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Natural Products Revolutionizing and Innovative Drug Discovery and Development Strategies: Healthcare Challenges and Future Perspectives

Dr. Ruchita Shrivastava[1*], Dr. Gajanand Modi[2], Partha Sarathi Satpathy[3], Dr. Sukanta Bandyopadhyay[4], Yogesh Kumar[5], Isha Yadav[6]

[1]Former Lecturer, (Horticulture, Adhoc), Department of Botany, Govt. Homescience PG Lead College, Narmadapuram(MP), India. Email: vaishnavi2122@gmail.com, Orchid: 0000-0002-2336-7433*

[2]Associate Professor, FOBAS RNB Global University, Bikaner, India. Email: gajanand.modi@rnbglobal.edu.in, Orcid: 0000-0003-0644-9178

[3]Assistant professor, School of Pharmacy, Driems University, Tangi, Cuttack, India. Email - debendrasatapathy9438@gmail.com,

[4]Associate Professor, Dept of Biochemistry, Rama Medical College Hospital & Research Centre, Mandhana, Kanpur(U.P) - 20921,India. E-mail: sukantoaxum@gmail.com,Orcid: 0009-0002-3664-0475

[5]Department of Pharmacy, Jagannath University, Jaipur, India. Email- yogesh.pharmacyxyz111@gmail.com, Orcid: 0000-0002-2754-1961

[6]Masters in Zoology (Specialisation in Entomology), DSB Campus, Kumaun University, Nainital, Uttarakhand-263002, India. Mail Id- yadavisha438@gmail.com, Orcid: 0009-0006-4993-6637

Plants and other organisms serve as sources of secondary metabolites that can be used as leads in the drug development industry. Increasing health issues such as antibiotic resistance and cancer require new drug development methods. Natural products offer a rich source of structurally complex molecules that have been selected to have an impact on multiple biological systems. Biotechnologies such as synthetic biology, computation, and high throughput screening are improving the discovery and characterization of natural product-based drug leads. However, there are difficulties in ensuring a continuous supply of these valuable natural products. The discovery of new drugs using plant-derived chemicals is a huge area but prospects can be enhanced through cross-cutting collaborations among research areas such as ethnobotany, chemistry and pharmacology. Sustainable therapeutics discovery for natural product-based medicines: integrated data-driven and traditional knowledge-based strategies for natural products discovery. In conclusion, natural products remain crucial in ensuring success in the future of providing medicine for increasing pressing healthcare needs.

Keywords: Natural products, Drug discovery, biologically active compounds, Healthcare challenges, Synthetic biology, Interdisciplinary collaborations

1. Introduction

A substance obtained from a living organism with medicinal properties can assist in creating and advancing new pharmaceuticals. Chemical components vary in structure and uniqueness in crude substances sourced from medicinal plants, animals, microbes, or fermentation broths.

The pharmaceutical and biotechnology industries depend significantly on natural products since numerous modern drugs are developed from naturally existing compounds. Various intricate medicinal compounds are mixed to create healing substances that can be administered through injection, ingestion, and inhalation (Mathur and Hoskins, 2017; Chen et al., 2020). A significant hurdle is presented by the high occurrence of infectious and non-infectious diseases and the difficulty in developing safe and efficient treatment choices. Even with the introduction of medications for the management and treatment of conditions

***Corresponding author:** Dr. Ruchita Shrivastava
*Email: vaishnavi2122@gmail.com

including HIV/AIDS, malaria, diabetes, hypertension, and cancer, these illnesses still affect a wide range of people globally and have substantial death rates. Novel approaches in Fig. 1, to drug discovery are required, departing from the present "blockbuster" Pharma R&D methodologies. As turning to "nature" for solutions has proven successful in the past when it comes to medication discovery, this strategy is still possible today. Natural products were the source of several anticancer and antimalarial medications that are useful in treating various illnesses, including quinine (*Cinchona* spp.), artemisinin (*Artemisia annua*), and vinblastine (*Catharanthus roseus*). Research and development (R&D) on natural products may be crucial to the discovery of novel drugs in the face of global public health issues. Though they can be found in any livable environment, most plants are located on land. Plants have developed different defense mechanisms to protect themselves from environmental insults and animal attacks due to their stationary nature and exposure to various stressors and challenges (Weng et al., 2012). The raw nature and lack of uniformity of these botanical extracts pose a difficulty for pharmaceutical researchers. Purification of plant components can occasionally result in a loss of medicinal efficacy and healing capacity. These extracts frequently have a variety of effects on biological systems, necessitating the clarification of their biological mechanisms of action. It is difficult to conduct studies on natural products and plant-based substances since these mixes are complex and may change once taken out of plants or microorganisms, losing their medicinal properties (Leonti and Verpoorte, 2017; Li and Weng, 2017).

While many diseases are complicated in nature, most of the time, medication discovery is based on the analysis of single chemicals. Therefore, research on individual chemicals for some disorders will not provide successful treatments. As a result, combinatorial methods are being used in drug development procedures to assess possible molecules. Additionally, scientists may now assess possible compounds' medicinal qualities and molecular impacts in more precise biological systems by using combinatorial methodologies made possible by new technology (Mathur and Hoskins, 2017; Weng, 2017). In contrast to conventional medicine, which uses complete plant extracts for therapeutic purposes, contemporary research demands the separation of specific chemicals from extracts and assesses them as possible medications. There are benefits and drawbacks to both using entire extracts and purifying components. When complete extracts are used without any purification steps, the therapeutic effects are superior to when individual components are used. Whole extracts contain compounds that are likely to operate in concert or synergistically to achieve the intended result. Conversely, modern medicine necessitates the isolation and assessment of specific molecules, which frequently makes the process of finding new drugs a drawn-out and costly endeavor. However, since three of the extract's constituents are known to function in concert, isolating them does not have a comparable impact. The development of innovative medications that can tackle current and future global health issues necessitates a combination of advanced technologies like artificial intelligence and original drug design. Innovative computational and analytical methods in new technologies are being used to isolate compounds from extracts and pinpoint those that have desired therapeutic benefits. Pharmaceutical firms must abandon the "one wonder" treatment approach and adopt a combination approach for treating many diseases that are treated with various pharmaceuticals. The use of omics technologies will help in studying how various drug combinations affect genes and proteins within cells. The advancement of biological models such as organoids and microfluidics will allow for the proper evaluation of these compounds in cells and tissues. The production, testing, and design of novel chemicals obtained from plant extract can all be facilitated by the development of computational tools (Özdemir, 2015; Özdemir and Hekim, 2018).

