validate calculated hits by looking for connections between traditional usage and expected behaviour.

***a. Natural Compound/Source Databases***

In a design suited for a natural compound/source database, the user ought to be able to find organisms or their molecules with references to organism names, families, genera, species, and naturalists. It is very recommended to include information on the organ, the amount present, and citations for each hit produced by combining substances and organism in an array.

Other information, such as a molecule's physico-chemical properties, known activities and targets, and 3D coordinates, might also be very helpful. Regardless of genetic differences between individuals, agricultural information about soil, climate, sowing, growing seasons, and harvesting conditions (such as place, time, and GPS - Global Positioning System - coordinates) is invaluable for helping organisms address the issue of variable phyto-chemical compositions, which has remained unresolved.

***b. Traditional Knowledge Database***

A wide range of information should be included in this database, from knowledge gathered by ethnopharmacologists in Amazonian or African tribes to the thorough literature of TCM or Ayurvedic medicine, collected in several volumes. Once a link between expected biological activity and recognised applications has been established, the scientist may utilise this knowledge of previous usage to evaluate RPG organism location in addition to helping them choose the right organisms. It is needed that Specific data sets are created specifically for ethnobotany [69] in order to both utilise and protect the tradition of ethnopharmacology [71]. In this way, the EbDB database[70] is an effort to offer public access to a multilingual repository.

***c. Existing Databases***

Many databases are somewhat compatible with RPG (Recurrent Parent Genome).

**Dr. Duke's phytochemical and ethnobotanical** databases were developed by James Duke in 1971 and are currently housed at the Agricultural Research Service of the U.S. Department of Agriculture. Its contents contain information about phytochemicals, including a list of substances, information about their plant origins, concentrations, biological functions, and bibliographic references. Unfortunately, the database's usefulness is compromised by the absence of molecular structures and the usage of names without synonyms. The depth of ethnobotanical information in Duke's database, as well as the variety of ways to query it, are its strengths. The following fields, however, are somewhat off-limits: plants, chemicals, activities, conventional applications, and references.

**The Chapman & Hall-edited Dictionary of Natural Products (ChemNetBase) (DnP)** provides information on molecules, their names and synonyms, structures, qualities, and summaries of source species. Although DnP is a fairly rich library of chemicals, it is sadly lacking in information on organisms and molecular relationships, which inhibits RPG from using it. DnP is a commercial database that only allows licenced users and pay-per-view customers access to the data.Another relational database that has been maintained by the University of Illinois at Chicago since 1975 is napralert. The database provides information on organisms, organic substances, and biological processes.Access is free, however all that shows on the screen is the amount of hits.Detailed findings are supplied in a summary together with accompanying pharmacological and ethnopharmacological information, as well as bibliographic references, once the fees have been paid.

**Napralert** is an extremely comprehensive database and a leading authority on natural products, but because it lacks molecular information, it cannot be properly integrated into an RPG strategy.The "Plant for a future" charitable foundation is in charge of maintaining the Plant for a Future (Pfaf) database. The founders of the organisation claim that "20 species currently supply 90% of our nourishment" [71-87]. The Pfaf database offers information on more than 7000 plants with claimed traditional applications based on this fact. It's interesting to note that every plant is unique, seldom utilised, and maybe edible. Additionally, each plant is given a number between 1 and 5, depending on how edible and medicinal it is. Pfaf is an extremely thorough database, and the uniqueness of the plants that have been documented makes it particularly fascinating for RPGs. A heterogeneous database containing target, natural chemical, organism, and conventional usage data is integrated into the Greenpharma RPG platform. GPDB is tailored for RPG and has been optimised for it.

**The Supernatural database** might be mentioned in this context. It is a database of natural compounds that compiles molecules from many providers. Numerous databases with a focus on molecules, such Pubchem (http://pubchem.ncbi.nlm.nih.gov) and Chembank (http://chembank.broadinstitute.org), include a significant amount of natural substances. However, the lack of corresponding biological data frequently restricts their interest in role-playing games [76].

**4. Greenpharma's Reverse Pharmacognosy Platform (GRPGPlatform)**

Data on natural substances, sources, traditional knowledge, protein targets, and techniques like inverse screening software and cheminformatics tools are all necessary for reverse pharmacognosy. These many kinds of information and resources are independently accessible online and may be utilised in an RPG method. However, in reality, switching between tools is ineffective and challenging due to tool incompatibility (e.g., input and output data must be transformed in several file formats).

Greenpharma developed the RPG idea into a working system to aid in its research initiatives. All required tools were integrated to provide an RPG-specific platform. Data are uniform and simple to utilise from one phase to the next. As a result, data access is optimised, and all procedures are time and money efficient. The primary component of this platform is a sizable database that combines extremely diverse data with a web interface (intranet) that offers several options for results analysis and multiple search capabilities.As a result, the GPDB includes information on natural substances, species, traditional knowledge, and biological targets that can be accessed through a single online interface.

