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A Schematic Approach for Drug Discovery While Using Plant Sources

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Abstract

The combination of declining numbers of new drug approvals and rising prohibitive costs poses serious challenges to drug discovery. The advent of combinatorial chemistry has given rise to renewed hope of increasing the success rate of new chemical entities (NCEs). But even this scientific development has not improved the success rate of new drug discovery. This scenario has allowed us to develop a new approach to integrated drug discovery where Ayurvedic wisdom can interact with drug discovery from botanical sources. The first step in drug discovery involves NCE identification. NCEs can be obtained by chemical synthesis or isolated from natural products by biologically active fractionation. The source of many new drugs and active ingredients in pharmaceuticals comes from natural products. A starting point for discovering new plant-based medicines is to use Ayurvedic wisdom, traditional documented uses, undocumented tribal uses, and extensive literature review to identify suitable candidates. A frequency analysis of the components of anciently documented formulations and an analysis of their Ayurvedic properties will allow the selection of suitable candidate plants for fractionation based on their biological activity. We can give you a complete idea about the dominance of Vedic properties. Integrating the wisdom of Ayurveda into pharmaceutical research requires a paradigm shift in the extraction process from sequential to parallel extraction. Bioassay-based fractionation of identified plants yields standardized extracts or isolated bioactive pharmaceutical compounds as new drugs. This integrated approach improves drug discovery success rates and saves cost and time.

Keywords: Drug discovery; Extraction; Ayurveda; Biological activity

Introduction

New drug development is a complex, time-consuming and expensive process. The time from drug discovery to clinic is about 12 years, and in today's context he needs more than $1 billion in investment. Fundamentally, drug discovery involves the identification of new chemical entities (NCEs) that demonstrate the properties required for drug compatibility and medicinal chemistry [1]. These NCEs can be obtained by chemical synthesis or isolation from natural products. The first success story in new drug discovery stems from the invention of medicinal chemistry, which led to the need to develop large chemical libraries through combinatorial chemistry. However, this approach proved to be less effective in terms of overall success rate. His second source of NCEs potentially used as drug molecules are natural products. Prior to the advent of high-throughput screening and the post-genomic era, more than 80% of drug substances were pure natural products or inspired by molecules from natural sources, including semi-synthetic analogues. An analysis of the sources of new drugs from 1981 to 2007 shows that almost half of the drugs approved since 1994 are based on natural products [2]. Between 2005 and 2007, 13 drugs related to natural substances were approved. There are many examples of plant-derived new drug development. Morphine was isolated from opium obtained from the seed pods of the poppy (Papaver somnifera) about 200 years ago. After World War II, the discovery of penicillin inspired extensive screening of microbes for new antibiotics, expanding pharmaceutical research. Antibiotics (e.g. penicillins, tetracyclines, erythromycin), antiparasitic (e.g. avermectin), antimalarial (e.g. quinine, artemisinin), lipid control agents (e.g. lovastatin and analogues), organ immunosuppressant's etc. Few drugs developed from natural sources that have arguably revolutionized medicine [3]. Transplantation (cyclosporine, rapamycin, etc.) and anticancer drugs (paclitaxel, irinotecan, etc.).

Over 100 naturally occurring medicines are in clinical trials and at least 100 molecules/compounds are in preclinical development. Most of these molecules in the development pipeline are derived from plant and microbial leads. Cancer and infectious diseases are two major therapeutic areas where drug discovery programs are based on natural products, but many other therapeutic areas are also covered, including: B. Neuropharmacology, cardiovascular, gastrointestinal, inflammation, metabolism, etc. [4].

Among the various projects in various therapeutic areas, about 108 projects are based on plants. Further analysis of these projects shows that 46 of them are in preclinical stage, 14 are in phase I, 41 are in phase II, 5 are in phase III and 2 are in pre-enrollment stage.

In general, NCE's sources have his six classes. The four classes are plant sources, fungi, bacteria, and marine sources. In addition to these four classes, Modern Medicinal Chemistry added his two categories of artificial substances: synthetic chemistry and combinatorial chemistry [5]. Among these natural resources, plant resources are of particular importance in the context of this overview. Botanical sources are known to provide the following classes of NCEs to the drug discovery process.

- Bioactive compounds for direct use as pharmaceuticals such as digoxin.
- A biologically active compound having a structure that can itself serve as a lead compound for more potent compounds. Paclitaxel from Taxus species.
- New chemophores that can be converted into pharmaceutical-grade compounds with or without chemical analogues.
- Pure phytochemicals for use as marker compounds to standardize

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raw plant materials or extracts. A pure phytochemical that can be used as a pharmacological aid.