Modern drug discovery techniques and treatment are focused on single-compound medication and reject the use of whole plant extracts. Using whole plants or extracts instead of separating their constituent parts, as is done in conventional medicine, results in a more potent therapeutic impact. This is significant since the majority of plant metabolites probably function simultaneously or in concert to provide the therapeutic action of the plant extract. Researchers need to investigate how whole plant extracts work at a molecular level to understand their medicinal properties. For instance, an anti-asthma herbal remedy derived from extracts of *Sophora flavescens*, *Glycyrrhiza uralensis*, and *Ganoderma lucidum* reduces bronchoconstriction in an animal model while restoring the cytokine balance, thereby extending the anti-asthma effect post-therapy (Srivastava et al., 2013; Yan et al., 2020). To address worldwide health concerns, creative drug development using natural substances is required due to technological progress, which triggers the need for cutting-edge computational and analytical methods to detect components in unprocessed plant extracts. It is essential to identify the specific chemicals causing the desired medical effects and streamline the extraction process to remove any unwanted substances. Research on the combinatorial effects of plant extracts on genes and proteins is crucial, using "-omics" platforms and microfluidics and computational analysis for drug discovery. New

techniques in analysis and bioinformatics have advanced technology, allowing for the creation and testing of new structures and compounds.

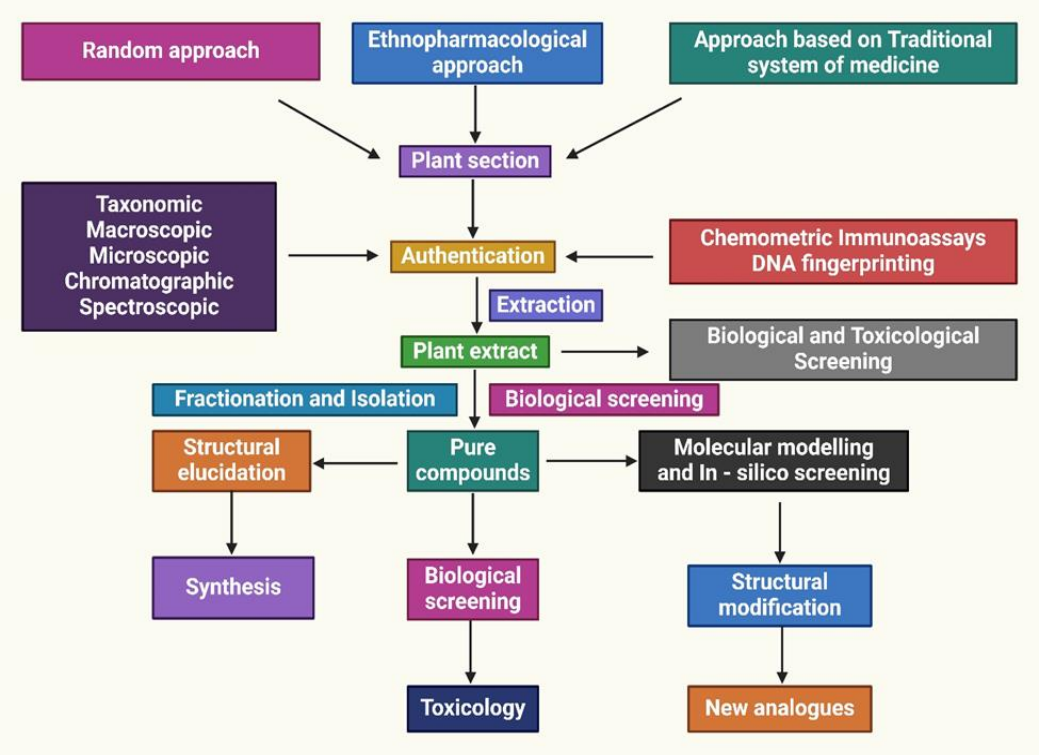

Fig. 1. Common methods applied in the current procedure of creating new medications from plants.

This article explores the transformative potential of natural products in drug discovery and development, highlighting their role in new therapeutic modalities, drug resistance, and safety profiles. It discusses the integration of modern technologies like artificial intelligence and genomic approaches, highlighting the potential of natural products in addressing healthcare challenges and providing sustainable solutions.

2. Novel approaches to medication development using natural ingredients

Innovative and interdisciplinary approaches must be developed to fully determine the development of new pharmaceuticals that are utilized in clinics and other medical practices using natural ingredients in Table 1. Combining these approaches is probably going to produce new medications that can solve today's health problems. The therapeutic value of natural products is reduced by isolating and assessing individual compounds as potential drug candidates, as most compounds, like those found in plants, exhibit synergistic effects. New techniques are needed to blend and assess chemicals for medicinal benefits, with system biology techniques aiding in understanding the efficacy of various compounds (Yang et al., 2013; Amaral et al., 2020). Natural products are a great place to find ingredients that are useful in medicinal research. However, during the last 20 years, their use has decreased, partly due to technological obstacles to high-throughput assays for natural product screening against molecular targets. Here are some natural product screening techniques that take advantage of the most recent technological developments to lower these difficulties. Genomic and metabolomic approaches can enhance the study of natural products, discussing their current applications as protein-protein inhibitors and potential antimicrobial medication candidates. The renewed interest in natural products for drug discovery may also be attributed to the increasing recognition of phenotypic screens and functional tests (Kim et al., 2015). Natural product discovery has been developing over the last seven decades; in the first thirty years, tactics were relatively straightforward, but in the next two decades, scientific and technological developments drove their growth, making them more diverse and complicated. Over the past 20 years, as interest in the pharmaceutical business has waned, overall efforts in natural product discovery have slowed. More recently, low-cost microbial genome sequencing has made entirely new approaches to secondary metabolite drug discovery possible (Medema and Fischbach, 2015).

