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Challenges to Natural Products

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ABSTRACT

The therapeutic properties of plants are immemorial,many pathological conditions are treated using plant-derived medicines. These medicines are used as concoctions or concentrated plant extracts without isolation of active compounds. Modern medicines requires the isolation and purification of one or two active compounds. Recent advances and emerging technologies for metabolic pathway engineering and synthetic biology have transformed the field of natural product discovery, production, and engineering. Despite these advancements, there remain many challenges in understanding how biosynthetic gene clusters are silenced or activated, including changes in the transcription of key biosynthetic and regulatory genes. This knowledge gap is highlighted by the success and failed attempts of manipulating regulatory genes within biosynthetic gene clusters in both native producers and heterogonous hosts. These complexities make the choice of native producers versus heterogonous hosts, fermentation medium, and supply of precursors crucial factors in achieving the production of the target natural products and engineering designer analogs. Nature continues to serve as inspiration to overcome the knowledge gaps and developing new research strategies. By exploiting the evolutionary power of nature, alternative producers, with the desired genetic amenability and higher titers of the target natural products, The acceptance of natural health products (NHPs) or "phytomedicines" by the Western medical community, questions related to active ingredients, mechanisms of action, toxicology, and drug interactions will need to be satisfactorily addressed. Since NHPs are generally manufactured from highly variable raw materials, identifying the therapeutically active ingredients can be challenging.

INTRODUCTION

The natural products also present challenges for drug discovery, those are technical barriers to screening, isolation, characterization, and optimization of the crude drug. the natural products are small molecules produced naturally by any organism including primary and secondary metabolites. They include very small molecules, like urea, complex structures like taxon.

The importance of natural products for medicine and health are introduced. Since our earliest ancestors chewed on certain herbs to relieve pain, or wrapped leaves around wounds to improve healing, natural products have often been the sole means to treat diseases and injuries.(1)

Natural products and their derivatives are commonly used as food additives in the form of spices and herbs, antibacterial agents, products are important sources for new drugs and are lead compounds suitable for further modification during drug development. The large proportion of natural products in drug development as stemmed from the diverse structures and the intricate-carbon skeletons.

Historically, natural products have played an important role in the development of pharmaceutical drugs for several diseases including cancer and infection.(2)

A natural product is a chemical compound or substance produced by a living organism—that is, found in nature. In the broadest sense, natural products include any substance produced by life. Natural products can also be prepared by chemical synthesis (both semisynthesis and total synthesis) and have played a central role in the development of the field of organic chemistry by providing challenging synthetic targets. The term natural product has also been extended for commercial purposes to refer to cosmetics, dietary supplements, and foods produced from natural sources without added artificial ingredients.

Within the field of organic chemistry, the definition of natural products is usually restricted to organic compounds isolated from natural sources that are produced by the pathways of primary or secondary metabolism. Within the field of medicinal chemistry, the definition is often further restricted to secondary metabolites. Secondary metabolites are not essential for survival, but provide organisms that produce them an evolutionary advantage. Many

secondary metabolites are cytotoxic and have been selected and optimized through evolution for use as "chemical warfare" agents against prey, predators, and competing organisms.

Natural sources may lead to basic research on potential bioactive components for commercial development as lead compounds in drug discovery. Although natural products have inspired numerous drugs, drug development from natural sources has received declining attention in the 21st century by pharmaceutical companies, partly due to unreliable access and supply, intellectual property, cost, and profit concerns, seasonal or environmental variability of composition, and loss of sources due to rising extinction rates. (3)

Foundations of organic and natural product chemistry

The concept of natural products dates back to the early 19th century when the foundations of organic chemistry were laid. Organic chemistry was regarded at that time as the chemistry of substances that plants and animals are composed of. It was a relatively complex form of chemistry and stood in stark contrast to inorganic chemistry, the principles of which had been established in 1789 by the Frenchman Antoine Lavoisier in his work. (4)

Isolation

Lavoisier showed at the end of the 18th century that organic substances consisted of a limited number of elements: primarily carbon and hydrogen and supplemented by oxygen and nitrogen. He quickly focused on the isolation of these substances, often because they had an interesting pharmacological activity. Plants were the main source of such compounds, especially alkaloids and glycosides. It was long been known that opium, a sticky mixture of alkaloids (including codeine, morphine, noscapine, thebaine, and papaverine) from the opium poppy (Papaver somniferum), possessed narcotics and at the same time mind-altering properties. By 1805, morphine had already been isolated by the German chemist Friedrich Sertürner and in the 1870s it was discovered that boiling morphine with acetic anhydride produced a substance with a strong pain suppressive effect: heroin. In 1815, Eugène Chevreul isolated cholesterol, a crystalline substance, from animal tissue that belongs to the class of steroids. (5)

