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NATURAL RESOURCES IN DRUG DISCOVERY, A BIOINFORMATICS PERSPECTIVE

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ABSTRACT

The use of natural resources in drug discovery offers a rich source of bioactive compounds with potential therapeutic benefits. However, harnessing these resources comes with numerous challenges. One of the main difficulties lies in dealing with compounds that have multiple chiral centers, which can be hard to manufacture on a large scale. Additionally, accessing and supplying the necessary raw materials can be a significant obstacle. The drug discovery process is further slowed down by technical barriers, including screening, isolating, characterizing, and optimizing natural products. These challenges result in significant costs and time investments. Despite these challenges, natural resources remain a vital source of anti-infective agents and potential cancer treatments. To fully leverage natural resources in drug discovery, it's essential to address the existing gaps in understanding the mechanisms of action of novel compounds. This study aims to provide a comprehensive overview of the opportunities and challenges in harnessing natural resources for drug discovery, with a particular focus on oncology. By exploring these complexities and challenges, researchers can unlock the full potential of natural resources in developing innovative and effective treatments.

KEYWORDS: Natural Resources; Anti-infective agents; Challenges; Oncology; Technical barriers.

INTRODUCTION

For thousands of years, natural substances like plants, minerals, and animals have been harnessed for their medicinal properties, with evidence of their use dating back to ancient civilizations, long before the time of Christ. In fact, medicinal plants and microorganisms have been the primary source of medicines for centuries, providing a rich foundation for the development of traditional remedies and modern drugs **(JOÃO, 2016)** . Several major drugs derived from natural products have been approved for clinical use, including antibiotics and cancer treatments **(Xu Z. E.-M., 2022).**

Natural product mixtures, including herbal supplements, can pose significant health risks due to the presence of harmful components. These components can cause severe adverse effects and interact with other drugs in harmful ways. For instance, certain herbal supplements have been linked to liver damage (hepatotoxicity) caused by the alteration of cytochrome activity. The neurotoxic plant Atropa belladonna can be fatal to children, while some constituents of natural products can pass through the placenta and harm the fetus, leading to birth defects, miscarriage, and other developmental issues. Furthermore, some compounds in medicinal plants can lead to long-term toxicity, cancer, and hormonal imbalances. These risks underscore the importance of exercising caution and ensuring proper regulation when using natural products in medicine **(Xu Z. E.-M., 2022).**

Natural products (NPs) have historically served as a cornerstone for the development of herbal remedies and conventional pharmaceuticals. Despite the advent of small-molecule drug discovery, NPs continue to represent a predominant source of inspiration. A comprehensive analysis of small-molecule medications approved between 1981 and 2019 revealed that approximately 63% exhibit a connection to NPs, with 5% comprising unmodified NPs, 28% representing NP-derived compounds, and 35% incorporating a NP pharmacophore or mimetic. This underscores the enduring significance of NPs in the evolution of medicinal chemistry and drug development **(Asadullah, 2024)**.

HISTORICAL BACKGROUND

The use of natural products dates back to ancient Mesopotamia, where clay tablets from around 2600 B.C. featured cuneiform writings that described the use of oils extracted from Cypress (Cupressus sempervirens) and myrrh (Commiphora species). These ancient remedies are still utilized today to treat various ailments, including coughs, colds, and inflammation, demonstrating the enduring relevance and effectiveness of these natural substances **(Dias, 2012)**. The Ebers Papyrus, an ancient Egyptian pharmaceutical text dating back to around 2900 B.C., contains a comprehensive record of over 700 plant-based medications. This extensive compilation includes a wide range of preparations, such as gargles, pills, infusions, and ointments, showcasing the sophistication and breadth of ancient Egyptian pharmacology. The papyrus provides valuable insights into the use of botanicals in traditional medicine, highlighting the significance of natural remedies in the treatment of various health conditions **(Urban, 2012).**

ROLE OF TRADITIONAL MEDICINE IN MODERN DRUG DISCOVERY

For thousands of years, Traditional Chinese Medicine (TCM) has relied on natural materials, including plants, animals, and minerals, to treat various ailments. As modern science evolved, researchers began to investigate the chemical properties of these materials, including insects like beetles, to identify the molecules responsible for their traditional uses. A review of TCM texts and articles revealed that 48 beetle species from 14 families are used in TCM, with 129 identified chemical constituents. While some beetle species used in TCM have not been chemically studied, related beetles have been analyzed, providing valuable insights. Additionally, some beetles are also used in Traditional Korean Medicine (TKM), highlighting the significance of insects in traditional Asian medicine **(Wong-Deyrup, 2021) .** Traditional medicine systems, such as traditional Chinese medicine, Ayurveda, and Unani, have been practiced for centuries and have evolved into well-structured systems of healthcare.