Table 1. Selected natural compounds with potential mechanisms of action and therapeutic indications obtained from plant and microbial sources in recent decades.

Natural compounds	*Source*	*Mechanism*	*Activity*	*Ref.*
Artemisinin	*Artemisia annua* L.	Development of free radicals that alkylate vital malarial proteins.	Treatment of malaria	Wen et al. 2005
Colchicine	Colchicum spp.	It inhibits microtubule construction, modifying several pro- and anti-inflammatory pathways.	Gout	Buriani et al. 2012
Ingenol mebutate	*Euphorbia peplus* L.	Two-pronged mechanism: a local pro-inflammatory reaction and an inducer of necrosis and cell death	Actinic keratosis	Harvey et al. 2015
Masoprocol	*Larrea tridentate*	5-Lipoxygenase inhibition	The antineoplastic drug used in chemotherapy for cancer	Katz and Baltz, 2016
Lodopyridone	*Saccharomonospora* sp	Cytotoxic to HCT-116 human colon cancer cells	It has anticancer activity	Meshnick, 2002
Podophyllotoxin	*Podophyllum emodi* Wall. and *P. peltatum* L.	Tubulin polymerization causes cell cycle arrest and inhibits the development of microtubules in mitotic spindles.	It has antitumor activity	Dalbeth et al. 2014
Retapamulin	*Pleurotus mutilins*	Preventing bacterial protein production by binding to the 50s ribosome	Impetigo is a topical skin infection treated with antibacterial agents.	Stockfleth, and Bastian, 2018
Salinosporamide A	*Salinospora tropica*	Prevention of 20S Proteasome	It has anticancer activity	Atanasov et al. 2015
Platencin	*Streptomyces platensis*	Blocking fatty acid production in cell membranes by inhibiting β-ketoacyl synthases I/II (FabF/B).	An antibiotic was effective against a range of Gram-positive bacteria, including those that are resistant to other treatments.	Maloney et al. 2009
Daptomycin	*Streptomyces roseosporus*	Disruption with bacterial cell membrane function	Systemic and life-threatening infection induced by Gram-positive bacteria	Ardalani et al. 2017

2.1 Function of proteomics in natural product medication discovery

Proteomic analysis is a valuable tool that complements transcriptomic and genomic methods in identifying the precise mechanisms of action of various natural compounds. Proteomics provides insights into protein expression, function, and biosynthetic cascades, aiding in the assessment of the quality of natural products (Jones et al. 2006; Feling et al., 2003). Mass spectrometry advancements like isotope tags and 2D electrophoresis can reveal protein profiles linked to natural products, revealing genetic information similarly. For instance, Panax ginseng, a Chinese herbal medicine plant, was effectively distinguished from *Panax quinquefolium* using mass spectrometry (Peterson et al., 2014; Miller et al., 2016). Furthermore, mass spectrometry can be used to study the biochemistry and chemistry of natural products to determine the metabolic pathways and biosynthesis linked to such products (Bumpus et al. 2009; Martínez-Esteso et al., 2015). Additionally, proteomics can be employed to identify the multitarget effects of various plant or natural product extracts (Lum et al., 2002). Finding the target proteins in natural products before using them as medications is crucial for preventing side effects throughout the drug discovery process. Affinity chromatography is a method used to study the interaction between natural compounds and proteins, allowing the natural product to be used without alteration. As a result, studies of natural compounds in their unaltered states help to determine their actual activity and therapeutic benefit. Stabilizing the result of natural product-protein interaction can be accomplished with new techniques, such as the cellular thermal shift assay. Utilizing target protein stability at higher temperatures, thermal proteome profiling is an additional technique. Artificial intelligence and technologies simplify bioinformatic analysis of substances' attachment to target proteins, revealing diverse biological features in natural products with multiple known structures. Furthermore, a wide variety of ligands can be bound by natural compounds. Therefore, it is crucial to identify and research certain protein targets of natural compounds. Given their intricate architecture, there is a great chance that they will have harmful side effects. Any natural substance with therapeutic promise needs to be assessed for toxicity, side effects, and the potential for off-target effects. Over the years, affinity chromatography has been used to identify target proteins and their biological characteristics in vivo (Thomford et al., 2018; Hung

et al., 2012; Li et al., 2011 Lao et al., 2014). This process involves pulling down the natural product and binding it to a solid, physical surface (Guan and Chen, 2014). Then, immunoblotting and mass spectrometry can be used to examine and identify the bound protein. A natural product's structure and activity may also change when it binds to its target protein. Therefore, techniques that prevent altering the natural product are required (Novick and Rubinstein, 2012; Rix et al., 2012). New label-free techniques have been developed to assess the response to proteomic and thermal treatment, as well as the interaction between the natural product and its target protein. Proteomic analysis and label-free techniques have shown that a single natural substance can contain multiple target proteins (Wang et al., 2015; McFedries et al., 2013).