Chemoinformatic tools are included to manage molecular diversity selection, compute physico-chemical characteristics, calculate and show complex 3Dstructures, or search molecules by substructures or similarities. Examples of these tools are Openbabel and Jmol.Selnergy, a proprietary software programme for inverse screening, is the platform's other key component.

Selnergy is built on FlexX and Sybyl elements, and it is connected to the GPD's target portion. This amounts to around 7000 protein structures, the majority of which were taken from the Protein Data Bank (PDB) and represented therapeutic proteins with co-crystallized ligands. If Selnergy can accurately replicate the binding mechanism of the co-crystallized ligand, a protein model is added to GPDB. Combining known active ligands with "decoy" compounds is a second validation step.According to the simulated interaction energy, Selnergy should be able to rank the active chemicals higher than the inactive molecules. For the same protein, several structures may occasionally be recorded in order to account for the protein's flexibility. Biological characteristics are connected to targets and ligands in GPDB.

The GPDB is continuously updated and now includes over 10,000 biological characteristics, approximately 150,000 chemicals, and 160,000 species. Tools for data mining and automated data import have been created to speed up GPDB updates.The RPG platform will eventually incorporate a wider collection of experimental evidence to allow the confirmation of fresh research concepts produced by GPDB through a network of collaborators for bioassays. Additionally, the analytical chemistry lab at Greenpharma has the ability to extract, purify, and characterise novel natural chemicals as well as produce physico-chemical experimental data, enhancing the database.

**Reverse Pharmacognosy and its relationship**

In order to supplement pharmacognosy in the study of novel substances or plants for use in cosmetics or pharmacy, Greenpharma has developed the idea of reverse pharmacognosy. It is divided into five sections: a target database, virtual screening tools, a three-dimensional (3-D) structural database of natural compounds with its counterpart of a natural compound library designed for HTS, and an ethnopharmacological database.

* **Virtual chemical database**

The proprietary Greenpharma database and the commercial databases' natural substances are combined to create the virtual chemical database (VCDB). More than 100,000 natural compounds with their 3-D coordinates created by Concord[Pearlman] are available in this virtual compound library. The database was constructed in the Unity [Tripos] format, which allows for the extraction of a representative subset of the database or the evaluation of diversity using fingerprints. Selected compounds share internal Lipinski rules-based drug-like characteristics (Lipinski et al., 1997).The ''rule of five'' is thought to be overly restrictive and to eliminate several medications, particularly natural chemicals, by a number of writers. Thorough investigation on the distribution of properties across pharmaceuticals, chemicals from combinatorial chemistry, and natural and derivative substances. The abundance of aromatic rings, the saturation of molecules, the number of complex ring systems, and the amount of heteroatoms are the most notable distinctions.

The following criteria is followed to filter natural compounds:

- A molecular weight of between 150 and 700 Da.

- A maximum of 10 hydrogen bond donors.

- A maximum of 5 hydrogen bond acceptors.

- A maximum of 20 rotable bonds.

- A maximum of one sugar.

- A maximum of no more than 6 atoms in an aliphatic chain.

- No nucleic acids or peptides.

- No metals.

The last criterion for choosing compounds for virtual screening is based on the chemical diversity of the molecules. The investigation of chemical diversity and natural compound characteristics was made possible by VCDB.A pure natural chemical library that is appropriate for experimental screening and HTS was developed using a highly diversified subset of the VCDB and compounds that could be easily or commercially obtained. This library, which was created by taking chemical diversity and druglikeness into account, is anticipated to produce results for a wide range of biological experiments [77].

* **Target database**

A collection of protein 3-D structures (now more than 1500 structures) identified by X-ray crystallography or internal homology models may be found in the Target Database. A Protein Data Bank (PDB) code or an internal code is used to index each structure, which is then followed by the technique used to obtain it, such as X-ray crystallography, NMR, or homology modelling. The target database includes proteins from different mammals, bacteria, viruses, protozoa, etc. even though the majority of them come from humans.

Protease, oxygenase, and other biological mechanisms are used to categorise proteins. The molecular characteristics of the targets are reflected in this categorization. Additionally, they may be divided into groups based on biological processes like pigmentation, lipolysis, inflammation, etc. A protein can, of course, belong to multiple therapeutic families. This categorization takes into account biological traits and processes. For calibration and validation of the virtual screening, the structure of the co-crystallized ligand, if any, is recorded independently from the protein.Information for our online screening tools The root mean square deviation (RMSD) of the predicted placements, the co-crystallized ligand location, and the interaction energy of FlexX are all reported for the protein/ligand couples [77].