Synthesis

A second important step was the synthesis of organic compounds. Whereas the synthesis of inorganic substances had been known for a long time, the synthesis of organic substances was a difficult hurdle. In 1827 the Swedish chemist Jöns Jacob Berzelius held that an indispensable force of nature for the synthesis of organic compounds, called vital force or life force, was needed. This philosophical idea, vitalism, well into the 19th century had many supporters, even after the introduction of the atomic theory. The idea of vitalism especially fitted in with beliefs in medicine; the most traditional healing practices believed that disease was the result of some imbalance in the vital energies that distinguishes life from nonlife. A first attempt to break the vitalism idea in science was made in 1828, when the German chemist Friedrich Wöhler succeeded in synthesizing urea, a natural product found in urine, by heating ammonium cyanate, an inorganic substance.

This reaction showed that there was no need for a life to prepare organic substances. This idea, however, was initially met with a high degree of skepticism, and only 20 years later, with the synthesis of acetic acid from carbon by Adolph Wilhelm Hermann Kolbe, was the idea accepted. Organic chemistry has since developed into an independent area of research dedicated to the study of carbon-containing compounds since that element in common was detected in a variety of nature-derived substances. An important factor in the characterization of organic materials is based on their physical properties (such as melting point, boiling point, solubility, crystallinity, or color). (6)

Structural theories

A third step was the structure elucidation of organic substances: although the elemental composition of purely organic substances (irrespective of whether they were of natural or synthetic origin) could be determined fairly accurately, the molecular structure was still a problem. The urge to do structural elucidation resulted from a dispute between, a silver salt of the same composition but had different properties. The elemental analysis shows that both salts contain equal quantities of silver, carbon, oxygen, and nitrogen. According to the then prevailing ideas, both substances should possess the same properties, but this was not the case. This apparent contradiction was later solved by Berzelius's theory of isomers, whereby not only the number and type of elements are of importance to the properties and chemical reactivity, but also the position of atoms within a compound. This was a direct cause for the

development of structure theories. They posited that carbon is tetravalent and can bind to itself to form carbon chains as they occur in natural products. (7)

Natural products are made up

Sr.no	Natural product
1	Traditional (Chinese medicine and Kampo system)
2	Ayurveda (Indian system of medicine)
3	Unani system of medicine
4	Homeopathic system of medicine
5	Naturopathy and yoga
6	Aromatherapy

Principle of Ayurveda

Ayurveda-ancient science of life is believed to be prevalent for the last5000 years in India**.** Ayurveda is based on the hypothesis that composed of 5 basic elements viz. space, air etc. They existing the human body in combined forms like (Vata, pitta, Kapha). Vata, pitta, Kapha together are called tridosha. Tridosha exists in the human body in 7forms called saptadhatu. (8)

Types Of Classical Ayurvedic Formulations

1) Ark (Distillation of Herbs) Asava & Arishta (Natural fermented Liquid Medicines)

2) Avaleh (Jams/paste-like products) Bhasma (Purified calcinations) Churna (Powders)

3) Ghrita (medicated clarified butters) Guggulu (Resins)

4) Kwath/Kashaya

The Ayurveda drugs are derived from vegetable sources from parts of the plant like root, leaf, flower; fruit extrude or plant **as** a whole. (9)

Method of Preparation

1. **Arishta and Asava:** made by soaking the herbs either in powder form or in the form of decoction in a solution of sugar or jugglery, as the case may be, for a specific period, during

which it undergoes a process of fermentation and generation of alcohol and facilitates the extraction of the active ingredients contained in the herbs.

2. Rasayan: Ayurvedic medicines containing mineral drugs as main ingredients are called Rasa rasayan or Ras-yoga. They are in pill form or powder form/ forest, minerals such as Anrala, Swarna, Rajata, Tamra, etc., and sulfur impurified state are used to convert in the form, called kajuali then other drugs are added in small quantities, mixed well and grounded to form a fine powder.

3. **Lauhakalpas** are made up of Loha Bhasma as the active ingredient with other drugs. The other active ingredients are made to fine powder and mixed with Loha Bhasma.

4.VatiorGutika Medicines prepared in the form of tablets or pills are known as vati or gutka, made of one or more drugs of plant, animal, or mineral origin**.**

5.Churna It is a fine powder form of drugs. All these herbs and other active ingredients are cleaned, dried, and powdered together by mechanical means to the fineness of at least 80 mesh.

6. lehya is a semi-solid preparation of drugs. Made by addition of jagger sugar or sugar candy and boiled with prescribed drug juices decoction, Honey, if required is added when the preparations are cold and mixed.(10,11)

Quality Control and Standards

At present there is no pharmacopeia standard on each of the active ingredients of ayurvedic medicine like allopathic medicine. For standardization and quality control of Ayurvedic drugs, various steps like physical description, physical tests, pharmacoginised techniques, etc, to ascertain the species of plant and study their pharmacognostic character for identification detection and analyzing the crude drug.