2.2 Function of genomics in natural product medication discovery

The development of plant-based drugs relies heavily on accurately identifying the plant species from which a chemical originated. Future studies on a specific component should be based on its therapeutic benefits being linked to the appropriate plant species and geographic area. It is important to prevent the risk of selecting the incorrect plant source. varied chemicals are present in varied concentrations in different plant species. New developments in genomic technology have made it possible to accurately identify plants and other sources of natural products. DNA barcoding is a precise method for identifying plant species and other natural product sources (Mateus et al., 2015). Therefore, compared to current traditional methods of plant identification based on morphology, DNA barcoding, and other more modern approaches can offer fast and accurate plant identification (Lomenick et al., 2009). DNA barcoding is now widely used in biodiversity inventories to accurately identify natural products and their origins due to its speed and precision (Chang et al., 2016) and quick identification of herbal products (Schirle et al., 2012). Using DNA barcoding, for instance, plant species including *Amaranthus hybridus* have been identified (Ganie et al., 2015; Ghorbani et al., 2017). It is now essential to have sources of natural products that consistently display the components they contain. Thus, the practice of growing plants under the same conditions until they are harvested, and natural components are extracted is known as bio-farming. DNA barcoding is then used to authenticate compounds or molecules from natural goods that were extracted under identical circumstances (Thompson and Newmaster, 2014). Genomic approaches can be used to form plant markers and genomic chips, enabling high-throughput genotyping and authentication of natural product sources (Cao et al., 2014). Furthermore, transcript analysis can be done quickly and effectively with the use of cutting-edge methods like microarray analysis (Mishra et al., 2016). Therefore, it is possible to test multiple genes at once (Chen et al., 2017).

2.3 Function of metabolomics in natural product medication discovery

Metabolomics technologies for chemical identification and evaluation are among the most creative approaches to finding novel medications to combat the growing threat to world health. Metabolites linked to a specific natural product can be identified and quantified by outlining the metabolomic profiling of that product (Pulice et al., 2016; Gantait et al., 2014). Conversely, metabolomics quantifies the total and dynamic metabolic modifications to an organism that result in changes to its biology and, most crucially, its DNA (Lv et al., 2017; Kiyama, 2017; Clish, 2015) UPLC-MS, a widely used technique, has been used in metabolomic profiling of natural products, revealing novel compounds with therapeutic properties. Certain plants, including *Newbouldia laevis*, *Cassia abbreviata*, and Panax herbs, have been found to contain medicinal chemicals (Liu et al., 2017; Nicholson and Lindon, 2008). Metabolomics is utilized to maintain the quality and uniformity of plant species utilization. Mass spectrometry and NMR have confirmed the authenticity of *Panax ginseng* and *Panax quinquefolius* as original plants (Perez-Pinera et al., 2012).

3. Techniques to Enhance the Diversity of Natural Products

Traditional bioactivity-guided approaches for natural product discovery are still being used successfully (Yarmush and Banta, 2003). The process involves solvent extraction and solvent-solvent partitioning of natural species, resulting in highly polarized or low/medium polarized fractions (Thomford et al., 2016; Xie et al., 2008). Pure active substances can be obtained by further separation using several chromatographic separation techniques, such as high-performance liquid chromatography and column chromatography (Park et al., 2014). However, because identified compounds are frequently reisolated, conventional bioassay-guided isolation produces unsatisfactory results. Chemists and biologists are increasingly interested in undiscovered natural sources like endophytes, as conventional, easy-to-collect metabolites are becoming harder to obtain for in-depth chemical research (Bucar et al., 2013; Ebada et al., 2008), uncultivable or poorly cultivable microorganisms (Kjer et al., 2010; Sticher, 2008; Kusari et al., 2012; Nisa et al., 2015), and marine organisms under harsh growth conditions (Newman and Cragg, 2015; Piel,

2009). Recent genomic advancements have shown that microbes have a significantly higher capacity for synthesizing novel and intricate secondary metabolites (Epstein, 2013). Genome-mining techniques enable the activation of biosynthetic gene clusters in microbes, enabling the extraction of cryptic natural compounds undetectable in standard laboratory conditions (Ling et al., 2015; Blunt et al., 2017). Recent developments in technology have led to a significant diversification of compound chemical scaffolds through the application of microbial biotransformation and enzymology (Navarri et al., 2016; Rutledge and Challis, 2015). Utilizing synthetic chemistry in conjunction with biological techniques, including the precursor-directed biosynthetic method, has encouraged prospects for obtaining molecules resembling natural products (Scherlach and Hertweck, 2009; Goss et al., 2012).

3.1 Automating drug discovery from natural products

Automation, often associated with negative emotions like job loss and robot dominance, has been effectively utilized to expedite drug discovery. High-throughput assays are widely used by pharmaceutical companies in the robust drug development process (Shen, 2015). Computers, through a variety of software programs, assist in both the design and synthesis of most synthetic substances. ADAM and EVE are software utilized for target and hit finding in drug design (Zheng et al., 2016). New software and hardware are being developed to reduce false positives and material usage in chemical design, synthesis, and biological testing (Harvey et al., 2012). Labs and pharmaceutical businesses are developing integrated microfluidics systems to manage liquids and heat for during-synthesis analyses, purification, compound screening, and synthesis (Chapman, 2003; King et al., 2009). AI and "organ-on-chip" technologies enable rapid testing of multiple theories, optimizing drug development and creating new drugs (Sparkes et al., 2010; Meanwell, 2016; MacConnell et al., 2017; Baranczak et al., 2017). With the help of these technologies, drug design, and optimization mistakes and biases have been reduced, the quantity of candidate compounds required for testing has decreased, testing times for candidate compounds have been shortened to a few days, and disease biology has been more effectively recapitulated than with in vitro assays (Merk et al., 2018). Innovation and technical advancements have frequently given rise to unmet expectations and false hopes. Drug discovery automation and innovation must be quick, but they must also be long-lasting (Zhang et al., 2017). Chemical or molecule design considers the product's ultimate biological action and ADMET features. The optimization of the drug discovery process involves several key aspects. Ultimately, the best compound activity and characteristics can only be obtained by striking a balance. Scientists will be able to choose the optimal compound design with appropriate ADMET characteristics and pertinent biological activity thanks to automation. Over the past few years, several concepts have been established to help with compound creation and developing compound collections with new chemical structures and ingredients. Examples of these concepts are biology-oriented synthesis (BIOS) and diversity-oriented synthesis (DOS) (Duch et al., 2007; Esch et al., 2015; Eglen & Randle, 2015.; Özdemir & Patrinos, 2017).

