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Research

A REVIEW ON THE SYMBIOTIC RELATIONSHIP BETWEEN NATURAL CHEMISTRY AND DRUG DISCOVERY

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Abstract:

The Chemistry of Drug Design and Development plays a pivotal role in modern pharmacology, contributing to the discovery and optimization of therapeutic agents for various diseases. This research paper delves into the intricate interplay between chemical principles and pharmaceutical applications in the design, synthesis, and optimization of drugs. By exploring molecular interactions, structure-activity relationships, and computational methods, this study elucidates the multifaceted strategies employed in drug design to enhance efficacy, selectivity, and safety profiles. Furthermore, the paper discusses the integration of diverse chemical approaches, including medicinal chemistry, organic synthesis, and computational modeling, in the development pipeline, highlighting the interdisciplinary nature of modern drug discovery. Although traditionally natural products have played an important role in drug discovery, in the past few years most Big Pharma companies have either terminated or considerably scaled down their natural product operations. This is despite a significant number of natural product-derived drugs being ranked in the top 35 worldwide selling ethical drugs. Recently, there has been a renewed interest in natural product research due to the failure of alternative drug discovery methods to deliver many lead compounds in key therapeutic areas such as immunosuppression, anti-infectives, and metabolic diseases.

Key words: Chemistry, drug design, drug development, molecular interactions, structure-activity relationships, medicinal chemistry, organic synthesis, computational modeling, interdisciplinary, pharmacology.

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Introduction:

enhance the role of natural products in this process are then discussed. Farnsworth and colleagues indicated (Farnsworth et al., 1985) that globally there were 119 compounds from 90 plants which were used as single - entity medicinal agents. Modifications to natural products, to enhance activity or selectivity and reduce side effects or toxicity, developed as organic chemistry grew in the late 19th century (Sneader, 1985). Aspirin was one of the earliest of these chemically modified natural products.

They conducted an analysis of drugs approved by the Food and Drug Administration in the United States in a 12-year period (1983-1994) and found that 157 of 520 drugs (30%) approved were natural products or their derivatives (Cragg et al., 1997a). When focused efforts are made to discover natural products for clinical use, the success level rises dramatically.

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Thus, in the same period, 61% of anticancer agents approved were natural products or their derivatives. In the absence of targeted programs involving natural products, there was no success; thus, there were no analgesics, antidepressants, antifungals, antihistamines, antivirals, anxiolytics, or cardiotonic derived from natural products which were approved in this time period (Cragg et al., 1997a).

The discovery of antibacterial filtrate "penicillin" by Fleming in 1928, re-isolation and clinical studies by Chain, Florey, and co-workers in the early 1940s, and commercialization of synthetic penicillin's revolutionized drug discovery research.6-9 Following the success of penicillin, drug companies and research groups soon assembled large microorganism culture collections in order to discover new antibiotics.

Natural products in drug discovery process

In order to understand the contribution that natural products can, will, and indeed must, make to the discovery and provision of medicinal and biological agents in the future, it is necessary to establish what are the steps in this discovery pathway and what are the sources of such agents. Some of the characteristics which would enhance the role of natural products in this process are then discussed.