Generally, ayurvedic products is fully dependent on the quality of raw materials and process of manufacture. The quality control process of some Ayurvedic formulations can be contained from ‘Pharmacopeial Laboratory of India Medicine, near ALTC, Ghaziabad(U.P).The products are to be manufactured as per Indian system of medicines of Ministry of Health.(12)

Challenges in natural health product research:

Sr.no	Challenges
1	Standardization
2	Challenges in the configuration
3	Bioactive Natural Products
4	Future Challenges of Natural Products and Medicines Security
5	Plant analysis
6	Technology
7	Publication of results

Standardization

Before there can be acceptance of natural health products (NHPs) or "phytomedicines" by the Western medical community, questions related to active ingredients, mechanisms of action, toxicology, and the drug interactions will need to be satisfactorily addressed. Since NHPs are generally manufactured from highly variable raw materials, identifying the therapeutically active ingredients can be challenging. Standardization according to all known bioactive components is critical to ensure consistent pharmacological and clinical results. Through the patented technology, ChemBioPrint. During early ChemBio Print product development, the optimal active components of the natural extract are identified and characterized chemically (chemical fingerprinting) and pharmacologically through a variety of activity assays (biological fingerprinting).

Subsequent manufacturing each batch is standardized accordingly and has consistent composition and efficacy. Case studies will be presented on two commercially available ChemBioPrint products: COLD-fX (an immune-modulator) and REMEMBER-fX (a neuro-modulator). Unique and important structure-function relationships exist between the major classes of bioactive molecules from the shared source materials, of these two products. Through numerous published and ongoing clinical trials and pharmacological studies, these ChemBioPrint products are consistent, safe, and effective nowadays. (13)

1. Challenges in the configuration

From a case-selective perspective, the planar structures of natural products determined with microgram samples, the configurational assignment continues to be a challenge. The relative

and absolute configurations of natural products assigned by devising original approaches, relying on carefully acquired data on a case-by-case basis. From this the most widely available methods and techniques for the absolute configuration determination of novel natural products are presented, selected illustrative examples, are original approaches integrating different chemical, spectroscopic, computational methods have been devised to solve stereochemistry issues of natural small molecules. (14)

2. Bioactive Natural Products:

Bioactive natural products are a rich source of novel therapeutics. the search for bioactive molecules from nature continues to play an important role in new medicinal agents. This volume, which comprises sixteen chapters written by active researchers and leading experts in natural products chemistry, brings together an overview of current discoveries in this remarkable field, also provides information on the industrial application of natural products for medicinal purposes.

38 natural product-derived drugs were approved in the decade from 2000 to 2010 for various indications including 15 for infectious diseases, 7 each for oncology, neurological diseases, and cardiovascular disorders, 4 for metabolic disorders, and 1 for diabetes. It is therefore not surprising that by 2008 more than a hundred of new drug candidates from natural sources like plants, bacteria, fungi and animals or from semi-synthetically were reported to be in clinical development with a similar number in preclinical development.

A more recent example is the cancer therapeutic paclitaxel (Taxol)derived from the Yew tree, which was discovered in the 1970s, but there are difficulties in obtaining commercial compound quantities only reached the market in late 1992, overall, only 244 prototypic chemical structures (over 80% came from animal, plant, microbial or mineral origin) have been used as templates to produce medicines up to 1995, and relatively few new scaffolds have appeared since. About half of the marketed agents in today's arsenal of drugs are derived from biological sources with the large majority being based on terrestrial natural product scaffolds. (15)

3. Future Challenges of Natural Products and Medicines Security

Natural products matter, for they are essential contributors to societal well-being and global health. Flavors, fragrances, essential oils, traditional medicines and phytopharmaceuticals, and prescription and over-the-counter products all utilize constituent materials from natural sources. However, these vast natural resources of Earth are disappearing, and climate change and market expansion by dramatically increasing and aging population will continue to train plant sourcing in the decades ahead.(16)

1. General

Constituent international and regional scientific groups and organizations collaborate and gain a "voice" to promote the importance of natural products and the irroles in society, particularly medicinal agents for global health care.

i) The intellectual property rights conflicts between the CBD/Nagoya Protocol and the TRIPS agreements be resolved to enhance investment in natural product development.

ii) Can groups (international organizations, NGOs, companies, academia, and regulators) come together to work for improved, integrated health care systems, based on natural products?

iii) Can multicenter, international collaborative research programs are developed aimed at enhancing traditional medicine and phytotherapeutical product quality, safety, efficacy, and consistency.