3.2 Computer-aided drug design from natural sources

Although many of the world's health problems can be resolved by synthetic compounds with structures modeled after natural products, many of the novel synthetic compounds would have been rejected as unsuitable for use in medication development (Praveen, 2024; Praveen et al., 2024). The rigid "rule of three" and "rule of five" criteria used in drug lead decision-making may not have been successful in some new designs (Maier, 2015; Basu et al., 2011). Many drug-making standards are influenced by human prejudice, limiting their effectiveness and applicability, especially in natural products (Kaiser et al., 2008; Wetzel et al., 2011; Lipinski, 2000). Computer-aided designs have been utilized to develop a diverse array of therapeutic synthetic chemicals, including several anticancer medicines (Congreve et al., 2003; Van et al., 2012; Zuegg and Cooper, 2012; Ntie-kang et al., 2014). For instance, complicated natural products were simplified using the Scaffold Hunter program to create virtual pieces of small, chemically appealing molecules (Grabowski et al., 2008). Such a computer program must preserve the biological activity of the mother chemical in the simple molecules it visualizes. Pyruvate kinase activators and inhibitors have already been found using this technique (Elumalai et al., 2015). Simple molecules synthesized from natural products may function less strongly than their original components. The PASS software has successfully predicted the biological activities of basic structures or chemical structures derived from the mother compound (Bon and Waldmann, 2010; Bon and Waldmann, 2009). The PASS software has predicted the anti-tumor properties of several marine alkaloids. It was correctly predicted that several St. John's wort constituents would likewise have cytochrome P450 modifying actions.

Numerous databases, online servers, and computational software programs have been created with the ability to forecast compound-target interactions. The majority of these software, if not all

of them, infer target and typical ligand-receptor docking based on how a novel molecule resembles well-known medications. If the new compound does not resemble any recognized drug, the SPIDER software can estimate the new compound's target by comparing computed properties between natural products and the new compound (Wetzel et al., 2009). One of the SPIDER software's accomplishments was the finding of G-protein coupled receptor ligands (Rodrigues et al., 2016). Drug development will continue to be impacted by the application of computational target prediction and drug design shortly. Only targets or proteins that have been previously investigated, though, can be anticipated. Computer-based quantitative structure-activity techniques can aid in understanding the molecular basis of natural products' therapeutic properties and predicting potential derivatives to enhance activity in drug development (Lagunin et al., 2000).

3.3 Application of analytical procedure

Traditional natural product-based drug research involves biological screening of "crude" extracts to identify a "hit" bioactive extract, which is then fractionated to isolate active natural products. Bioactivity-guided isolation, despite its time-consuming nature and numerous drawbacks, can be mitigated using various strategies and technologies. Crude extracts can be pre-fractionated into sub-fractions suitable for automated liquid handling systems, enabling the creation of libraries for high-throughput screening. Furthermore, it is possible to modify the fractionation techniques such that molecules having drug-like qualities (usually moderate hydrophilicity) are preferentially present in subfractions. When compared to crude extracts, such methods can yield more results and provide more effective follow-up on promising hits (Stepanchikova et al., 2003). The technique known as "metabolomics" was created to analyze many metabolites in biological samples at once. Metabolomics, primarily used in agricultural and biomedical sciences, has been largely influenced by advancements in chromatography and spectrometry. Improvements in the analytical tools employed in natural product research (Reker et al., 2014; Scheinder et al., 2014), along with computational techniques that produce natural product analog structures and corresponding simulated spectra (Sliwoski et al., 2014), have made it possible to apply "omics" techniques, such as metabolomics, to natural product-based drug development. Metabolomics accurately reports on the metabolite composition in natural product extracts, prioritizing natural product isolation and expediting dereplication (Wagenaar, 2008; Wolfender et al., 2018) as well as annotating fresh natural product scaffolds and unidentified analogs. Metabolomics helps identify metabolite composition variations in organisms' physiological states, aiding in hypothesis development and providing comprehensive profiles for molecular characterization of phenotypic traits.

3.4 Advances in techniques for growing microbes

The cultivation conditions of organisms producing nanoparticles significantly influence the likelihood of discovering novel nanoparticles due to their intricate regulation in response to environmental cues. Techniques have been developed to enhance the discovery of new nanoparticles by allowing uncultured microorganisms to thrive in simulated natural environments (Stuart et al., 2020). A well-researched strategy to facilitate the discovery of new nanoparticles is to adjust culture parameters like pH, temperature, and nutrient availability. This tactic might activate silent gene clusters, which would encourage the synthesis of various N natural products. This method was first referred to as "One Strain Many Compounds" (OSMAC) approximately 20 years ago (Allard et al., 2017), however, the idea has a longer history, since the 1960s, industrial microbiology has routinely used it (Allard et al., 2018; Hubert et al., 2017). Although OSMAC is still frequently employed to identify novel bioactive chemicals, it is not very good at simulating the intricacies of natural environments (Lewis et al., 2010; Schiewe and Zeeck, 1999). The bacterium's response to unpredictable stimuli, including compounds from other microbial communities, can be explained through co-culturing using "helper" strains (Zähner, 1977). Recent investigations that have shown the generation and identification of novel NPs have been made possible by co-culturing specific fungi with species of Streptomyces (Newman, 2017; Hussain et al., 2017).

4. Returning to Natural Product-Based Drug Research

Chemical synthesis failed to meet expectations, leading to a decrease in the introduction of new medications to the market. Between 1981 and 2010, only 36% of 1,135 new medications were entirely synthetic, with over half derived from natural sources, analogs, or derivatives, highlighting the failure of chemical synthesis (Hemphill et al., 2017). Between 1981 and 2002, natural products accounted for 61% of 877 new medications based on small molecules, with 6% natural products, 27% natural product derivatives, 5% synthetic compounds, and 23% modeled after natural products (Vartoukian et al., 2010*;* Moussa et al., 2019). The number of pharmaceuticals approved by the US FDA from 45 in 1990 to 21 in 2010 declined, not increasing (Abdel-Razek et al., 2018; Newman and Cragg,

2012). The causes of this downward tendency are numerous and intricate and perhaps the most significant piece of evidence is that the synthetic libraries' molecules frequently have almost little chemical diversity at all (Yuliana, et al. 2011). The majority of HTS-compounds libraries can contain the same molecules due to identical techniques used, a phenomenon known as "attrition rate." Compounds are often rapidly selected from libraries based on their potency values (Kingston, 2011), yet in terms of ADMET, they may also correlate negatively (David et al., 2015).

