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Review Article

Natural Product Research for Drug Development: Methods, Limitations, and Potential Applications

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ABSTRACT

The multifaceted strategy used in contemporary exploration on the development of new medicines from medicinal shops combines botanical, phytochemical, biochemical combinatorial chemistry, and bioassay- guided separation ways. Natural coffers continue to offer an volition to pharmacological leads in the fight against multitudinous deadly conditions as diabetes, cardiovascular complaint, cancer, etc. There's a huge global demand for medicinals that are both safe and effective moment. Scientists are now turning again to natural coffers as a possible source of drugs for the treatment and operation of similar habitual and deadly conditions as a result of this. Still, there are also significant obstacles and constraints in this area, similar as the scale- up and commercialization of active substances, which only allow one out of every a thousand lead motes to be turned into a drug. Medicine development requires a rigorous, scientific approach as a abecedarian component from natural resource. This mini review provides an overview of the styles involved in natural product exploration starting from crude factory excerpt to bioactive pharmacological lead. Also, it also discusses the limitations of working concerning the bioactivity of medicinal shops.

INTRODUCTION

The term "natural products" refers to a very broad and varied variety of chemical compounds that are separated from and obtained from biological sources like plants, minerals, and organic materials [1]. Since more than a thousand years ago, there has been interest in natural goods [2]. Natural products have seen a rise in popularity in drug-discovery programs in recent years, largely because of their greater chemical variety versus synthetic compound libraries and their drug-like characteristics. Numerous commonly used medications that come from natural sources can be found as food supplements, nutraceuticals, and complementary and alternative medicines. In reality, certain commonly used medications for

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some fatal conditions come from natural sources (Table 1). This brief overview offers a methodical approach that can lead us from from nature to therapeutics with practical examples. It will discuss the methods involved in natural product research starting from crude plant to complete isolation, purification and characterization of active compound.

BIOACTIVE COMPOUNDS FROM MEDICINAL PLANTS

Bioactive compounds in plants can be defined as secondary plant metabolites inspiring pharmacological or toxicological goods in man and creatures.

The typical bioactive substances are created as secondary metabolites in shops. In addition to the primary biosynthetic and metabolic pathways of substances directed at factory growth and development, similar as carbohydrates, amino acids, proteins, and lipids, secondary metabolites are created within the shops. They can be allowed of as derivations of metabolic "side tracks " in factory cells and aren't needed for the factory to serve typically on a regular base. These composites can be distributed into different classes- glycosides, tannins, flavonoids, alkaloids, steroids etc. and are proved to be used against numerous ruinous conditions. Few examples of bioactive compounds are tabulated in Table 2.

Table 1. List of widely used drugs deived from natural sources.

Name of Drug	Source	Disease
Metformin	Galega officinalis	Diabetes
Vincristine	Vinca rosea	Cancer
Taxol	Taxus brevifolia	Cancer
Acetyldigoxin	Digitalis lanata	Cardiovascular disease
Digitoxin	Digitalis purpurea	Cardiovascular disease
Berberine	Berberis vulgaris	Bacillary dysentery
Atropine	Atropa belladonna	Neurological disorders

Table 2. Bioactive compounds isolated from natural sources.

Name of plant	Active compound	Reference
Diabetes		
Eugenia jambolana	α-Hydroxysuccinamic acid	[3] US patent-6426826, 2002 Indian patent 230753, 2009 (Sharma et al.)
Cassia auriculata	Coumarin derivative	[4] Patent filed (Sharma et al.)
Glycine max	Guanidium derivative	Patent filed (Sharma et al.)
Momorandica charantia	Charantin	[5]
Gymnema sylvestris	Gymnemic acid	[6]
Cardiovascular Diseases		
Eugenia jambolana	α-Hydroxysuccinamic acid	[7] Indian patent 230753, 2009 (Sharma et al.)
Terminalia arjuna	Arjunolic acid	[8]
Vitis vinifera	Resveratrol	[9]
Glycine max	Genistein	[10]
Cancer		
Taxus brevifolia	Taxol	[11]