This RMSD measures the accuracy of a docking by estimating the spatial divergence between the estimated position of a ligand and the position determined by X-ray crystallography. Models having RMSD values higher than 1.5 should be carefully assessed. The retrieval of known active ligands from a sample of 100 inactive molecules is another stage in the validation process. This phase gives our virtual screening algorithm the ability to discriminate.

Interesting findings using virtual screening on models generated from rhodopsin homology modelling were recently published [77]. Amazing hit rates, which may reach 70%, were obtained when antagonists and agonists of G-protein coupled receptors (GPCR) were screened. Our target database also contains models, such as GPCRs or proteins having crystallised homologues, such as protein subtypes like phosphodiesterases.

* **SelnergyTM**

One area of molecular modelling that is rapidly developing is virtual screening.There are three different methods that may be distinguished: fragmental description (2-D), 3-D pharmacophores, and screening based on ligand characteristics, or physico-chemical properties (1-D data) [77]. An exclusive virtual high throughput screening (vHTS) technology called Selnergy incorporates the proven 3-D Target Database. FlexX is the docking engine. In the Tripos package's Sybyl 6.9, Selnergy is implemented. It enables the Target Database's list of proteins to be screened against the VCDB.

* **Ethnopharmacological database (ETPHDB)**

It was created a proprietary database with ethnobotanical information, botanical information, natural chemical structures, and results of biological tests for extracts and compounds. The information includes information on the family, genus, species, common names, synonyms, organs utilised in traditional medicine, and ethnic groupings. From the scientific literature or internal experiments, molecular structures and families are also preserved together with their biological activity. The applications of Selnergy includes Building therapeutic focused libraries, Building family focused libraries, Estimating biological properties of a compound library, Protein flexibility, Lead leveraging (from Pharmacognosy to lead & lead to Pharmacognosy)

Molecules and plants containing these hits, which were meant for insect bites, animal bites, etc. in ethnopharmacological usage, were prioritised for biological testing for in vitro validation in order to react to the pharmaceutical and cosmetic sectors. Our extraction technology was used to create plantextracts using various polarity solvents.We replenish molecules, purify them, or synthesise new ones.

With unique scaffolds and cyclooxygenase 2 extract, we are testing the in vitro activities of a number of natural substances. In order to create a bio-focused chemical library, similar molecules to the ones that were chosen were gathered (synthetic derivatives can also be created for the 16 Lead molecules from natural products: discovery and new trendspharmaceutical industry), and "similar plants" to the ones that were selected (i.e., the same family, biotope), were also extracted.

In the event of supply issues or patents, these bio-focused libraries will enable us to identify more powerful hits and quickly switch to related substances or plants. Invitrogen biological tests are always required for validating hits: passing from virtual and possible hits to genuine hits. Knowledge or virtual screening-based moleculeselections are effective methods for prioritising which compounds must be investigated. These examinations comprise cellular and/or binding experiments.

* **Repositioning of compounds**

Typically, chemical compounds are researched and created for a specific use.The fact that chemicals may have several biological impacts is widely recognised, nevertheless.Drug side effects and therapeutic effects are the most prominent example. The lack of selectivity against undesirable protein interactions is typically to blame for this. Selectivity is a relative notion since it depends on the compound's concentration. Additionally, it depends on how many side interactions one can afford to research. Selectivity is typically examined for subtype proteins.

As a result, the one molecule on target paradigm has obscured numerous potential "side" functions for a particular molecule.In order to discover new biological mechanisms, i.e. proteins that have not yet been discovered for interacting with EV and applications for this molecule, we do research on e-viniferin (EV). Previous research has shown its effectiveness in a wide range of fields, including anticancer, antioxidant, and hepatoprotector [77-78].

On the whole target library, EV was screened using Selnergy.There were many targets found that may interact with EV. For additional experimental research, PDE4 (the sole subtype found by Selnergy) was used. PDE4 binding tests (IC50 14 4:6 mm) were used to validate the activity of EV on PDE4. TNF-a and Interleukin-8 secretion tests on cells were used to further confirm EV. By suppressing PDE4 subtype, our research showed that EV has anti-inflammatory capabilities [77-78].

**Conclusion:**

India has advanced in its support of Ayurveda's global applicability in the context of health care through international networks. Raising public awareness of Ayurveda in other countries has been identified as a key thrust area. Hence Reverse Pharmacognosy helps to find out Novel chemical compound which cures serious illness as it uses Virtual Screening. The current review elaborates about to develop newer drug discovery strategies in Reverse Pharmacognosy which provides newer chemical structures with potential biological activities by combining the principles of reverse pharmacology with Ayurveda, Siddha, and other traditional medical systems.

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