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NATURAL PRODUCTS: A SOURCE OF NOVEL THERAPEUTIC AGENTS

Sabana Dabir[1]*, Jyotisri Jibanendu Mohapatra[2], Goutam Sahoo[3], Jyotirmaya Biswal[4], Upendra Kumar Das[5], Bitarkita Routray[6], Subhasmita Malick[7] and Bijayalaxmi Jena[8]

[1]Associate Professor, Department of Pharmaceutical Chemistry, Orissa College of Pharmaceutical Sciences, At - Patimal, Post - Mahulipada, Dhekanal, Odisha, 759027.
[2]Assistant Professor, Department of Pharmaceutics, Orissa College of Pharmaceutical Sciences, At - Patimal, Post - Mahulipada, Dhekanal, Odisha, 759027.
[3,8]Assistant Professor, Department of Pharmaceutics, Orissa College of Pharmaceutical Sciences, At - Patimal, Post - Mahulipada, Dhekanal, Odisha, 759027.
[4]Assistant Professor, Department of Pharmacology, Orissa College of Pharmaceutical Sciences, At - Patimal, Post - Mahulipada, Dhekanal, Odisha, 759027.
[5]Assistant Professor, Department of Pharmaceutical Analysis & Quality Assurance, Orissa College of Pharmaceutical Sciences, At - Patimal, Post - Mahulipada, Dhekanal, Odisha, 759027.
[6,7]Assistant Professor, Department of Pharmaceutical Analysis, Orissa College of Pharmaceutical Sciences, At - Patimal, Post - Mahulipada, Dhekanal, Odisha, 759027.

***Corresponding Author: Sabana Dabir**

Associate Professor, Department of Pharmaceutical Chemistry, Orissa College of Pharmaceutical Sciences, At - Patimal, Post - Mahulipada, Dhekanal, Odisha, 759027. **DOI:** https://doi.org/10.5281/zenodo.18093681

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ABSTRACT

Natural products have been historically used as an inspiration and tools for the discovery and development of new therapeutic agents and that has carved the path of modern medicine. The present work aims to review their historical perspective, the traditional use as a starting point for the understanding of their evidence-based activities, the evolution of discovery routes as a main contribution to the pharmacopeia among others. The main sources of natural products, plants, microorganisms and marine life are reviewed. The mechanisms of action and nature of the most recognized therapeutics will be analyzed. Applications of natural products and their derivatives to common and rare diseases will also be covered. Some of the challenges of drug discovery and development starting from natural products, supply issues, characterization and synthesis of the active principles will be discussed. Some of the advances in current discovery and development strategies will be outlined as well as the expected contribution of natural products to the discovery of new therapies for the treatment of infectious and non-communicable diseases in the near future.

KEYWORDS: Natural Products, Drug Discovery, Bioactive Compounds, Therapeutic Applications and Biodiversity Conservation.

INTRODUCTION

Over centuries, nature has been an unparalleled source of novel compounds to be used in drug discovery. Natural products are those which are isolated from living organisms including plants, fungi, bacteria, and marine species. Historically, natural products have been the most preeminent form of therapeutics in tradition medicine and also continues to be a source for discovering new chemical entities in modern drug research. Due to their vast chemical diversity, the compounds found in nature have unique mechanisms of action and most often cannot be synthesized in the laboratory. As the interest in finding optimal treatments for a wide range of diseases is increasing, natural products will undoubtedly continue to be a reliable source for obtaining new lead candidates. There is no denying that natural products have been, and will continue to be, integrated in the drug discovery

process and a contribution to its success as a discovery pipeline.

Historical Perspective on Natural Products in Medicine

The use of natural products in traditional and early established medicine was a common keeping in the records of early civilizations. The historical texts and classic pharmacopoeia provide evidence for the practical application of botanicals, minerals, and animal-based products to restore health and prevent and treat illnesses all over the world and across cultures. Instead of being isolated into traditions, herbal medicine and related products have increased acceptance in the world as the basis of therapeutic approaches in various societies (EOJ Ozioma et al., 2019). The historical impact of more popular uses and the resulting access to empirical data and potential candidates for scientific exploration naturally shaped the development of modern therapeutics towards traditional remedies. Nevertheless, the leap of natural products from history into modernity, where their use continues even if their safety and efficiency perception is still being challenged for improvement, indicates their impact on the medical field (EOJ Ozioma et al., 2019).

Equally, ancient civilizations, also used extracts from plant, animal-based substances and minerals as primary means to cure disease with the reliance on trial-and-error as a guiding principle. Plant extracts, animal secretions and minerals were methodically produced, stored and applied without any necessarily deep scientific understanding or fact, but rather on the basis of a priori belief. Eventually, these empirical approaches led to broader practical knowledge, whereby effective procedures were kept and shared across time. While the buildup of this information was spontaneous in nature, once the scientific approach emerged, the features of the ancient remedies started to be scientifically approached through the techniques of chemical extraction and isolation of the active ingredients, bioactivity screening and human clinical trials, creating a logic as opposed to an instinctive process to the identification of therapeutic agents (Najmi et al., 2022). This paved the way for the cross-section of a high number of scientific disciplines, which still today participate in the process of discovery and development of medicinal agents from nature (Najmi et al., 2022). Natural products originate from diverse biological sources, including plants, microorganisms, marine organisms, and animals. Plants remain the most abundant contributors, offering alkaloids, flavonoids, terpenoids, and taxol, which demonstrate analgesic, anticancer, antimalarial, and anti-inflammatory activities (Awuchi & Amagwula, 2020; Câmara et al., 2024; Chaachouay & Zidane, 2024). Microorganisms such as bacteria and fungi provide antibiotics like penicillin and streptomycin along with quorum-sensing inhibitors that target resistant pathogens (Wu et al., 2019). Marine organisms—including sponges, algae, and invertebrates—yield compounds like spongothymidine and various anticancer metabolites with antiviral and anti-inflammatory properties (Banday et al., 2024; Shinde et al., 2019). Animal-derived toxins and peptides further contribute antihypertensive, analgesic, and cardioprotective molecules (Calixto, 2019) shown in table-1.