Another study examines the connection between natural products, traditional medicines, and modern medicine, seeking to identify concepts and methods that can inform drug discovery. The study summarizes the distinctive features of eight traditional medicine systems, including their theories, applications, current status, and modern research. Despite the fact that only a small

fraction of plant species have been scientifically investigated for bioactivities, natural products and traditional medicines have already made significant contributions to modern medicine. Their advantages in drug development include extensive clinical experience and diverse chemical structures and biological activities, making them a valuable resource for developing new drugs **(Yuan, 2016).**

ONCOLOGY

In earlier times, natural products have been essential in the development of novel medications. More than half of all contemporary clinical medications come from natural sources, and many of them work well to treat cancer. The 1950s saw the US National Cancer Institute start to uncover natural chemicals with anticancer characteristics, which resulted in major breakthroughs in the therapy of cancer. The Pacific yew tree provided the first known instance of Taxol (paclitaxel), for example, demonstrating how organic substances can provide powerful anticancer medicines. Nevertheless, in order to yield useful levels of the medication, the extraction procedure is difficult and resource-intensive, requiring a significant quantity of plant material **(Asma, 2022)**.

Numerous biological processes found in natural goods can be used to treat cancer. These substances frequently target particular pathways that are important in the metastasis, apoptosis, and development of cancer cells. For example, the derived from plants substances vincristine and vinblastine, that are used to treat different types of cancer, function by preventing the production of microtubules, which causes cell division to be disrupted **(Asma, 2022).**

DIVERSITY OF NATURAL PRODUCTS

According to recent reviews, including an updated survey by **(Lautie, 2020)**, a significant proportion of drugs on the market have natural origins. Between 1981 and 2016, out of 1,328 new drugs approved, only 359 were entirely synthetic, while 549 were derived from natural compounds or inspired by them. Furthermore, in the field of anticancer drugs, a mere 23 out of 136 approved non-biological compounds between 1981 and 2014 were purely synthetic, highlighting the significant contribution of natural products to drug discovery. These findings underscore the importance of natural products as a source of inspiration and material for drug development. Furthermore **(Cragg, 2007)** added that the term "natural origin" can be defined in various ways, and these authors categorized it into three groups: unaltered natural products, defined mixtures of natural products, and natural product derivatives. These derivatives include products isolated from living organisms like plants, fungi, and microorganisms, and modified through medicinal chemistry.

Examples of drugs with natural origins include anticancer agents like docetaxel, paclitaxel, and etoposide, steroidal hormones like progesterone and cortisone, cardiac glycosides like digitoxigenin, and antibiotics such as penicillin, streptomycin, and cephalosporins. These examples illustrate the significant contribution of natural products to the development of various drug classes.

ANTI-INFECTIOUS AGENTS

The hunt for novel antimicrobial agents sourced from natural sources has escalated due to the rising incidence of antibiotic resistance. Natural compounds have proven to be highly effective against a variety of infections. These products can come from plants, microbes, and animals. The World Health Organization (WHO) highlights the possible use of medicinal herbs as supplements or substitutes for traditional therapies, especially in areas with limited access to medications **(Stan, 2021).**

One of the main sources of naturally occurring substances having antibacterial qualities is medicinal plants. Families with a high concentration of bioactive chemicals include the Anacardiaceae, Cucurbitaceae, and Asteraceae. Compounds from the Anacardiaceae family, for example, have demonstrated efficiency towards HIV and Salmonella typhi, whereas compounds from the Asteraceae family demonstrate activity against Cryptococcus neoformans **(Luo, 2022).**

MICROORGNISMS

The search for of novel antibiotics has also been aided by microbial sources, including bacteria and fungi. Many of the antibiotics used in medicine today are natural substances made by fungus and bacteria that live in the soil. Tetracycline and streptomycin, for instance, are only two of the many antibacterial drugs that Streptomyces species are recognized for producing **(Chaachouay, 2024)**.

MARINE ORGANISMS

The possible use of marine species as reservoirs of new antibacterial chemicals has been highlighted by recent investigations. Several secondary metabolites with important biological activity are produced in marine habitats due to their particular environmental circumstances **(Chaachouay, 2024)**.