- Herbal extracts, such as green tea extract, as herbal medicines.

Advantages and Disadvantages of Drug Discovery from Natural Resources

Using plant sources as a starting point for drug development programs has several tangible advantages. In most cases, the selection of candidate species for study can be based on long-term human use (Ethno medicine) [6]. This approach is based on the assumption that active ingredients isolated from such plants are likely to be safer than those derived from plant species not previously used by humans. At some point, the synthesis of active molecules can be attempted to relieve pressure on resources [7]. Drug development, such as Rauwolfia serpentine and Digitalis purpurea, has historically fallen into this category of approaches. Such approaches can lead to the development of new molecules derived from the source due to the inherent limitations of the original molecule. For example, podophyllin from Podophyllin headroom has been subjected to dose-limiting toxicity. Such limitations could be largely overcome by the semi synthesis of topside, which is still used today in cancer therapy [8]. Similarly, camptothecin (first he was isolated from Camptotheca sp. and later from Mappia sp.) led to the development of new anticancer molecules such as topotecan and irinotecan. Natural resources as a starting point have a two-way promise of providing the original isolate as a candidate or development of semi-synthetic molecules to overcome the inherent limitations of the original molecule.

On the other hand, drug development from natural resources also has the following drawbacks:

In most cases, drug discovery and eventual commercialization can put significant pressure on resources and lead to undesirable environmental problems. Synthesis of active molecules may be an option, but all molecules are fully synthetic [9]. Therefore, some dependency on the lead resource persists. For example, anticancer molecules such as etoposide, paclitaxel, docetaxel, topotecan, and irinotecan continue to rely on highly sensitive plant sources for their starting materials, due to the impossibility of complete synthesis. Meanwhile, about 25,000 plant species are expected to become extinct by the end of this century.

As time goes on, the protection of intellectual property rights related to natural products becomes confusing. Broadly speaking, hints are based on some association with traditional usage. As more countries become Parties to the Convention on Biological Diversity (CBD), the process of access to basic lead resources, benefit sharing at the commercial level, etc. [10]. has become very complex in many countries. These processes tend to impede the pace of the discovery process at various stages, regardless of the concerns that lead to such processes.

Drug ability of Isolated Phytochemical Compounds

The challenges in drug development fall into two main categories. The dominant paradigm of drug discovery in the large-scale pharmaceutical industry and technical limitations in identifying new compounds with desirable activity [11]. Koehn and Carter enumerated the following unique characteristics of compounds isolated from natural products.

- Many chiral centers
- Increased steric complexity
- high number of oxygen atoms
- Low ratio of aromatic ring atoms to total heavy atoms
- High number of solvated hydrogen bond donors and acceptors
- Rub molecular stiffness
- Broad distribution of molecular properties such as molecular weight, octanol-water partition coefficient, and ring system diversity.

As medicinal chemists begin to develop analogues, either to improve the absorption or to reduce the toxicity and improve upon efficacy, which is frequently achieved by addition or deletion of selected functional groups, these distinctive characteristics of chemical entities of natural origin present a number of challenges [12]. As per a review different bioactive plant compounds were isolated in China from 1911 to 2000 like alkaloid, steroid, triterpene, limonoid, diterpene, sesquiterpene, monoterpene, tanin, isoflavonoid, flavonoid, polycyclic aromatic, lignan, coumarin, simple phenoloic, aliphatic, etc. Alkaloid may be distributed as 20%, flavonoids as 15%, triterpenes and simple phenolics around 10%, and remaining others below that, with limonoid being the least [13].

Although many natural compounds are biologically active and have good ADMET profiles (absorption, distribution, metabolism, excretion, and toxicity), it is safe to assume that they do not meet the requirements for "drug resemblance" [14]. Building a physico-chemically adjusted natural product library in line with lead generation is the task in order to market natural products to their maximum potential. Lipinski propagated simple set of calculated property called “rule of five” basis the drug candidates reaching Phase II clinical trials [15]. This rule is so named because it is an algorithm that consists of four rules where most of the cutoff numbers are 5 or multiples of 5. To be drug-like, candidates must have:

- less than 5 hydrogen bond donors
- less than 10 hydrogen bond acceptors
- Molecular weight less than 500 Da.
- Partition coefficient log P less than 5.

The purpose of the "Rule of Five" is to demonstrate bioavailability problems that can occur when two or more properties are compromised. Paclitaxel would never have been a drug if Lipinski's Law had been applied [16]. One of the major challenges is finding alternative drug eligibility criteria for naturally occurring compounds because they do not meet the rule of five. A major challenge, therefore, is to find eligibility criteria for alternative medicines to naturally occurring compounds.