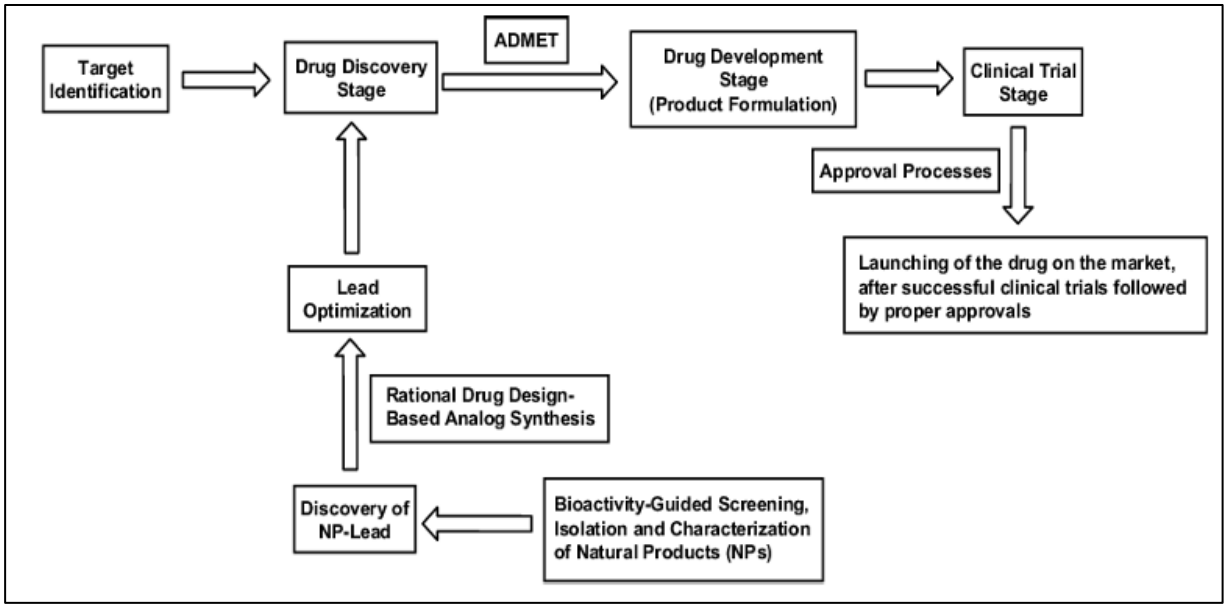

Fig 1: Process of natural products in drug discovery

Methodology

Keap1/nrf2 pathway:

Natural products that activate the KEAP1/NRF2 pathway an example of a pathway affected by diverse natural products (NPs) is the KeaP1/NrF2 pathway. This pathway regulates the expression of networks of genes encoding proteins with versatile cytoprotective functions and has essential roles in the maintenance of redox and protein homeostasis, mitochondrial biogenesis and the resolution of inflammation.

Activation of this pathway can protect against damage by most types of oxidants and pro inflammatory agents, and it restores redox and protein homeostasis200. The pathway has therefore attracted attention for the development of drugs for the prevention and treatment of complex diseases, including neurological conditions such as relapsing–remitting multiple sclerosis and autism spectrum disorder.

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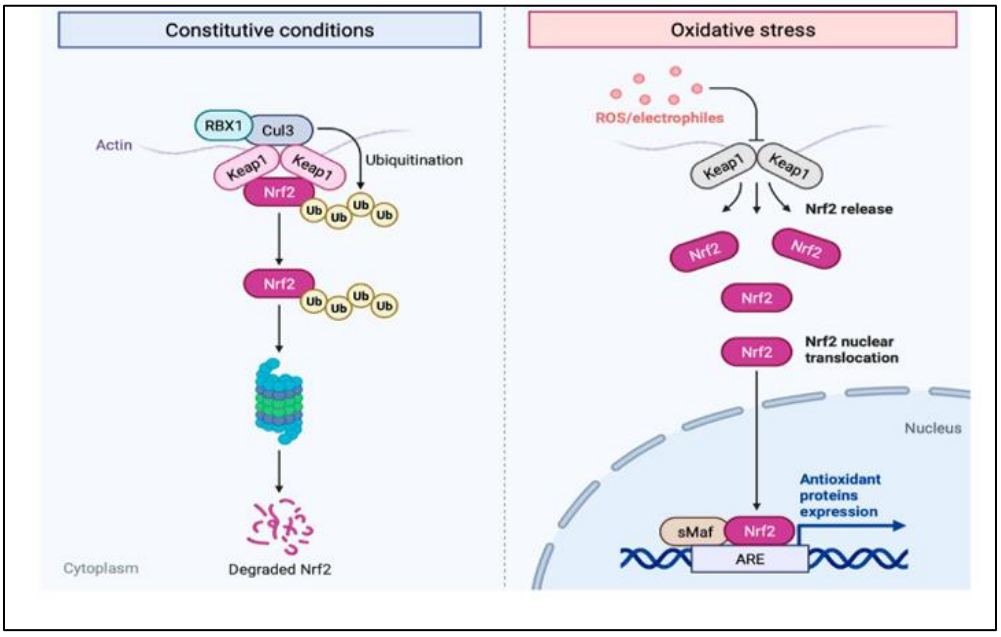

Fig 2:Schematic picture of Nrf2 under constitutive (left) and oxidative stress conditions (right).

