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Natural Products in Drug Design-Past, Present, and Future †

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† Presented at the 1st International Electronic Conference on Molecular Sciences: Druggable Targets of Emerging Infectious Diseases, online, 01-14 September 2021.

Academic Editor: Clemente Capasso

Published: 31 August 2021

Abstract: Throughout history, natural products have played a major role in the discovery of drugs, especially cancer and infectious diseases. Natural products and their similarity and historical composition have contributed greatly to the healing of medicine. However, natural products have their own drug discovery challenges, such as technical barriers to testing, classification, performance, and efficiency, leading to a reduction in their research by the pharmaceutical industry. In recent years, many technological and scientific advances, including improved analytical tools, genetic engineering, engineering techniques, and the development of microbial farming, are facing these challenges and opening up new opportunities. Here, we summarize the latest technological advances that enable the availability of drugs for natural products, highlight selected applications and discuss key opportunities. Recent advances in genomics and structural biology over the past few decades paint a vivid picture of protein variations targeted at natural product molecules. Apart from this, current leadership strategies have led to a renewed interest in natural products in drug discovery. As a result, interest in natural products such as drug lead is rekindled, especially in dealing with antimicrobial resistance. We continue to attract readers' interest in acknowledging that a certain number of natural products/products are actually produced by bacteria and/or bacterial interactions with the "host where they have been set aside"; therefore, we consider this area of natural product research should be greatly expanded. In the concluding section, we draw attention to the potential future indications of a natural product in drug design and development.

Keywords: Discovery; Natural products; Genetic; Medicine; Pharmaceutical

Citation: Ram, D. Natural Products in Drug Design-Past, Present, and Future. **2021**, *volume number*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s):

Received: date
Accepted: date
Published: date

1. Introduction

Throughout the ages, humans relied on natural products. Natural products have earliest records from 2900-2600 BC documenting the uses of approximately 1000 plants derived substances such as the oil of Cedrus species (cedar), Commiphora myrrha (myrrh), Cupressus sempervirens (cypress), Glycyrrhiza glabra (liquorice) and Papaver somniferum (poppy) [1]. In addition to plants around 120 minerals were listed including Arsenic sulphide, Sulphur, Lime, Potassium permanganate and even rock salt. The first Egyptian record is 'Ebers papyrus' dating from 1500 BC, document about 850 drugs such as Aloe vera (aloe), Boswellia carteri (frankincense) and oil of Ricinus communis (castor) [2-5]. At the same time the Chinese 'Materia medica' was documented dating from 1100BC [6] (WuShi Er Bing Fang with 52 prescriptions). Likewise, docu-mentation of the Indian ayurvedic system dates from before 1000 BC with charaka and samhitas having 341 and 516 drugs respectively [7,8]. Further the Greeks and Ro-mans with Hippocrates (father of medicine) ~ 460 to 377 BC cover use of natural products which includes Extract of poppy, Henbane, Mandrake, Juniper and Saffron [9]. Dioscorids (100 AD) compiled De Materia medica, which described the dosage and efficacy of about 600 plants derived

medicines and laid the-foundation of pharmacology in Europe [10]. In 5 to 12 century the Arabs published their work in 'Canon medicinae' influenced by work of Ibn-Al-Baiter [11].

2. Different Sources for Natural Products For Drug Discovery

Despite the rise of combinatorial chemistry as an integral part of lead discovery process, natural products still play a major role as starting material for drug discovery. Drug products have been obtained from various sources which include plants, animals, marine, and microbial metabolites [12]. Plants have been part of traditional medicine systems, which have been used for thousands of years in our county [13,14]. These plant-based systems continue to play an essential role in health care, and it has been estimated by the World Health Organization (WHO) that approximately 80% of the world's inhabitants rely mainly on traditional medicines for their primary health care [15]

(a) Anti-Inflammatory Agents: Inflammation is known to be one of the important causes responsible for many diseases [16]. Natural products used for inflammation include Withanolides from Withania somnifera. They are found to be active in arthritis and are potent inhibitors of angiogenesis, inflammation, and oxidative stress. Inhibition of NFkB and NFkB regulated gene expression is primarily responsible for their anti-arthritis action [17].

(b) Car-dio-Vascular Agents: Cardiac glycosides or cardenolides are commonly used. They are steroidal in nature with a lactone group. They inhibit the membrane bond Na-K ATPase pump resulting in depletion of intracellular K and increase in serum K which result in decrease electrical conductivity through a decrease in heart rate and increase cardiac output [18].

(c) Anti Diabetic Agents: India is a 'Diabetic capital of world' several remedies are used for their treatment. Most common example is Charantin (14) a steroidal saponin have an insulin like activity [19]. Sylvestre Gymnema (gurmar) from which gymnemic acid is obtain known to show hypoglycaemic activity [20]

(d) Anti Obesity Agents: There are many natural products that have been used for anti obesity agent. Tea polyphenolics like 3-o-gallate show a potent lipase inhibitor activity [21].