iv) The internet sale of TMs and natural products be regulated to enhance patient protection from fraud.(17)

2) Sustainability

i) Can all medicines, natural and synthetic, be regards as sustainable commodity, and the needs for 2030 etc.be met through sustainable sourcing.

ii) Can the impact of climate change on the accessibility to TMs be assessed and ameliorated to foster the sustainable sourcing of plants for health care.

iii) Can traditional medicine research be placed on a sustainable basis by manufacturing

companies).

iv) Can medicinal plant genome resource centers be established to preserve critical medicinal plants for the future?

v) Can waste products from food, medicinal plant, and essential oil processing be developed for the isolation of compounds for a) drug synthesis, b) the potentiation of synergistic drug activity) overcoming drug resistance.(17)

3) Patients

i) Can traditional medicines be developed to become consistent, safe, and effective, and remain accessible to a global population.

ii) Can the translation of meaningful research results on traditional medicines and phytotherapeuticals to products and practice be made more effective for patient benefited.

iii) Can evidence-based, ineffective TMs be eliminated from practice? TM products become a patient reality In other words, can patients be appropriately protected from adulterated and contaminated TMs.

iv) Can an effective medicine balance be struck between "Western-based" medicinal agents and those derived from TCMs, Ayurveda, etc. to optimize affordable and integrated care for more diverse populations? (18)

4) Plant analysis

i) Can plant extraction, separation, purification, and identification be conducted using the most sustainable technologies?

ii) Can a consolidated database of the DNA barcodes of all traditional medicines be achieved?

iii) Can the UHPLC-MSn analysis of a plant extract be made extremely fast (< 5 min), and concomitant with the preliminary database identification of the metabolites?

iv) Can automated compound dissolution and characterization from a crude plant or organism matrix be achieved).

v) Can molecular networking be used to discover new botanical relationships, and for the drug discovery of biologically active metabolites. (19)

5) Synthesis

Vegetables, or other sustainable and recyclable natural reagents become an integral aspect of the production of both drugs and chemicals.

i) Can the complete synthesis of a complex drug molecule be achieved using only recyclable and renewable reagents?

ii) Can plants be engineered to produce renewable organic chemicals for synthesis?

6) Traditional medicine

i) Can the 300 most important traditional medicinal plants that must be sustainably developed be identified and conserved?

ii) Can the global harmonization of the diverse regulations applied to traditional medicines become a reality?

iii) Can a new category of standardized, accessible effective natural product preparations be developed for clinical use in developing countries?

iv) Can evidence-based TM products be regulated other than as “drugs”, and limited claims be allowed in developed countries?

v) Can traditional medicines, using an evidence-based approach, fill some of the chasms in health care in concerned drug therapy for the prevalent diseases of the majority?

vi) Can network pharmacology reduce the biological requirements (and therefore the time and cost) for the approval of medicinal agents in both the developing and developed worlds?

vii) Can a global database of the summed knowledge (cultural and scientific) of traditional medicine and medicines be created and developed for open access?

viii) Can the optimum times for accessing, and the methods for processing, a medicinal plant be determined?

ix) Can the origin(s) of the biological activity of medicinal plants be traced to the plant metabolites or plant-associated microbial metabolites?

x) Can metabolomics answer critical analytical questions to optimize TM cultivation and to understand the outcomes of natural products on animal and human metabolism?

xi) Can the importance of the secondary metabolites in foods and spices, as modulators of pharmaceutical care, be established?

xii) Can the illicit trade in threatened and endangered medicinal products (rhino horn, bear gall bladder, bear paw, etc.) be stopped?.(20)

7) Technology

i) Can the important emerging spectroscopic, chromatographic, remote sensing, and deep learning technologies be continuously integrated into the natural product sciences?

ii) Can databases for the online searching of raw proton and carbon-13 NMR and mass spectral data of natural products be developed?

iii) Can the microfluidics, biosensors, and in silico technologies needed to conduct effective "pharmacognosy in a suitcase" be integrated and mobilized?

iv) Can new TMs and individual drugs be developed, based on in silico network pharmacology databases of purified natural products, to address important global health care needs?

v) Can the expanded use of in silico screening techniques enhance the discovery of lead molecules, including those for orphan diseases?

vi) Can synergistic and antagonistic effects within complex TMs be predicted and the mixture rationalized, thereby eliminating unnecessary plants and enhancing sustainability, and improving patient outcomes.

vii) Can the "innovation deficit" of natural products in the US be eliminated or dramatically reduced?

viii) Can chromatographic methods be developed which rapidly separate a complex natural product matrix by molecular size and biological function (microSPE-microLC systems)?

ix) Can a plant be identified, and its properties, chemistry, and uses were made available using a digital image, through the integration of diverse natural product data sets?