Genome mining and engineering:

Advances in knowledge on biosynthetic pathways for NPs and in developing tools for analyzing and manipulating genomes are further key drivers for modern NP-based drug discovery. Two key characteristics enable the identification of biosynthetic genes in the genomes of the producing organisms. First, these genes are clustered in the genomes of bacteria and filamentous fungi. Second, many NPs are based on polyketide or peptide cores, and their biosynthetic pathways involve enzymes — polyketide synthases (PKSs) and non-ribosomal peptide synthetases (NRPSs), respectively — that are encoded by large genes with highly conserved modules**.**

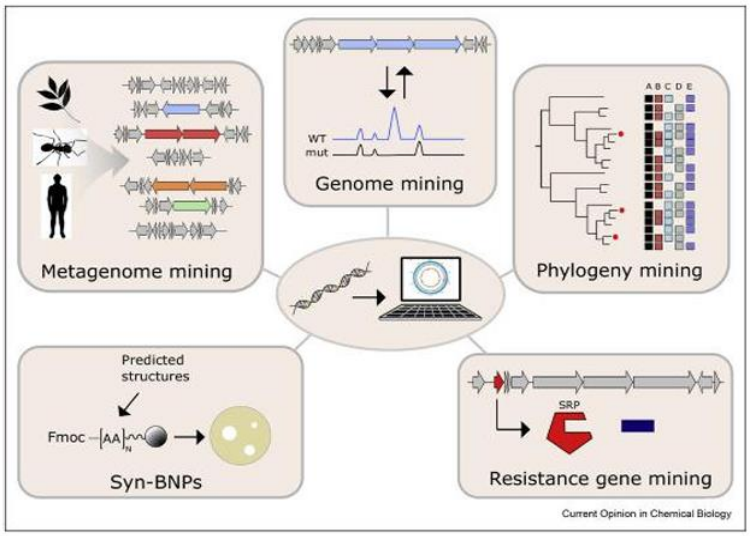

Fig 3: Natural product discovery through genome mining and engineering

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Advanced in microbial culturing systems:

The complex regulation of NP biosynthesis in response to the environment means that the conditions under which producing organisms are cultivated can have a major impact on the chance of identifying novel NPs. Several strategies have been developed to improve the likelihood of identifying novel NPs compared with monoculture under standard laboratory conditions and to make 'uncultured' microorganisms grow in a simulated natural environment.

One well-established approach to promote the identification of novel NPs is the modulation of culture conditions such as temperature, pH and nutrient sources. This strategy may lead to activation of silent gene clusters, thereby promoting production of different NPs. The term 'One Strain Many Compounds' (OSMAC) was coined for this approach about 20 years ago, but the concept has a longer history, with its use being routine in industrial microbiology since the 1960s

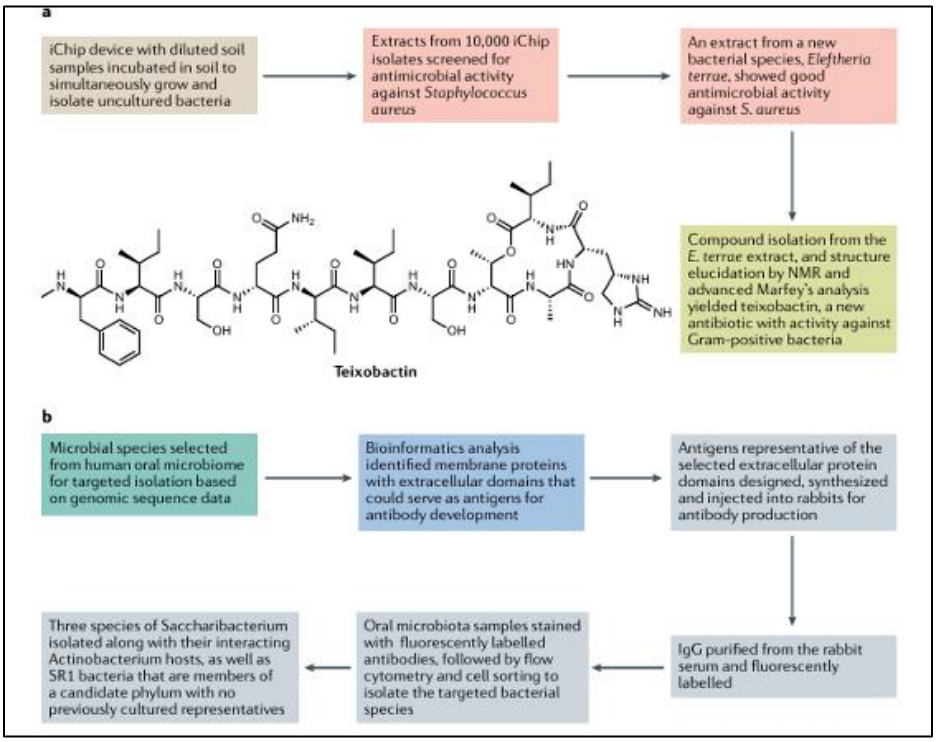

Fig 4: Application of advanced microbial culturing approaches to identify new natural products.