(e) Anti Malarial Agents: A number of medicinal plants have been used traditionally in the treatment of malaria. Several biflavonoids from Selaginella Bryopteris which includes amentoflavone have been investigated for their anti-protozoal activity in vitro against K strain of Plasmodium fal-ciparum [22].

(f) Immunomodulators: An immune modulator is defined as a biological or non-biological substance that directly influences a specific immune function or modifies one or more components of immune regulatory net-work to achieve an indirect effect on a specific immune function [23-25]. Many plant derived natural products have been found as an immunomodulator.

(g) Anti Leshmanial Agents: A large number of molecule be-longing to various class of natural products have been isolated which include Diospyrin(36). It has been isolated from Diospyros spp. And found to have very potent antileishmanial activity against Leishmania donavani [26-27]

(h) Anti Viral Agents: Several natural products have been used as anti viral drug which include alkaloids, phenolids and terpenoids. Theasinensin a phenolic compound found in Tea (thea sinensis) has been shown to exhibit a good antiviral activity [28].

(i) Anti Neoplastic Agent: There are few examples of natural products which have been used as antineoplastic agent. Arnebin a napthoquinone found in an Arnebia nobeles have been found to be active against walker carcinoma in rats [29].

3. Drug Discovery Process from Natural Products key points: [30-35].

The drug development from the natural resources has some pros as well as con's are as follows:

PROS

- 1. Natural products are very large in numbers with an excellent chemical diversity.
- 2. Natural products are "natu-rally bioactive". They come from life organisms and have been tailored to play a biological role.
- 3. Long term history of usage.
- 4. Wider public acceptance.
- 5. Limitations of original molecule can be overcome if the natural resources serve as starting point, as it has a bilateral promise of delivering the original isolate as a candidate or a semi-synthetic molecule development.

CONS:

- 1. The choices to be made between crude extracts, fractions and pure compounds for thepharmacological screening are very difficult.
- 2. Concentration of active compounds in a fraction or in an extract is unknown.
- 3. Biological interferences occur between NP and enzymatic based screening tests.
- 4. NP is often chemically complex for medicinal chemists.
- 5. The access of biodiversity is considered to be complex, too expensive; with uncertain and difficult re-supply issues.
- 6. The convention on biodiversity recognizes access of biodiversity to everybody. But in practice, it is difficult to find the right office or administrative centre which has the legal mandate to deal with these issues.
- 7. The rights attached to natural products are sensible and complex.
- 8. Difficult to patent NP.
- 9. Longer Derelictions and isolation steps
- 10. When we isolate an active product, hemi synthetic or synthetic derivatives of this compound have to be made to improve activity and to get quantitative structure activity-relationship information.
- 11. The drug discovery and eventual commercialization would pressurize the resource substantially and might lead to undesirable environmental concerns [36-39].

4. Challenges in Drug Discovery for NTDs and Challenges/Limitations of Current Therapies

Drug discovery and development for NTDs is faced with a number of challenges. Firstly, investment in these therapeutic areas by major pharmaceutical companies is not financially attractive owing to the prospect of poor financial returns. For this reason, drug discovery against parasitic diseases, including NTDs, has not been motivated by commercial reasons [40].

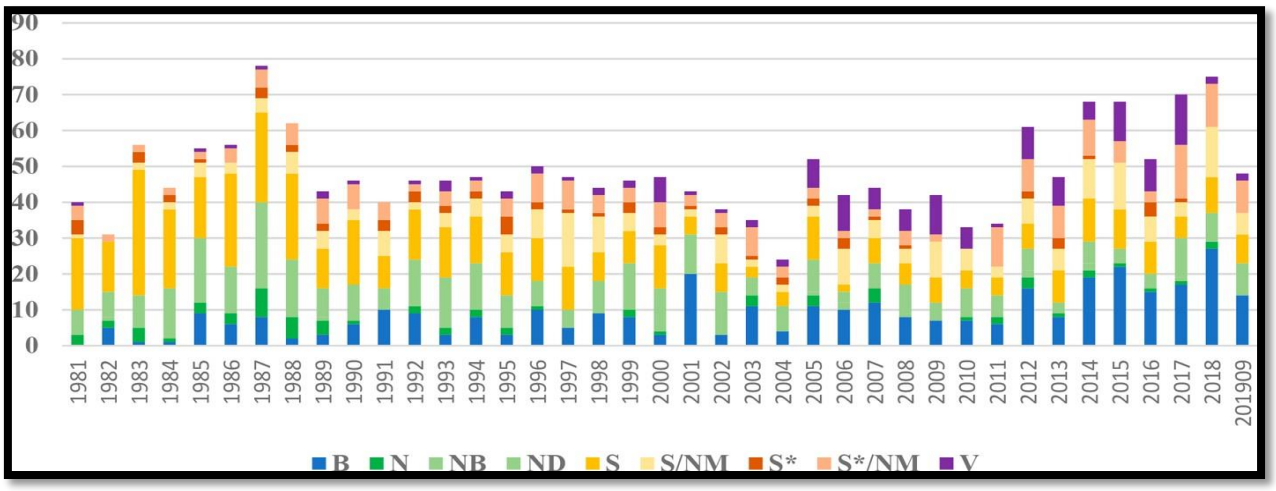

Figure 1. All new approved drugs by source/year; n = 1881.(B : biological macromolecule, 1997, N:unaltered natural product, 1997, NB: botanical drug (defined miXture), 2012, ND: natural product derivative, 1997, S: synthetic drug, 1997, S*: synthetic drug (NP pharmacophore), 1997, V: vaccine, 2003, /NM: mimic of natural product, 2003).