4.1. Comparing Combinatorial Chemistry with Natural Product Chemistry in Drug Discovery

Large pharmaceutical companies initiated natural product discovery programs targeting infectious disorders, antibacterial, and antifungal targets, following the "Golden Age of Antibiotics" and global antibiotic search drive. These projects provided lead chemicals for cancer treatment, microbial infections, hypercholesteremia, and organ transplant tissue rejection (Kola and Landis, 2004; Bauer et al., 2010). In the 1990s and 2000s, pharmaceutical corporations abandoned NPD initiatives, focusing on automated high throughput screening and combinatorial chemistry for producing "drug-like" molecules. Pharmaceutical companies disbanded or sold screening extracts due to the ongoing discovery of isolated compounds and the complexity of natural products, which required total synthesis and derivatization (Scannell et al., 2012; Gleeson et al., 2011). HTS technologies utilize combinatorial chemistry to create extensive chemical libraries, but supply issues have hindered the development of natural products from extract hits to pharmaceuticals. Over the past 20 years, molecular target-based drug discovery in Fig. 2 has significantly replaced traditional natural product chemistry, utilizing vast combinatorial libraries to identify effective "hits". Technological advancements and sensitive instrumentation are improving the method of discovering new natural products, enabling quick identification and structure clarification of bioactive compounds. Starting in the 1980s, combinatorial chemistry was believed to offer numerous unique carbon skeletons, therapeutic leads, or new chemical entities (NCEs). The FDA has only approved one combinatorial NCE, sorafenib, for renal cancer treatment since 2005, indicating that this is not the case (Baker et al., 2007). Combinatorial chemistry has revolutionized the process of discovering new active chemical leads for synthesizing structural analogs. Synthetic chemists discovered in the late 1990s that combinatorial libraries, which contained hundreds to thousands of novel compounds, lacked the complexity of complex natural products. Synthetic chemists are using diversity-oriented synthesis (DOS) to create molecules mimicking natural product topologies, with biological screens being conducted to determine their potential for novel pharmacological entities. Between 2000 and 2006, natural products were involved in or contributed to approximately 50% of all small molecule testing, according to an investigation into NCE approval rates. Between 1981 and 2006, 30% of the 1184 NCEs across all diseases, countries, and sources were synthetic, despite significant pharmaceutical industry investment in HTS and combinatorial chemistry. 52% of these chemicals are natural products, mimics, or chemically modified versions of pharmacophores found in current natural products (Ojima, 2008).

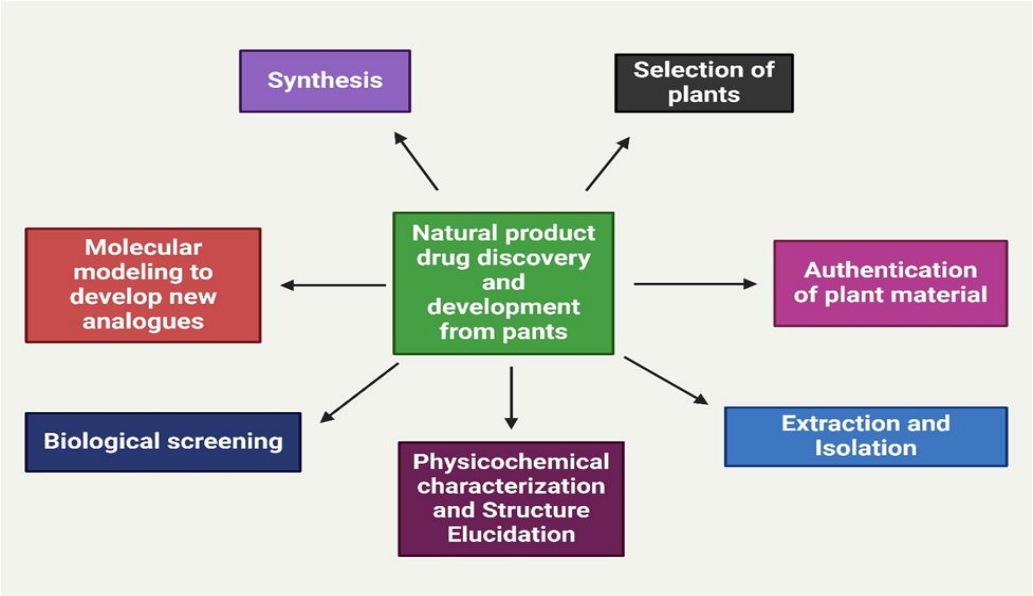

Fig. 2. Unlocking Nature's Potential: procedures in Research and Development of plant-derived Products

5. Current Applications of Natural Product-Based Medications

Natural products' significance in treating and preventing diseases is determined by their number of ailments treated, usage rate, and the introduction of new chemically diverse entities (Von Nussbaum et al., 2006). Pharmaceutical research primarily utilizes natural products due to the ineffectiveness of alternative drug discovery methods in producing lead molecules for crucial therapeutic areas like metabolic and anti-infective diseases. Natural product research continues to develop innovative methods for the pharmaceutical sector to identify lead chemicals for drugs, making natural products crucial sources of new therapeutic agents. Synthetic therapeutic agents, created using computational chemistry and various chemical sources, have fewer negative side effects and therapeutic effects compared to traditional drug metabolites (Luzhetskyy et al., 2007). These building blocks are not present in nature. Natural sources of medicinal substances may not cause adverse effects due to their pharmacological and physiological effects on live cells. Furthermore, a greater range of molecular characteristics, including a smaller molecular mass, a partition coefficient, and structural diversity, are present in natural products (Newman, 2008). Additionally, natural products interact with other biological molecules, proteins, and enzymes more frequently. Moreover, compared to synthesized compounds and combinatorial libraries, natural products have higher molecular stiffness and fewer heavy metals (Newman and Cragg, 2007).