x) Can a hand-held device be developed for the stand-off assessment of medicinal plants to optimize cultivation? (21)

8) Secondary metabolism

i) Can "real-time" secondary metabolite production is monitored.

ii) Can the complete secondary metabolic profile of a plant be determined?

iii) Can the metabolic pathways of a plant be assembled and regulated in vitro (yeast, bacteria) to produce only those metabolites which are of medicinal or biological importance?

iv) Can new classes of antibiotics, which will not develop resistance, be discovered through microbial genome mining?

v) Can dormant secondary metabolic pathways for new natural product scaffolds be discovered in plants? (21)

9) Publication of results

i) Can the reliance on for-profit, scientific journals for the distribution of scientific information be significantly diminished?

ii) Can all research publications be retained as the property of the creators, the scientists?

iii) Can all research that is submitted for publication be published, and then filtered through post-publication review, which may lead to recalibration (editing, withdrawal, and/or resubmission) over an extended period?

iv) Can the publication process of submission, review, and editing be made completely transparent and accountable, with attributed reviews (comments) readily available?

v) Can data assembly, literature background, and qualified commentary of the context of

the results for research publications be prepared mostly through manuscript assembly algorithms?

vi) Can research publications be instantly and completely translatable into the major global languages?

vii) Genomics and the Future Development of Natural Products -

Underpinning many aspects of the development of natural products for the long-term future is a deep understanding of how metabolites are synthesized naturally, where, and how long that process takes, and whether biologically and commercially important molecules can be assembled expeditiously and completely in heterologous sites. Additionally, the sequencing of bacterial genome systems has revealed that even “simple” organisms are packed with untapped biosynthetic capacity, where a few isolates may have been characterized from one pathway, and genomic evidence supports the existence of may be 25 or more additional secondary metabolite biosynthetic gene clusters, as demonstrated for Streptomyces avermitilis and S. griseus.

If these numbers obtained through bioinformatics-designated cluster scanning for unusual genes are translatable to other bacterial genomes, then their relationship to other established gene clusters in terrestrial and marine native and symbiont microbial systems becomes an important measure of the high potential for the discovery of new natural product scaffolds and their subsequent tailoring. Such in silico strategies, keenly in line with the philosophies of ecopharmacognosy, will allow those new biosynthetic gene cluster constructs to be targeted before culturing and isolation/dereplication. Turning to plants, where significantly less is known about secondary metabolic genes, in part because they are fragmented, it is probably the case that several additional classes of the plant-derived natural product remain to be uncovered for biological assessment, or that new sources of known desirable natural products may be identified. (22)

The ability to accumulate and assemble the requisite, plant-derived genes for the complete secondary metabolite production of valuable opiate alkaloids in a heterologous organism was recently demonstrated in yeast and *E. coli*. These events represent a huge practical step forward toward the realization of assuring a renewable, sustainable supply source for a medicinal agent, irrespective of its source. This is a foundational pillar of ecopharmacognosy and for the development of natural product medicine's security. In the future, four major areas

of genetics will dramatically impact these aspects of metabolite discovery and production. Genomics and bioinformatics will be predicting the nature of the products from previously unexplored biosynthetic gene clusters, microbial ecology will examine how the genes for metabolite formation are distributed in the terrestrial and marine organisms on Earth, which will indubitably provide a nexus for intellectual property rights issues. Synthetic biology will expand into exploring the substrate specificity of encoded genes to specifically engineer new or known metabolic pathways and express them in insects, yeast, and E. coli.

Meanwhile, systems biology is projected to unravel the regulatory issues related to natural product formation and, through metabolomic networking, explore the complexity and interrelationships of natural product biosynthesis in an organism. The enhanced production of medicinal natural products and essential oils will undoubtedly be an important factor as Earth's population continues to increase, and as enhanced life expectancy becomes a major contributing factor to these intensified natural product requirements. (23)

4. Natural Products role in Drug Discovery

4.1 Plant Source –

i) Most of the biological active natural products are plant secondary metabolites with complex structures.

ii) Plants are considered to be one of the richest sources of lead compounds. E.g., Morphine – Papaver somniferum and Cocaine - Erythroxylum coca Digoxin – Digitalis Quinine – Cinchona

Common challenges in the production of plant-based natural products

Current challenges to the use of natural products and difficulty in accepting their therapeutic efficacy include:

(1) lack of standardization procedures

(2) lack of isolation of pure chemical products or compounds

(3) lack of elucidation of biological mechanisms and rarely undergoing so-called controlled and

(4) documented clinical trials according to “standards”.

Historically, there is scientific evidence on the therapeutic efficacy of natural products, and as previously mentioned this led to the development of some blockbuster conventional medicines. Searching for new drug candidates from natural products is often made difficult by the complexity of the molecular mixtures. The therapeutic activity of plant extracts is usually because of the synergistic and simultaneous action of several chemicals.