Many pharmaceutical companies have adopted an opportunistic approach by utilizing drugs which were historically developed for other disease indications for repurposing against NTDs. Furthermore, the utility of such an approach may not be viable any more due to widespread resistance to certain chemical classes [41]. Since NTDs affect re-source-constrained countries, it is usually a challenge to tailor drug candidates' target product profiles to what is re-quired in resource-poor settings. For instance, optimising a drug candidate for safe use without close medical super-vision is one such obstacle [42]. Current clinically used drugs against NTDs are far from ideal. Some of the limitations associated with current chemotherapeutic agents include widespread drug resistance, severe adverse effects, lengthy treatment duration, unfavourable toxicity profiles, and complicated drug administration procedures—which may be a challenge in the resource-poor communities affected by the NTDs. The use of some drug regimens is also jeopardized by their limited availability [43].

5. Backgorund: Current Context of Drivers and Barriers In Natural Product Development

A brief but representative selection of NP development and drug discovery-related opinion, review, and primary li-terature published over the last two decades shows a range of varied, often contrasting viewpoints on the potential of NPs as drug leads/candidates (Table 1), [44].

6. New Trends in Field Of Natural Product Drug Discovery [45-46].

The processes of drug discovery from natural products have been modified by some new advances: 1. The SepBox from Sepiatec Company is enabling to do Automatic isolation. This apparatus is able to prepare pure compounds from a crude extract by preparative HPLC extract by iterative HPLC. 2. NMR has moved forward with an impressive boost in sensitivity with high fields (900MHz), capillary-NMR, cryogenic probes, LC-NMR. It is possible, in theory, to screen in a NMR tube proteins ligand interactions. 3. After HPLC separation with Kiadis Company device, On-line multi pharmacological detections are today possible which allow parallel flow bioassay lines for biological activity, selectivity analyses and spectrometric data in order to obtain structural information. 4. Progress in metabo-lomics will soon permit to predict the chemical composition of a plant extract through the genome, transcriptome and proteome (enzymes) data [47-48].

7. Conclusion

NPs are seen as important sources of new medicines by industry stakeholders, yet, the industry is spending fewer and fewer resources on their discovery and development. In the last decade numerous voices have highlighted this concern with the vast majority of these originating from academic and industry observers (Niedergassel and Leker, 2009; Tra-lau-Stewart et al., 2009; Khanna, 2012). Two thirds of panel responses cited HTS as the preferred strategy for drug discovery in industry today and NPs are seen as yielding higher "hit rates," thus industry attention must not turn away from NPs if the industry seeks innovation. This gap must be explored if we are to move natural product drug discovery forward and virtual non-ligand machine learning, at least for alkaloids, can serve as a starting point to guide multidisciplinary drug discovery efforts [49]. While this study has some limitations both in terms of the overall size of the sample and the (self-) selection of participants, the voices from within clearly highlight some key concerns, which can be overcome by implementing a modified strategy in NP-driven drug

development. Minimizing one of the most commonly cited barriers (i.e., supply) by seeking to quantifying it and developing strategies for incorporating solutions at an early stage of screening programs is one approach which has demonstrated promise for alkaloids and can be applied to other NP drug discovery efforts. The work also strengthens the case that "weeds" are an important source of drugs (Stepp, 2004), but offers a quantifiable parameter to assess such "weediness." Continuing along the current path of large "numbers-driven" screens which boast millions of compounds not only has irritated many, at all levels, in the industry but more importantly stifled the growth and development of the single most productive source of potential leads for new medicines to date; nature. Natural products as building blocks for molecular libraries, Instead of viewing natural products as a stand-alone approach distinct from combinatorial synthesis, it is now much more effec-tive to implement strategies that combine both approaches. In various principle, it is seems the unique molecular diversity of natural products can be leveraged in the design of combinatorial libraries [50-52]. The target-oriented or focused-library approach seeks to elaborate structural modifications onto an existing bioactive natural- product scaffold in analogue patterns, systematic fashion in order to ameliorate its inherent biological activity or drug-like properties. Presently, the drug discovery engine operates at an accelerated pace in comparison with the era in which natural products were pre-eminent sources of drug leads, numerous approaches have been developed to capture their intrinsic value. The essential breakthroughs in separation and structure determination technologies have lowered the hurdles inherent in screening mixtures of structurally complex molecules. The confluence of these technologies with advances in genomics, metabolic engineering and chemical synthesis offer the new method along with the technologies to explore the remarkable chemical diversity of nature's 'small molecules' in the pursuance for new drugs.

Acknowledgments: Author thanks to Noble Pharmacy College for all support.

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