6. Drug development for natural products

Pharmaceutical corporations have reduced or discontinued natural product research, despite natural goods being crucial in drug development. Advanced methods like combinatorial chemistry, high throughput screening, and metagenomics are causing this, but due to intricate structural makeup and time and cost, not all natural compounds can be fully synthesized. The pharmaceutical and biotech sectors are reevaluating natural products for therapeutic applications due to improved drug discovery and medicinal chemistry knowledge. Therapy is often required for hard-to-treat diseases or clinical conditions like cancer, obesity, and infections caused by multi-resistant microorganisms. Plants, fungi, bacteria, and microbes have proven to be valuable sources of natural compounds in the search for new drugs. More sophisticated and potent treatment medications are needed to combat the different multi-resistant infections. Out of the 250,000 species of terrestrial plants now in existence, only 5–15% have undergone thorough chemical and pharmacological analysis efficiently to be used as medicinal agents.

The microbial domain accounts for 90% of all-natural variety, with less than 1% of it found. Natural diversity is at risk of extinction due to global warming, toxic waste from manmade chemicals, and multidrug resistance to conventional treatments. Demonstrating the value of natural diversity and bioresources is crucial for guiding research methodologies in biotechnological and pharmaceutical industries for drug development. Drug discovery procedures aim to identify promising lead compounds for treating diseases like cancer, infections, neurological disorders, high blood pressure, and metabolic disorders (Newman and Cragg, 2007). Scientists use various methods to isolate and purify lead compounds from their natural source during the early drug design stages, based on structural diversity, stability, and quantity. The lead compounds have been screened using high throughput screening against predetermined targets. Important pharmacological and biochemical testing are then performed, and the compounds that show promise for the particular targets are chosen. Scientists alter lead compounds' structures to increase selectivity in drug design, leading to in vitro and in vivo testing in specific illness facsimiles if these changes improve selectivity.

7. Progress in Chemical and Biological Characterization of Marine Natural Materials for Drug Discovery

The process of discovering new drugs from natural sources is fraught with difficulties. The first is getting into the marine environment, which is followed by the chemical and biological characterization of the natural chemicals that show promise but are frequently isolated in extremely small quantities. Therefore, improvements in target identification methodologies, structure determination tactics, and sampling techniques are important stages in the marine drug development process.

i. Sampling techniques

The fact that sampling the ocean requires more sophisticated methods and tools may have been a major deterrent to exploration for a very long time. Many chemicals have been discovered from easily accessible near-shore marine sample collections; however, additional challenging ocean locations may be harboring unidentified macro- and microorganisms and, as a result, novel therapies. Fenical and colleagues focused their efforts on looking for promising antibiotics in the difficult-to-reach deep-sea marine sediments. Their quest was motivated by the well-known antibiotic production

of the bacteria that live in soil. As a solution to the access problem, they were able to design a system that would allow them to take samples from the sea floor at depths greater than 2000 meters while utilizing comparatively tiny boats (Chin et al., 2006).

ii. Determination of the structure of nanomoles

Although NMR spectroscopy remained an essential tool for elucidating structures, its limited sensitivity in comparison to other methods, including mass spectrometry, continued to be a constraint. Up until a few years ago, a compound's structure could not be fully understood without more than a micromole of the chemical. This need has altered due to recent developments in NMR structure elucidation techniques, and several studies have examined trace levels of natural products at the nanomole or even picomole scale (Valecha et al., 2010). Recently, Molinski evaluated those developments and provided a clear illustration of how his group's use of the microscale approach has significantly improved the chemical characterization of uncommon marine materials (Pascouluyyi et al., 2014). Researchers discovered cytostatic and antifungal macrolides, phorboxazoles A and B, from the 1995 collected marine sponge Phorbas sp. off Muiron Island in Western Australia (Lahlou, 2013). Phorbasides A-E were discovered using minor chromatography side fractions (0.78-3 mg) using a 5-mm cryoprobe (Fenical and Jensen, 2006).

The chemical diversity of a marine organism was explored using a sensitive 1.7-mm, 600-MHz cryo-microprobe. The researchers successfully reported the structures of four additional phorbaside analogs at the nanomole scale, such as four additional phorbaside analogs (7–16 μg) (Montaser and Luesch, 2011), hemi-phorboxazole A (16.5 μg, 28 nmol) (Fellenberg et al., 2010), and the novel macrolide muironolide A (90 μg, 152 nmol). The new macrolide was a unique carbon skeleton with previously unexplored characteristics (Searle and Molinski, 1995). The researchers utilized nanomole-scale NMR spectroscopy and mass spectrometry, circular dichroism, and chemical synthesis to fully solve structures, including stereochemical projects. More recently, it used specialized sample preparation methods and instrument setup to record spectra of picomole quantities of oligosaccharides, considerably narrowing the practical limits of NMR spectroscopy.

iii. Identification of the target

To identify therapeutic candidates that alter biological pathways, phenotypic screening has drawn interest from both academia and business (MacMillan et al., 2008). Finding a hit compound's cellular target and mode of action remains a barrier to turning it into a medication after it has been identified in one of those screens. This mechanistic understanding is essential to foresee any adverse effects and, as a result, to prevent expensive clinical failures. Moreover, it offers biomarkers for preclinical and clinical trials and enables lead optimization. This stage was made easier by several significant advancements in drug target-identification techniques, which raised the likelihood of drug discovery and development (Dalisay and Molinski, 2010). Target-identification techniques can be categorized into indirect methods like global profiling based on genomes, proteomics, or metabolomics, and direct methods like affinity chromatography, expression cloning, and protein microarrays. Affinity chromatography is a traditional technique used to identify targets. To address the challenges with this strategy, which typically necessitates the addition of a label, there are a few further adjustments. "Drug affinity responsive target stability" is a sophisticated label-free approach that relies on binding to a bioactive molecule or substrate to stabilize the target protein more effectively against proteolysis (Dalisay and Molinski, 2009). After nontarget proteins are broken down, target proteins are more easily detected and enriched. For example, the molecular target of sidemen B was first determined by affinity purification techniques and subsequently verified by drug affinity responsive target stability, offering additional proof of the usefulness of this innovative method. Theonella sp. is the source of the antifungal bicyclic dodecapeptides known as Theonellamides A–F (Chan et al., 2010; Hart, 2005). Using a variety of direct and indirect methods, Nishimura et al. were able to determine the onellamides' mode of action (Lomenick et al., 2011). Ergosterol, a key sterol in fungal cell membranes, was identified as a direct target of onellamides in fission yeast through chemical-genomic profiling and fluorescence labeling. Theonellamides, marine secondary metabolites, exhibit unique sterol-binding activity, indicating they belong to an unidentified sterol-binding compound family, and a novel labeling method was used to identify their cytotoxic target (Crews et al., 1994).