Given the complex nature of many diseases including cancer and degenerative diseases, it is not surprising that the reliance on single compound-based drug discovery has failed to provide effective cures. Plant-based drug discovery therefore must start with a combinatorial approach when evaluating candidate compounds. The advent of novel technologies including quantum computing, profiling techniques, computational biology techniques, big data, and artificial intelligence will enable scientists to use a combinatorial approach to harness the therapeutic properties of plant-based natural products and simultaneously study their molecular effects in physiological conditions.(24)

4.2 Animal Sources –

Animals can sometimes be a source of new pharmacologically active naturally derived products. For example, A series of antibiotic peptides were extracted from the skin of the African clawed frog, and a potent analgesic compound called epibatidine was obtained from the skin extracts of the Ecuadorian poison frog.

Common challenges in Animal-origin natural products:

Translational Failures Using Animal Models

Many participants discussed the inability of animal models to accurately predict efficacy as a challenge to drug development. Although animal models work reasonably well to prioritize reagents for a clinically validated target, they are not as useful to prioritize reagents aimed at novel targets, opined Chas Bountra, head of the Structural Genomics Consortium and professor of translational medicine at the University of Oxford. In addition, animal models can be poor predictors of clinical efficacy and therapeutic index. This is most likely due to animal models’ inability to fully mimic diseases, as demonstrated by a groundbreaking study of the failure of mouse models in human inflammatory diseases. Potential mismatch of

preclinical and clinical endpoints could be another reason for translational failures, although corresponding preclinical and clinical endpoints may not be sufficient enough to predict clinical efficacy. Austin noted that there are many examples of a lack of drug efficacy in clinical trials after successful animal studies (i.e., failure of efficacy) as well as the presence of human toxicity not previously shown in animal studies (i.e., failure of toxicity). Some of these failures relate to the lack of understanding of mechanisms for disease; how can successful animal models be created based on unknown mechanisms?

Two speakers noted that the limitations of existing animal models have resulted in translational failure. Lawrence Goldstein, director of the UCSD Stem Cell Program and distinguished professor in the department of neurosciences at the UCSD School of Medicine, highlighted several challenges related to existing animal models of AD, including the inability to develop all the symptoms of AD; overexpression of proteins linked to disease (e.g., APP) at levels high enough to produce abnormal phenotypes; transgenic mouse models that fail to fully recapitulate AD pathology lack of sporadic AD models, which account for 95 percent of cases, and the in ability of drugs found efficacious in animal models to translate to clinical trials. Wayne Drevets, scientific vice president and disease area leader in mood disorders at Janssen Pharmaceutical Companies of Johnson & Johnson, echoed similar comments for depression, one of which is the lack of animal models for spontaneously recurring mood disorders (e.g., bipolar disorder). To summarize, Bountra noted that animal models do not always accurately predict dose, tolerability, efficacy, and research priority. (25)

Challenges of animal-derived food safety

Microbial pathogens- Animal-derived food safety challenges associated with microbial pathogens may be divided into those dealing with problems caused by pathogens of current concern, pathogens of potential concern in the future, pathogen changes and adaptations, and the involvement of the environment in microbial pathogens. (26)

4.3 Microorganisms Source –

Microorganisms are another potent source of drug leads. The classic example of such a drug discovery is that of penicillin by Alexander Fleming.

Common challenges in the production of microbial natural products

Genome mining efforts, enabled by advancements in DNA sequencing and bioinformatics, have allowed for the identification and prioritization of bacterial strains, harboring biosynthetic gene clusters that encode privileged natural product scaffolds and/or novel chemistries, for discovery. The challenges lie in activating the identified biosynthetic gene clusters for natural product discovery. Two complementary approaches have been commonly considered—(i) activating the gene cluster in the native producer, which may require genetic technologies that are not readily available, or (ii) expressing the gene cluster in a heterologous model host, which can take advantage of the expedient genetic tools developed. While applications of the common engineering technologies to manipulate gene expression are generally easier in heterologous hosts, the natural regulatory pathways between the native producers and the gene cluster are severed upon transfer of the gene cluster out of its native producer.

Conceptually, one could imagine developing a "universal" system for producing natural products, in which any biosynthetic gene cluster could be introduced into a genetically tractable and highly-producing chassis tailored to a desired natural product of interest.

However, despite great effort and access to many of the emerging engineering tools, many challenges remain.