BIOINFORMATICS APPROACHES IN NATURAL PRODUCTS DRUG DISCOVERY

CHEMOINFORMATICS

Drug candidates originating from natural products are identified and optimized in large part through the use of cheminformatics technologies. Among these techniques are:

- **Molecular docking:** Measuring natural chemicals' propensity for binding to specific protein targets **(Lagunin, 2014)**.
- **Pharmacophore modeling:** Recognizing shared structural elements that give rise to biological activity **(Lagunin, 2014)**.
  QSAR: Quantitatively determining structure-activity connections in order to forecast novel compound performance **(Lagunin, 2014).**
- **Machine learning:** Utilising computers to forecast a natural product's bioactivity based on its chemical composition **(Gaudêncio S. P.-M., 2023).**

HIGH-THROUGHPUT SCREENING AND VIRTUAL SCREENING

A critical stage in NP drug development is high-throughput screening (HTS), which enables the quick assessment of sizable compound libraries for bioactivity. Structure-based virtual screening, which employs computer techniques to forecast a compound's binding affinity to a target protein, has improved HTS thanks to bioinformatics. This method can save time and money by drastically lowering the quantity of substances that require experimental testing **(Gaudêncio S. P.-M., 2023).**

THE CHALLENGE OF NATURAL RESOURCE-BASED DRUG DISCOVERY

Effective data sharing poses a significant challenge, which can only be overcome by establishing standards across the entire data lifecycle. This includes setting common guidelines for collecting, processing, storing, and merging data from diverse sources with different structures **(Poo, 2018)** . Professor **(Yang, 2018)** highlighted the significant contributions of Artificial Intelligence in drug molecular design and clinical management, showcasing its potential in the field. However, he relied on foreign databases for his research, underscoring the gap in domestic data collection and storage in China. Despite the progress made, there is still a need to improve data infrastructure in China to fully leverage AI capabilities in healthcare and pharmaceutical research.

DIFFICULT DISEASE-RELATED PROBLEMS: THE EMERGING DILEMMAS

Treating central nervous system diseases is a formidable challenge, arguably even more daunting than combating cancer. However, a groundbreaking approach in gene therapy offers new hope. Scientists are harnessing the rabies virus, repurposing it as a drug delivery vehicle that selectively targets specific neurons, paving the way for potential treatments of neurological disorders. This innovative method is currently in clinical trials, holding great promise for future breakthroughs in the field **(Zhou, 2018).**

TECHNICAL CHALLENGES

ISOLATION AND CHARACTERIZATION

The separation and characterization of bioactive chemicals is one of the main problems in the drug discovery process for natural products. Natural products are frequently found in complicated mixes, which makes it challenging to isolate and refine specific components for examination. The procedure, which calls for advanced methods like mass spectrometry and chromatography, can be labor- and time-intensive. Furthermore, the presence of several chiral centers in many bioactive chemicals makes their synthesis and identification more difficult **(Xu Z. E.-M., 2022)**.

SCREENING AND OPTIMIZATION

There are also many obstacles in the way of effectively screening natural materials for possible pharmacological leads. The wide variety of chemicals present in natural extracts may render conventional screening techniques ineffective. Furthermore, because of the complex structure of NPs, optimizing these chemicals to increase their efficiency and decrease toxicity is frequently difficult **(Jeandet, 2022).** High attrition rates in the later stages of drug development can result from the dependence on phenotypic tests for lead identification, which can further confound the knowledge of the processes of action **(Atanasov, 2021)**.

ECOLOGICAL AND SUSTAINABILITY CONCERNS

Natural product exploitation brings up significant ecological and conservation challenges. Excessive harvesting of plant and animal species for pharmaceutical uses can endanger these species' survival and cause a loss of biodiversity. For endangered or endangered animals that might be the source of priceless bioactive chemicals, this problem is especially pressing. Sustainable sourcing methods are essential to preventing the depletion of natural resources, which might provide moral conundrums when it comes to benefit-sharing with indigenous groups that have historically utilized these resources **(Atanasov, 2021)**.