METHODS IN NATURAL PRODUCT CHEMISTRY

Depending upon the objects, different styles could be followed in hunt of the active composites from shops. This includes biochemical combinatorial chemistry and bioassay- guided separation approaches. The most favored fashion used in natural product chemistry is Bioassay- guided

separation. It's generally used when the active element isn't known. After insulation of a pure substance, the task of expounding its chemical structure can be addressed. For this purpose, the most important methodologies available are nuclear glamorous resonance spectroscopy (NMR) and mass spectroscop(MS)(13). General strategy for factory- deduced medicine discovery is bandied as follows

Collection and Identification of Plant Material

Depending on where the metabolites of interest (if they're known) accumulate, the entire factory or a specific section can be gathered. Age of the factory and environmental parameters (similar as temperature, downfall, quantum of daylight, soil parcels, and altitude) can have an impact on the collection of factory accoutrements (13). To establish a reproducible profile type and quantum) of metabolites, it's pivotal to take this into account when collecting data(14). The complete verification of the factory, including its bracket into its class, order, family, rubric, and species, should be carried out by a factory taxonomist or botanist(15). Any point related to the collection, similar as the name of the factory, the identity of the corridor collected, the place and date of collection, should be recorded as part of the testimonial(a dried instance pressed between wastes of paper) deposited in a herbarium for future reference.

Extraction of Plant Materials

Factory accoutrements are generally uprooted by means of liquid detergents in what's known as the "solid-liquid detergent birth". A typical solid-liquid detergent birth process for factory accoutrements involve drying and grinding of the factory material, choosing a suitable birth detergent and birth procedure(16).

Maceration

This method, which is easy but widely used, includes leaving the pulped plant to soak in a appropriate solvent and save it in an enclosed field at room temperature. [13].The extraction velocity can be elevated by way of the use of mechanical shakers or mixers, which involve every now and then or continuously stirring the practise. Maceration includes soaking the plant material in the perfect solvent, the extraction is focused and then processed through filtering. [17].a chilly solvent is used to gradual down the decomposition system; it additionally takes longer to complete and calls for larger volumes of solvent. "

Percolation

This is similar to the maceration process, but hot solvent is refluxed through the plant material. It's far faster and uses much solvent but decomposes because heat may occur [17].

Soxhlet Extraction

Soxhlet extraction is a form of non-stop percolation with clean solvent, which makes use of special glass ware. On this procedure, the plant cloth is separated from the extract by way of encasing it in a paper thimble below the dropping condensed solvent. Whilst complete, the solvent within the thimble siphons off into the principle vessel containing the extractant, and the technique maintains [17]. The benefit of this method is that clean solvent always extract the plant cloth extra successfully with minimal solvent, however, heating and therefore decomposition of compounds is once more a drawback.

Steam Distillation

There is a special apparatus for distilling volatile oils which are immiscible with water. However, the system is less useful because a large volume of aqueous extract is produced, If composites being uprooted are water soluble. Still, in some cases, a partition system may be used to concentrate the extract(17).

Sequential Solvent Extraction

Still, a accessible and constantly used procedure is successional solvent extraction, If the opposition and solubility of composites that are insulated aren't known. In successional solvent birth, the

factory material is uprooted with a series of detergents of different opposition. The usual way is to start with anon-polar detergent and completely prize the factory material followed by a series of more polar detergents until several excerpts are attained by adding solute opposition. For illustration, a first step, with dichloromethane, will extract terperoids, less polar flavonoids(flavones, flavonols, flavononeS) and other less polar accoutrements (17). A posterior step with acetone or ethyl acetate will extract flavonoid glycosides and other medium polar ingredients. A posterior extraction with alcohol or water will extract largely polar ingredients (17). The chemical profile of solvents used for extraction is diagrammatically presented in (Fig. **1**).