Even with enabling technologies to sequence DNA, and clone and express biosynthetic gene clusters in various heterologous hosts, the feasibility and practicality of a universal system is currently unattainable due to a gap in knowledge of natural product production between native producers and heterologous hosts. Recent studies, such as a so-called "pressure test" to produce ten natural products in 90 days, highlight this knowledge gap and demonstrate how little we truly know about interactions between biosynthetic gene clusters and host regulatory systems. Successful examples of heterologous production of natural products are dominated by small, low-complexity gene clusters, with few operons, with exceptions seen only on a case-by-case basis.

Therefore, the notion that heterologous expression of biosynthetic gene clusters can systematically facilitate natural product production is far from reality. (27)

4.4 Marine Sources –

i) Marine natural products can be defined as biologically active products as secondary metabolites as well as enzymes, lipids, and heteropolysaccharides.

ii) In recent years, there has been a great interest in finding pharmacologically active natural products from marine sources.

iii) Coral, sponges, fish, and marine microorganisms have a wealth of biologically potent chemicals with interesting inflammatory, antiviral, and anticancer activity.

iv) For example, curacin A is obtained from a marine cyanobacterium and shows potent antitumor activity. Other antitumor agents derived from marine sources include eleutherobin, discodermolide, bryostatins, dolo statins, and cephalostatins.(28)

Challenges Associated With Marine Drug Development

Seventy percent of the earth's surface is made up of oceans with a prolific resource of various biological and chemical entities. So why aren't we able to exploit these useful resources for the development of user agents, despite their known medicinal use? There are many pitfalls for the development of marine-sourced drugs on which we want to throw some light.

Oceans contain a huge source of useful organisms no doubt, but the majority of these areas are still inaccessible to researchers. The collection of entities at areas easy to reach was favored for a long period. However, the question remains on the inaccessible regions, which needs a good collaboration between researchers and the oceanographer. Developments in under water life-support systems have tried to provide new potentials for the exploration of new regions and depths, which should be exploited in a better way.

Genetic engineering, which deals with the transfer of genetic information in the host cells from the desired compound, is under expansion for the betterment of drug development. This is an important domain for controlling the isolation and the expression of genes of marine organisms, which will help us have a more targeted approach in developing lead compounds from the marine environment.

Many times, natural products are isolated from higher marine organisms such as marine invertebrates. These products, which are a product of symbiotic association, are difficult to

develop separately from cultures, as their growth depends directly or indirectly on the host. Hence, many times if these products are tried to develop *in vitro*, many of the important genes will remain silent. For such cases, the concept of metagenome analysis should be considered, which is very much in an underdeveloped phase.

Another important issue is the availability of an sufficient amount of resources from the marine environment of a particular compound. Only if the pharmaceutical industry is sure that they can very much address the availability issue of a marine compound, if they find the lead compound of marine origin effective in clinical trials, only then they will try to invest in these trials. Ecological feasibility is a valid concern, considering the exorbitant costs of the clinical trials. The cost feasibility will also play an important role when we consider the need to induce structural modifications to enhance the properties of the drug.

Challenge is to find ways to isolate and cultivate organisms and thus realize their contributions to the treatment of human disease.

The major difficulty is the evaluation in a wide range of targeted assays and scarcity of the compounds, which are isolated in minute quantities insufficient to supply a library for repeated rounds of bioassay.(29)

4.5 Venom and Toxins –

Venom and toxins from animals, plants, spiders, scorpions, insects, and microorganisms are extremely potent since they have very specific interactions with a macromolecular target in the body. Venom and toxins have been used as lead compounds in the drug development of novel drugs.

E.g., Teprotide a peptide isolated from the venom of Brazilian viper was a lead compound for the development of the antihypertension captopril.

Poisons and the toxins found in venomous and poisonous organisms have been the focus of much research over the past 70 years, most of which have been directed at understanding the biochemical and physiological mechanisms by which they elicit their dramatic pathological consequences. Much knowledge has been gained in terms of how poisons and venoms and their composite toxins give rise to the syndromes associated with envenoming and poisoning and in some isolated cases there have been a few such agents promoted for therapeutic use.

However, it has only been in the past decade that an explosion of interest has occurred in mining these natural, highly evolved libraries of bioactive toxins and poisons for use in pharmacotherapeutics as drugs or drug leads as well as in diagnostic applications.

We ascribe this recent phenomenon to advances in toxicology which have provided investigators with a relatively thorough understanding of the nature of venoms and their biologically active toxins: particularly the peptidomes and proteomes of venoms. This is in conjunction with our greatly improved understanding of the etiology of many human diseases and the identification of sites of potential therapeutic intervention. In this review, we provide an overview of some of the toxins, toxin derivatives, or poisons from animal venoms and secretions which are in various stages of development for use as pharmaceuticals or diagnostics in human diseases. As one will recognize, developments in this field suggest that toxicology is now entering a golden age interms of the identification and use of toxins as potent novel pharmaceuticals. (30)

Challenges Regarding Basic Research

One of the bottlenecks when studying toxins from small or rare venomous species, such as scorpions and spiders, is the hardship in obtaining large amounts of venom and purified toxins.