8. Benefits and Limitations of Natural Products as Therapeutics

Roughly 50% of the medications used in clinical practice today are thought to have natural product origins (Matsunga et al., 1989). Among many other instances, natural product-derived medications like quinine, theophylline, penicillin G, morphine, digoxin, vincristine, cyclosporine, and vitamin A are essential components of contemporary pharmaceutical treatment. Natural materials, especially plants, have been utilized for ages to prevent and cure illnesses, and this has led to the

discovery of most contemporary pharmaceuticals (Matsunga et al., 1995). Medicine was practiced by the ancient Egyptians as early as 2900 BC. The earliest known documentation of Egyptian pharmacy practice, known as the "Ebers Papyrus," dates to approximately 1500 BC. Beer, milk, wine, and honey are frequently employed as drug transporters. The papyrus lists over 700 plant-based medications, including gargles, snuffs, poultices, infusions, tablets, and ointments, with most being of plant origin. Discords documented the use of natural ingredients for therapeutic purposes in 78 AD, with thousands of described plants still being useful in contemporary medicine (Nishimura et al., 2010). These plant components are nevertheless valuable sources of refined active ingredients, which are the pillars of contemporary therapy, even though they are no longer employed as raw drug compositions. Only thirteen medications made from natural products were authorized between 2005 and 2007 (Hughes et al., 2009). Additional recently authorized medications, thoroughly reviewed in specialized reviews (Clark, 1996), comprise substances obtained from microbiological, plant, and animal sources in addition to semi-synthetic substances created from natural product models. Along with having a broad range of therapeutic applications—including anti-diabetic, anti-infective, and anti-cancer—they also exhibit a remarkable variety of chemical structures.

Half of the newly discovered small molecule natural product-derived medications that had their chemical characteristics analyzed were found to comply with Lipinski's Rule of 5 for oral pharmaceuticals (Azad et al., 2024; Soejarto and Farnsworth, 1989). Large pharmaceutical companies are hesitant to pursue natural product-based medication discovery due to supply and accessibility issues, chemistry intricacies, and intellectual property rights concerns. They also rely on combinatorial chemistry for synthetic chemicals (Butler, 2008; Lam, 2007).

9. Challenges and Limitations in NTD Drug Discovery and Current Therapies

Numerous obstacles must be overcome in the drug discovery and development process for neglected tropical diseases (NTDs). First off, the likelihood of low financial returns makes major pharmaceutical corporations' participation in certain therapeutic areas unappealing financially. Because of this, the search for drugs to treat parasite illnesses, such as NTDs, has not been driven by profit (Ganesan, 2008; Shi et al., 2020). Several pharmaceutical companies have taken an opportunistic stance, repurposing medications that were previously developed for purposes unrelated to diseases (NTDs). Sadly, despite the clear benefits of this approach—such as lower development costs—it does not result in the release of chemically unique medications onto the market. Furthermore, because of the widespread resistance to several chemical classes, the usefulness of such an approach could no longer be feasible. Since NTDs primarily impact countries with few resources, it is typically difficult to modify the target product profiles of therapeutic candidates to meet the needs of these environments (Praveen, 2024). One such challenge is optimizing a medicine candidate for safe usage without rigorous medical supervision. The medications now employed in clinical trials to treat NTDs are far from optimal. Current chemotherapeutic agents face drawbacks like drug resistance, severe side effects, long treatment durations, unfavorable toxicity profiles, and complex administration procedures, particularly in resource-poor communities affected by NTDs. The scarcity of certain pharmacological regimens poses a threat to their efficacy (McChesney et al., 2007; Rishton, 2008; Pink et al., 2005).

10. Conclusions

Natural products' diverse chemical compositions and biological activities offer a rich source of therapeutic candidates, ranging from traditional remedies to advanced pharmaceuticals, demonstrating significant potential in drug discovery and development. Researchers are using innovative strategies and interdisciplinary approaches to discover new pathways for drug discovery, identifying solutions for complex diseases. Advancements in technology, like artificial intelligence and genomic sequencing, are enhancing our ability to explore and exploit the vast reservoir of natural compounds in healthcare. To fully utilize natural products, challenges like sustainability, scalability, and standardization must be addressed through sustainable sourcing, optimized production processes, and quality control. Natural products have proven to be invaluable resources in revolutionizing and innovating drug discovery and development strategies. Natural products' diverse chemical structures and biological activities have led to the discovery of therapeutic agents for healthcare issues, ranging from traditional remedies to modern pharmaceuticals. Advances in technology, including high-throughput screening, metabolomics, and bioinformatics, are enhancing our ability to explore and exploit the vast biodiversity of natural sources in drug discovery. The integration of multidisciplinary approaches, such as synthetic biology and combinatorial chemistry, holds significant potential for rational design and optimization of natural product-derived drugs. Natural product-based drug discovery faces challenges like resource depletion, sustainability, and scalability, which must be addressed for its continued success. Natural products are pivotal in drug discovery, offering innovative healthcare solutions, paving the way for

personalized medicine and improved global health outcomes.

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