THE ROLE OF BIOINFORMATICS IN NATURAL RESOURCE-BASED DRUG DISCOVERY

Developing new drugs is a long, intricate, and costly process that's vital to the pharmaceutical industry's mission to improve global healthcare. This endeavor spans multiple phases, requires significant investment, and involves a wide range of expertise. The ultimate goal is to create innovative, safe, and effective treatments that address unmet medical needs and make a meaningful impact on healthcare outcomes worldwide **(Somda, 2023) .** Bioinformatics has revolutionized the field by accelerating target identification, enabling rational drug design, streamlining the analysis of vast datasets, and facilitating the development of personalized medicine biomarkers. While this discipline has made tremendous strides, it has also faced numerous challenges, hindering its progress and necessitating continued advancements to overcome these obstacles and fully realize it’s potential **(Kpordze, 2023).**

COMPUTATIONAL TOOLS AND METHODS

Computational mutagenesis is a valuable approach that has proven effective for optimizing natural products, such as antibodies with potential therapeutic properties. This method involves creating a template structure and then systematically introducing mutations to generate a library of candidate compounds. These virtual libraries can then be screened using computer simulations, such as molecular docking, to identify promising structures that can be engineered in the laboratory. Antibodies are particularly well-suited to this approach, as modifying amino acids in their binding regions can enhance their efficacy, allowing researchers to design and develop optimized antibodies with improved therapeutic potential **(Romano, 2019).**

DATA-DRIVEN APPROACH

Data-driven approaches in drug discovery involve the collection, analysis, and interpretation of large amounts of data to identify potential drug targets, predict drug responses, and optimize drug development processes. This is the big data. Big data refers to vast, complex, and varied datasets that exceed traditional computational capabilities. Originating in IT, big data is now permeating all scientific fields, including drug discovery. Characterized by the "ten Vs" - volume, velocity, variety, veracity, validity, vocabulary, venue, visualization, volatility, and value - big data in drug discovery presents both opportunities and challenges in storing, analyzing, and visualizing large datasets to extract valuable insights and drive innovation **(Zhao, 2020).**

MOLECULAR DOCKING AND VIRTUAL SCREENING

Researchers can forecast the interactions between tiny compounds, such as natural products, and protein targets by using molecular docking simulations. Via virtual screening of sizable natural chemical libraries, prospective leads with advantageous binding affinities can be found. By drastically lowering the number of molecules requiring experimental confirmation, this computational technique streamlines the drug discovery process **(D.Romano, 2019).**

LIMITATIONS

- **High Clinical Trial Failure Rate:** In Phase I human clinical trials, about 95% of lead chemicals or medications that exhibit promise in preclinical investigations are found to be unsuccessful.
- **Limited Effect on Overall Survival:** The overall survival of cancer patients is not significantly affected by several medications that have been licensed by the FDA or that the WHO recommends for therapeutic use.
- **Obstacles in the Study of Natural Products:** Natural products' innate slowness, particularly when studying novel species that haven't been well investigated before challenges in separating ultra-trace levels of active ingredients from minute amounts of crude extracts, which are made up of millions of different chemicals.
- **Reduction in Exploration by Pharmaceutical Companies:** A number of pharmaceutical businesses have either discontinued or reduced their studies on drug lead isolation as a result of the aforementioned difficulties.
- **The complex nature of bioactive chemicals:** particularly those derived from natural resources and possessing many chiral centers, can provide difficulties in their subsequent manufacture for market supply.
- **Access to Crude Materials:** The development of new natural product drugs may be hampered by obstacles in obtaining and providing the crude materials required for commercial use.
- **Technical Obstacles:** The drug discovery process may be slowed down by a number of technical obstacles pertaining to the screening, isolation, characterization, and modification of natural products.

- **Cost and Time:** Because the process of discovering drugs can be very expensive and time-consuming, there has been an emphasis on repurposing already-approved medications that are derived from plants to treat various illnesses. These restrictions bring to light the difficulties and complexities involved in drug discovery, especially when looking for possible therapeutic leads and compounds in natural resources.

GAPS AND FURTHER DEVELOPMENTS

The absence of a thorough discussion on the creation of anti-infective agents, especially anti-bacterials, is where the papers fall short. The paper notes that not all disease areas receive the same level of in-depth examination, even if it highlights two novel natural products described in this field by the same academic group. This gap suggests that there may be need for more research and analysis in the area of developing natural products-based antibacterial drugs. Furthermore, more research and debate are required to determine the precise mechanisms of action of the new chemicals found in natural resources. Although the study notes the effectiveness of some substances as cancer cell line inhibitors, including HCT-116 and MDA-MB-231, it does not go into great detail about the precise molecular pathways by which these compounds work.

Thus, conducting in-depth studies on the target molecules, pathways, and interactions associated in the anticancer activities of these natural chemicals could be a viable topic for improvement or more research. Not only may knowing the exact mechanisms of action help us better understand these substances, but it can also make it easier to optimize them for possible medication development. Through filling this knowledge gap and offering more insights into the molecular features of the compounds found, the study may provide a deeper comprehension of how natural resources might be used for oncology-related lead/drug discovery.

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