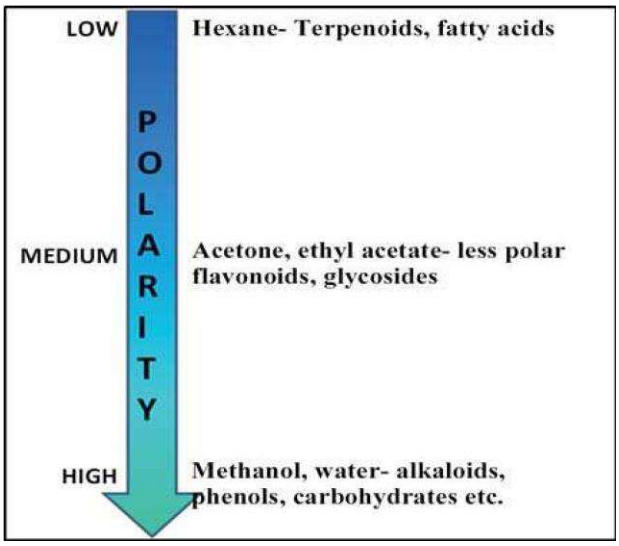

Fig. (1). Chemical profile of commonly used solvents for extraction.

Once the extraction is complete, the extractant is usually concentrated under vacuum, for large volumes or solvents and blown down under nitrogen for small volumes, ensuring at the same time that volatiles are not lost. Aqueous extracts are generally freeze-dried and stored at 20^{o}C as this low temperature reduce the degradation of the bioactive natural product.

Extraction protocols may sometimes be modified depending on the type of molecules being extracted, e.g. acids may be added to extract alkaloids as their salts [17].

SCREENING THE EXTRACT FOR BIOLOGICAL ACTIVITY

Once the extract has been attained, the natural activity is generally demonstrated by in vitro bioassay system. In vitro screening styles for natural exertion are generally divided into two formats; the low- throughput screening and high-throughput screening styles, depending on the number of extracts to be screened. In low-throughput screening (LTS), small figures of extracts(a single extract up to hundreds of extracts) are allocated into a format that's compatible with the bioassay(e.g. a microtitre plate or sample tube). This approach is used extensively in academic laboratories where only a fairly low number of excerpts are assessed. In high- throughput screening(HTS), thousands of excerpts are allocated into a format(generally a microtitre plate with numerous wells,e.g. 384 wells per plate) and screened in the bioassay. This approach is favored by the pharmaceutical assiduity. This may have thousands of samples(both natural and synthetic) for natural evaluation. The large scale approach means that opinions can be made fleetly about the status of an excerpt, which has an impact on the cost of the medicine discovery process(18).

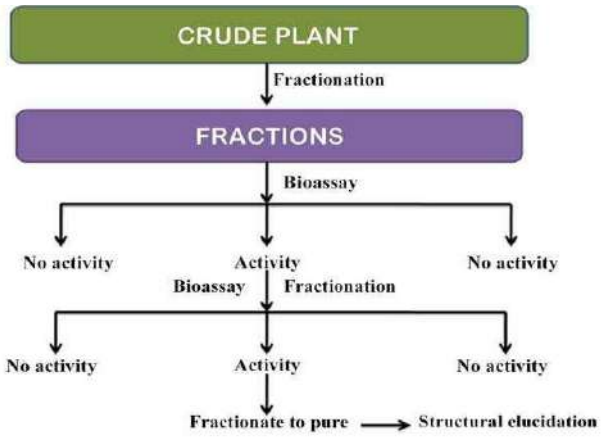

Fig. (2). General scheme for bioassay-guided isolation of active compounds.

BIOASSAY GUIDED FRACTIONATION AND ISOLATION OF ACTIVE COMPOUNDS

A bioassay-guided fractionation method is used to separate active fractions. In bioassay-guided fractionation (Fig. 2), a crude mixture is divided into its component fractions using chromatographic techniques, and each fraction is then biologically assessed (through a bioassay). For further fractionation, only fractions that exhibit biological activity in the bioassay are chosen. Until a pure product with the appropriate activity is isolated, the cycle of fractionation, testing, and further fractionation is repeated [19].