For example, the venom glands from the cupiennius Salei spider contain only10ml of venom, and venom regeneration in milked animals requires from 8 to 16 days (wigger et al., 2002). On the other hand, the snake Lachesis muta. Muta is able of injecting large venom amounts (milliliters of venom yielding 200-400 mg of toxins) (Stransky et al., 2018). The higher amount of collected snake venom is one of the reasons that may explain why most of the approved animal toxins-based drugs come from these animals.

Mucus-rich samples, such as toad and frog poisons, is also another issue, which may hinder the use of omic approaches. In this context, studies comprising animal toxins are not a simple task since many challenges must be addressed. The small amount obtained from different poisonous and venomous animals, together with the nature of the venom/ poison allied with the difficulty in isolating specific toxins, are the main limitations faced during basic research. (31)

Challenges Regarding Preclinical evaluation

Problems in the development of toxin-based drugs encompass Selectivity, mechanism of action, formulation, stability, and Production cost (Zhang and Falla, 2009). Besides the modern Approaches using omic techniques, molecular biology, Bioconjugation, and nanomaterials in animal venom research, Venom components do not always meet all the requirements for a Potential therapeutic application. Drug metabolism and Pharmacokinetics properties of animal toxins, for instance, are key factors that need to be carefully optimized.

In this regard, after overcoming the challenges imposed during The basic research, like obtaining enough amount of the toxin, it Becomes necessary to stand up against some pitfalls faced during Preclinical evaluation. Some compounds may not cross Pivotal barriers in the organism, including the blood-brain barrier, Which may interfere in their delivery. Additionally, the susceptibility To blood proteases, as well as their immunogenicity, which are Directly linked to biopharmaceutical degradation in vivo, are also important factors to be considered. Due to the relatively large size And other specific physicochemical properties, parenteral Administration is currently the most used delivery route for Approved venom-based drugs.

Considering all the challenges at this phase, preclinical studies Are usually costly and lengthy, since they must attend all the Requirements stated by the regulatory agencies throughout the World. In this respect, regulatory issues, together with problems Related to lack of funding, and manufacturing problems, have Been a hindrance for academics pursuing to advance their drug Candidates into the clinical trials. (32)

Challenges Regarding Clinical Trials

Randomized clinical trials are the gold standard to evaluate specific drug-related issues such as the efficacy and, to a lesser extent, the safety of new medicines before marketing approval. But these studies are not often able to evaluate special populations, such as children, pregnant women, and the elderly. To overcome these limitations, studies using electronic healthcare records of post-marketing comparative drug safety may complement traditional spontaneous reporting systems to predict which drugs require further epidemiological investigation.

For instance, a multi-country healthcare database network identified new signals of potentially drug-induced acute liver injury in children. A method of enhancing the

effectiveness of therapeutic agents using taxane nanoparticles co-administered with the therapeutic agent has been recently patented.

On this point, the obstacles faced during the process of approving a new drug are harder to overcome than just improving its drugability, with two main issues contributing at this stage.

First, new therapeutic drugs must achieve very high standards to be accepted, since they may have to compete with older and well-known drugs on the market, which may be more effective and cheaper, in most cases (because of the expired patent, for instance). Another problem is when the role of the toxin's target on the disease, the state is less relevant than previously thought for the manifestation of a particular disease, resulting in low efficacy. Even more, unexpected and unwanted effects could be observed in vivo if the target is expressed at different cells or if the toxin binds promiscuously to other targets In this context, adverse effects, lack of efficacy, and dose-limiting toxicity are responsible for the interruption of many clinical trials. (33)

Animals Toxin -Based Drug Developments Challenges

Animal toxins are most often used as pharmacological tools for Target validation. However, in the section Achievements With Animal Toxin-Based Molecules, it was shown that they have also been successfully used as therapeutic agents.

Although there are examples of success, there is a gap between the Number of compounds with interesting pharmacological properties Obtained from animal poisons and venoms and those that are Approved. Drug development programs may be discontinued due to several factors like intellectual property disputes, changes in the Program leadership, lackof funding, among other business Decisions. The lack of publications regarding important data, during the different stages of their development, also contributes to several program discontinuations.

While we sought to retrieve this information from the scientific literature, this fact impairs most of the process, concealing most of the key events. The subsections Challenges Regarding Basic Research to Challenges Regarding Clinical Trials will address the challenges Related to basic research, preclinical evaluation, and clinical trials During the development of animal toxin-based drugs. However, many challenges faced during these stages are not available in the Scientific literature, since much of this information is under

Intellectual property law for compounds that are still being Developed or for which the development stopped because of internal issues.(34)

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