Intellectual property rights:

One of the most contentious areas in natural products chemistry and biology at this time is that of intellectual property rights. There are many aspects to this broad topic, most of which are beyond the breadth of this discussion; some highlights are worthy of mention, however (Reid et al., 1993). Long before the Convention on Biological Diversity, the so-called Earth Summit, it was recognized that countries had the right, within their legal boundaries, of ownership of their biological property, both marine and terrestrial, and that indigenous peoples also had the right to protect and seek compensation for the knowledge which they had developed, over the generations, based on their local biodiversity (Reid et al., 1993; Cragg et al., 1997b). Many scientific societies and groups developed policies and statements which reflected concerns in these areas (Cordell, 1993a).

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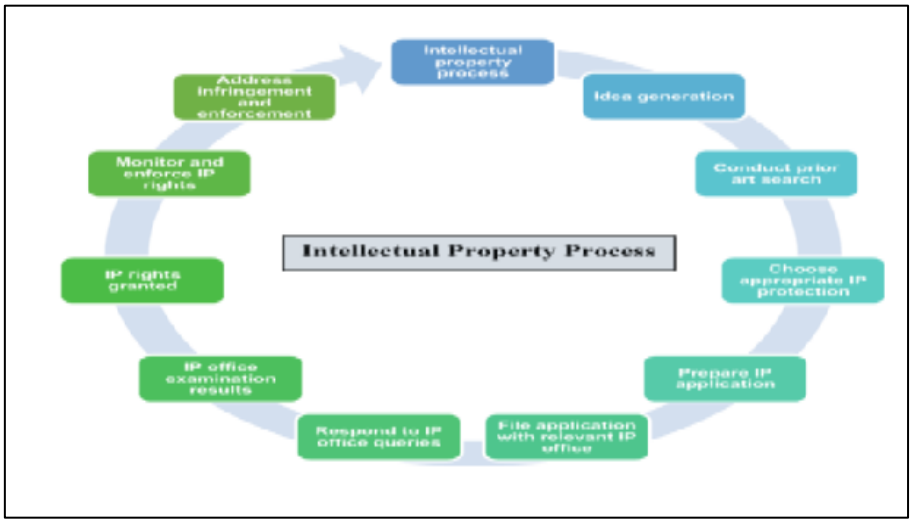

Fig 5 : Intellectual property process

Issues and opportunities for natural products:

Even though there is an awareness of the history of natural products in relation to current medicinal agents, and it is well recognized that natural products offer a diversity of structure which simply cannot be matched through even the most active imaginations of the synthetic organic chemists, questions remain.

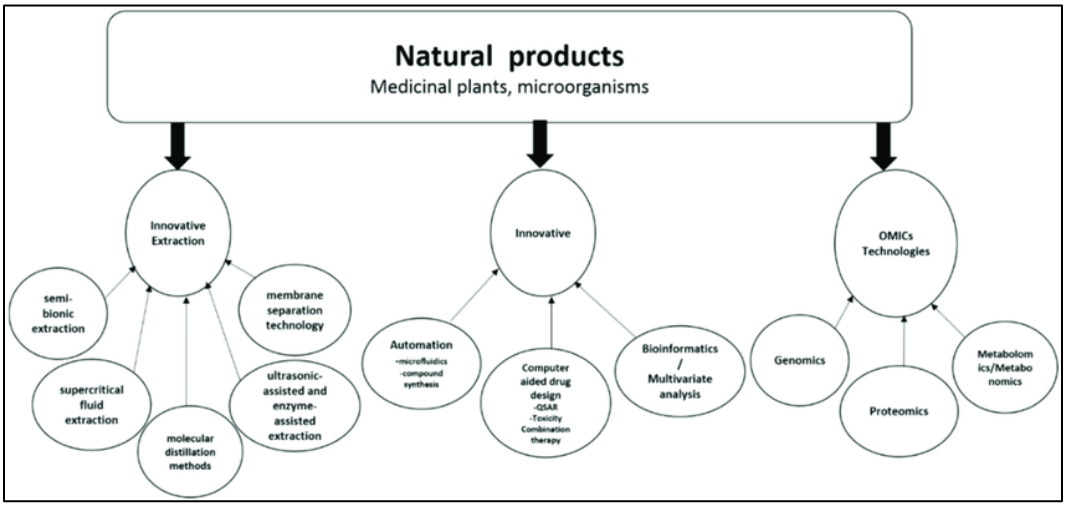

Fig6: Innovative technologies for natural product drug discovery. Application of these technologies can potentially lead to novel drug candidates from natural products.