CHARACTERIZATION AND STRUCTURE ELUCIDATION OF ISOLATED COMPOUNDS

The chemist will try to attempt the elucidation of the compound once the biological evaluation has been completed and the separation of the natural product has been accomplished. The traditional spectroscopic methods used for structure elucidation include nuclear magnetic resonance (NMR), 1-D and 2-D proton NMR, C-13 NMR, infrared (IR), mass spectrometry (MS), and X-ray analysis [13].

MECHANISM OF ACTION: NECESSITY OF THE DAY

The best source of chemotype diversity for the development of new medicines is found in natural ingredients. In the modern world, a drug's mechanism of action must be clearly understood before it can be approved. Understanding each drug's mechanism of action is crucial for its use in court. Numerous research teams are striving to clarify the mechanism of action of natural goods after observing its benefits in treating conditions like diabetes and cancer.

An anti-diabetic medication, for instance, may exert its function by extra-pancreatic action, pancreatic action, or both. Since diabetes mellitus is caused by a relative or absolute insulin deficit, the estimation of insulin after drug therapy would reveal if the medication lowers blood glucose via stimulating insulin action. Insulin signaling pathways are also impacted by diabetes. The insulin receptor tyrosine kinase, whose activity is drastically decreased in type 2 diabetes, is the essential alteration.The expression of several genes involved in insulin signalling pathways is also affected during diabetes. Among these, gene which expresses glucose transporter 4 (GLUT4) in skeletal muscles, adipose tissue and heart is important. In diabetes, decreased expression of GLUT4 as well as attenuation in its trafficking to the plasma membrane leads to impaired glucose disposal by these tissues.

STRUCTURE-FUNCTION RELATIONSHIP-PARADIGM BEHIND ACTIVITY

The backbone behind natural conditioning of any emulsion lies in its molecular structure. The major handicap in the field of natural product exploration is lack of complete structural characterization of purified composites. Recent High throughput technologies combined with advanced logical technologies have handed new path for structural characterization of natural products. Several microarrays and customized PCR arrays have simplified the identification of molecular targets for particular conditions. These arrays can be customized for specific complaint. The coupling of chromatographic styles similar as high performance liquid chromatography(HPLC) with diode array discovery, mass spectrometry(MS) or nuclear glamorous resonance spectroscopy(NMR) or, and with, on- line bioactivity assays, is an important tool for high throughput screening of natural product fusions. The effective use of automated procedures and databases in the insulation, identification and natural profiling of bioactive composites from natural sources will be the stylish guarantee to the continued discovery of new chemotypes from nature(20). Structure-exertion studies of these leads, preferentially

combined with computer visual model structure, should affect in motes with optimal exertion and bioavailability, smaller side goods and an respectable remedial indicator and for the development to new medicines.

Structure-activity studies of these leads, preferentially combined with computer graphic model building, should result in molecules with optimal activity and bioavailability, fewer side effects and an acceptable therapeutic index and for the development to new drugs.

Innovations in analytical technology have often played an important role in the progress of natural product chemistry.

High performance liquid chromatography(HPLC) is used routinely in phytochemistry to ' pilot ' the preliminary isolation of natural products(optimisation of the experimental conditions, checking of the different fragments throughout the separation) and to control the final chastity of the isolated composites(21, 22). The development of LC- hyphenated ways related to this effective separation fashion in the once 20 times has handed important new tools similar as LC/ UV photodiode array discovery(LC/ UV- pater)(23), LC/ mass spectrometry(LC/ MS)(24) and veritably lately LC/ nuclear glamorous resonance(LC/ NMR)(25). The combination of the high separation effectiveness of HPLC with these different sensors has made possible the accession of on- line reciprocal spectroscopic data on an LC peak of interest within a complex admixture. As crude factory excerpts represent veritably complex fusions containing up to hundreds of ingredients, these new LC- hyphenated ways have been fleetly integrated for the study of crude factory excerpts(26).