Biological Activity Guided Fractionation for Compound Isolation

Biological activity-based fractionation was a process employed to identify lead drug candidates from any phytochemical matrix. However, there is no uniformity in methodology [17, 18]. Two approaches can be followed for the design of bioactive-guided fractionation extractions leading to the isolation of compounds that serve as lead compounds.

Parallel approach

This approach is applicable when the plant's bioactivity is known

from its traditional uses. The goal of this approach is to isolate the compounds responsible for activity based on their biological activity. In the parallel extraction approach, 3 different extracts are obtained [19, 20]. 100% methanol extract, 50% methanol extract, and 100% aqueous extract from raw plants. The most active fractions based on primary bioactivity screening are selected for further extraction and evaluation.

Sequential approach

This approach is useful when the biological activity of the plant in question is unknown and a random selection strategy is applied to the plant. Extraction is based on solvent polarity and fractions are obtained in sequential steps using hexane, chloroform, ethyl acetate, and butanol as solvents.

Further extraction includes purification steps during which structure elucidation of various compounds is performed. Biological activity is assessed in two steps, so two different models should be selected with endpoints in mind. Stage I screening models should be designed to assess efficacy [21]. On the other hand, screening models for secondary screening should be designed based on mechanism of action. For example, the glucose uptake assay can be used as a primary screening model to find potential antidiabetic molecules from natural sources. At stage II, it would be desirable to choose secondary assay models that are indicative of mechanism of action, such as Glut 4, PI3K, and IRTK [22]. It is also desirable to include cytotoxicity studies during the secondary screening level to determine the safety profile. In any case, bioactivity-based fractionation of crude extracts from natural sources can lead to different results at different stages [23]. Moreover, these results may provide unexpected opportunities to refine the design of discovery in subsequent phases. Possible consequences of a typical bioactivity-induced fractionation. Broadly speaking, natural products can offer three different possibilities when shortlisted based on knowledge of existing applications (either from ethnomedical leads or structured healthcare systems).

Conclusion

There is an urgent need to renew scientific enthusiasm for natural products for inclusion in drug discovery programs. One of the major concerns associated with natural products is the predictability of hit rates during various stages of drug development. Given the overall complexity of NCE plant sources, we would expect this predictability to be low if candidate species were randomly selected. Strategic selection and preselection of candidate species are required to improve predictability. Documenting clinical experience with herbal medicines can simplify problems associated with poor predictability as codified in the traditional medical system. New functional hints from traditional databases of knowledge and experience can help reduce three specific hurdles in drug development: time, cost, and toxicity. An integrative approach by combining different discovery tools with the emerging field of integrative biology is key to success in natural product drug discovery and development. Plant selection is the most critical step and requires a well-thought-out strategy.

To choose a suitable plant, you can follow the scheme below:

- Botanical Identification: Through tactical application of traditional wisdom, especially in relation to frequency of use. It is recommended that you list the prescriptions for the therapeutic segments that have been used.

- List of all formulas and their herbal ingredients (no need to consider metal and herbal mineral formulas).

- Component frequency analysis.

- To achieve the desired Rasa, Guna, Veliya, Vipaka, etc. Ayurvedic hypotheses. To reach a certain therapeutic range, for example in diabetes, the medicines Kathu and Tikta Rasa, Laguna, Ushna Velia and Kathu Bipaka should predominate.

- Map the above ingredients to these Ayurvedic attributes.

- Pre-selection of plant species for both frequency analysis and Ayurvedic properties.

Once the task of enumerating potential candidates for screening is completed, the extraction procedure can be done by a parallel approach rather than a sequential approach followed for randomly selected species. The rest of the investigation process follows these steps:

- Screening for biological activity in selective assays.

- Bioassay fractionation of identified plants.

- Isolation and structure elucidation of active ingredients.

- Evaluation of chemical feasibility, feasibility and patentability.

- Do-or-not decision based on safety, biological activity screening.

It's time for large pharmaceutical companies to start their development strategies. With the cost of new drug development rising, alternative approaches such as developing herbal extracts that hit multiple targets for new drugs should be seriously considered. Obviously, development costs are much lower for herbal extracts. Such strategies should not only increase the likelihood of success in delivering effective and safe medicines, but also minimize the risk of post-market recalls. Such complementary scenarios can go a long way in protecting the interests of both the pharmaceutical industry and the public.

Conflict of Interest

The author declares has no conflict of interest.

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