Rules for successful natural products:

log P is the lord of the rules Although natural products in the 'parallel universe' may appear to break all the rules, they are remarkably compliant with regard to log P. This Underlines the central importance of log P in drug discovery. Although an increase in log P can often yield a higher affinity for the target, it tends to be outweighed [20]by

pharmacokinetic liabilities such as solubility, permeability, plasma protein binding, metabolic turnover, and toxicity. The single most important lesson from natural products lies in their ability to maintain low log P regardless of other characteristics. In the Lipinski universe, average log P Is 0, while In the parallel universe, it has only risento2.2 despite an average molecular weight of 917.It is thus possible to operate in non-Lipinski space with high molecular weight and large numbers of H-bond acceptors and PSA, provided lipophilicity is not compromised. To do so requires the presence of polar functional groups, and this is compatible with biosynthetic pathways which are extremely chemoselective and regioselective. Making such compounds is a lot more challenging for medicinal chemists, and is likely to involve long routes with protection and deprotection schemes for specific functional groups. Consequently, when compounds with higher molecular weight are made synthetically, log P usually suffers. To quote Lipinski, if you look at companies that are selling compounds they usually quote Rule of Five compliance rates and typically what you find is that the parameter that is most difficult to control combinatorially is lipophilicity's.

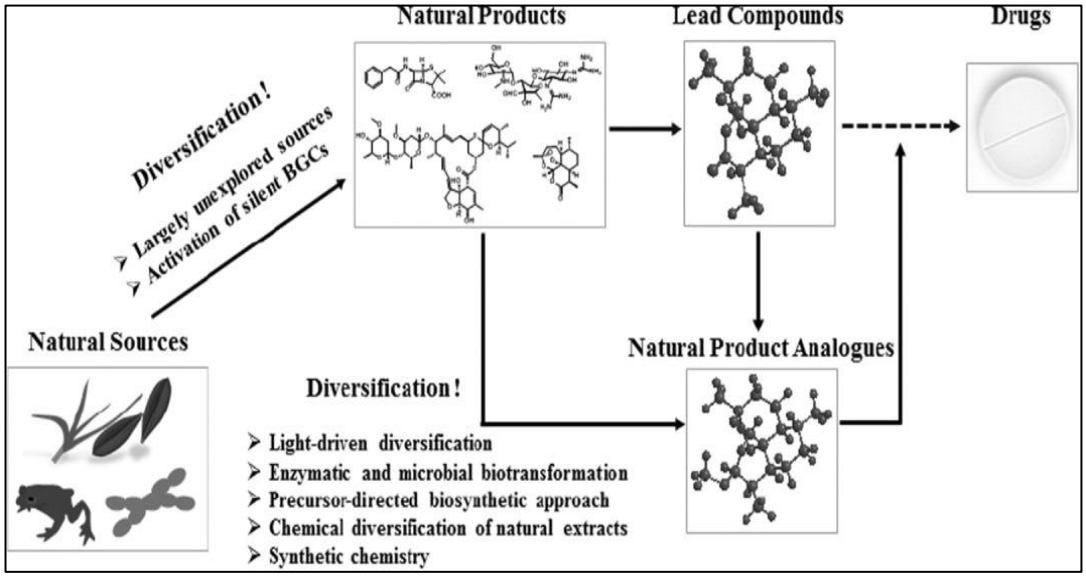

Fig 7: Strategies to diversify natural products for drug discovery

Conclusion:

The relationship between natural chemistry and drug discovery is deeply symbiotic, with natural products serving as a vital source of novel chemical structures and bioactive compounds, acting as lead compounds for drug development while simultaneously driving innovation in synthetic chemistry techniques to further optimize and modify these naturally derived molecules. This dynamic interplay has historically led to the development of numerous life-saving medications and continues to be a critical pillar in the ongoing quest for new therapeutic agents, highlighting the indispensable role of nature's chemical diversity in modern medicine.

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