In natural product chemistry, the combination of UV, MS and NMR spectroscopic data of pure ingredients has frequently permitted their unequivocal structure determination. Other ways similar as IR or X-ray crystallography have been used less frequently and substantially when the other spectroscopic styles failed to give a complete structure assignment. Advancement in NMR spectroscopy has led scientists to have a better view of their composites. Currently ultramodern NMR spectroscopy performed with cryospectrometers operating at high glamorous field(up to21.14 Tesla, i.e. 900 MHz for 1H) and able of executing a variety of sophisticated, multipulse and multidimensional experiments.

Another advancement in this field is solid state NMR.

PRECLINICAL AND CLINICAL STUDIES

Large quantities of the lead compound are isolated when its novelty and structure have been established. It is then decided whether the compound can be manufactured from scratch or whether chemical modification is necessary to increase its biological activity. Extensive in vivo tests will be performed on the lead chemical to determine its activity, toxicity, and effectiveness. Preclinical investigations are what we refer to as these. Clinical studies, the most thorough review stage of a drug candidate after preclinical studies, are when a drug lead fails due to toxicity or a lack of efficacy in humans. The chemical is now a medication after these trials are successfully completed, which typically leads to a product licensing. Given the complexity of the process described above, it is not surprising that many natural product drug leads fail to make their way onto the market. Some estimates state that only 1 in 10,000 of plant-derived drug leads may actually make their way to the market [18]. The process is also lengthy and it may take 12-15 years from the collection of the original plant material to the granting of a license for the new drug.

LIMITATIONS

As discussed earlier in this minireview there are many plants and their bioactive compounds which can be utilized for human welfare. Although, around 95% of isolated compounds derived from

natural sources could not reach the market as drugs. There are several serious limitations in this field:

The process which leads to an active compound is very lengthy and tedious. The isolation procedure usually starts with a number of active fractions, even though the HTS is available today; it is a prolonged process to reach the bioactive component. Secondly, the bioactive compounds usually have poor yield (0.01%0.9%).

This process requires huge amount of funds which are not available. Starting from the solvent costs to the cost of bioassays involved in isolation and characterization procedures, the path from nature to therapy is an expensive affair.

Lack of awareness of the systematic methodology which can lead to potential drugs- However, many research groups in the world are working in the field of drug development but the knowledge regarding preliminary screening and purification still requires lots of further understanding.

Difficulties faced by researchers for commercialization of compounds- Commercialization of any compound as a drug requires collaboration with pharmaceutical company whose absolute prerequisite is series of toxicological and clinical trials. Therefore, this process from natural source to drug is a long, time consuming and money requiring process.

Failure in toxicological studies- There are different phases of toxicological studies- acute, sub-acute, chronic which require large amount of active compound and it is difficult to scale up the compound collection even after discovery of high throughput techniques.

Lack of structural diversity: Plants are a rich source of natural products, but their structural diversity may be limited compared to synthetic compounds. This may limit the range of biological targets that can be addressed.

Complexity of purification: Plant extracts contain a mix of compounds, some of which may be bioactive while others may not. Isolating the target compound can be challenging, especially if it is present in low amounts.

Reproducibility: Natural products obtained from plants can vary in composition depending on factors such as season, soil conditions, location, and plant genetics. This can affect the reproducibility of experiments.

Pharmacokinetics: Many natural products have poor pharmacokinetic properties, such as low bioavailability, rapid metabolism, and poor solubility. These factors can limit their effectiveness as drugs.

Intellectual property issues: Many natural products are not patentable because they are already known in the art or occur naturally. This can make it difficult for companies to recoup the costs of drug discovery and development.

Sustainability: Plant-derived natural product research relies on the extraction of compounds from plants, which can have negative environmental impacts and may not be sustainable in the long term. Alternative methods of producing natural products need to be explored.

CONCLUSION

In conclusion, natural products discovered from natural sources have provided various clinically used drugs. As drug discovery from natural sources has traditionally been so time-consuming, faster and better methodologies for bioassay screening, compound isolation, and compound development must be employed. Even with all the limitations facing drug discovery from natural products isolated from medicinal plants can be predicted to remain an essential element in the search for new medicines.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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