Table 1: Major Sources of Natural Products and Key Examples.

Source	Representative Bioactive Compounds	Therapeutic Uses	Key References
Plants	Alkaloids (morphine, quinine), flavonoids, terpenoids, taxol	Analgesic, antimalarial, anticancer, anti-inflammatory	Awuchi & Amagwula (2020); Câmara et al. (2024); Chaachouay & Zidane (2024)
Microorganisms (Bacteria & Fungi)	Penicillin, streptomycin, quorum-sensing inhibitors, biofilm inhibitors	Antibacterial, antifungal, anti-resistant pathogens	Wu et al. (2019); Rf-s572478
Marine Organisms	Spongothymidine, marine toxins, algal metabolites, anticancer compounds	Antiviral, anti-inflammatory, anticancer, anti-resistant	Banday et al. (2024); Shinde et al. (2019)
Animals	Peptide toxins (captopril precursor), venom peptides	Antihypertensive, analgesic, cardiovascular therapy	Calixto (2019)

The landmark achievements in the field of natural products research have also been instrumental in translating it toward significant progress in the field of pharmaceutical development. The isolation of morphine from opium poppy in the early 1900s was a breakthrough as it created a significant change to have an active principle that is accountable for the medicinal effect; this was closely followed by the isolation of quinine from the cinchona tree. It paved the way of transforming the health practice of treating malaria and validated natural products to be the source of disease-specific anti-infectives. (Chaachouay & Zidane, 2024); aspirin, which was derived from willows bark too, was another example of progress where the knowledge of botany had diverted toward designing synthetic drugs and further ceased the boundaries between the natural and artificial medicine. These achievements not only refine the therapeutic approach but also strengthen the logic of science to hold the same rationale in translating research for finding

bioactive ingredients from the natural habitat (Chaachouay & Zidane, 2024).

Major Sources of Natural Products

The natural product sources can be derived from plants, micro-organisms, marine organisms and animals that each contributes different classes of biomolecule to the reservoir of therapeutically useful agents. Plants have been a historically valuable source for traditional medicine and pharmaceuticals as they are the most common sources to find and possess a large variety of secondary metabolites with a wide range of biological activities. With new technologies to cultivate and screen library of compounds, micro-organisms or more specific fungi and bacteria have proven to be a promising source of specific molecules for drug development as well (Newman & Cragg, 2020). Marine life which includes sponge, algae and mollusk holds distinctive scaffold structures, unique compounds that add to the library of chemical diversity from land based species. Lastly, animal sourced biomolecules though not the most popular also play a role in providing unique bioactive peptides and proteins. Together they exhibit the sheer potential of extraordinary range of bioactive chemistry that nature has to offer (Newman & Cragg, 2020).

Specifically, the plant kingdom is a broad source of living organisms that have diverse molecular structures of bioactive agents, many of which are the original prototypes of important drugs widely used in the clinical practice today. One of the examples of a plant-based bioactive compounds is alkaloids, the greater chemical diversity of which is related to a wide range of corresponding pharmacological activities, including anticancer, antimalarial, antiasthmatic and, to a lesser degree, stimulating and psychotropic effects (Awuchi & Amagwula, 2020). The second example is flavonoids, which are members of one of the major classes of polyphenols with varying degrees of metabolic and biological activity and are widely used in the production of functional foods and medicinal formulations. Terpenoids also are among the most numerous classes of phytocompounds, which are characterized by complicated biosynthetic pathways and are known for their major biological functions, antioxidant, antimicrobial, anti-inflammatory and anticancer activities, among others (Câmara et al., 2024). These vocable molecules, on the one hand, are an integral part of the health-promoting practices of various traditional cultures, and on the other hand, are promising sources for innovative pharmacology, whereby the plant world is an inexhaustible source of compounds diverse in structure and function, which can be resilient and permanent reliable source for further discoveries in the development of novel drugs.

De manera análoga, los microorganismos como las bacterias y los hongos también han sido una fuente madre en el descubrimiento y producción de antibióticos y otros terapéuticos de importancia clínica. El hallazgo clásico fue el de la penicilina proveniente del hongo Penicillium notatum que cambió el curso de las infecciones bacterianas, dando pie al uso de los antibióticos como primera línea terapéutica para su manejo. Estudios posteriores revelaron que los microorganismos no sólo producen antibióticos, sino que también compuestos que inhiben factores de virulencia en las bacterias, comprometiendo su supervivencia y patogenicidad (Wu et al., 2019). Por ejemplo, se han aislado productos naturales de diferentes orígenes bacterianos y fúngicos, activos en procesos como el "quorum sensing" y la formación de biopelículas, dos mecanismos implicados en la permanencia de cepas resistentes como Staphylococcus aureus. De esta forma, se destaca la importancia de los microorganismos como fuentes versátiles en la búsqueda de nuevos fármacos para el tratamiento de infecciones clásicas y la cada vez más emergente resistencia a los antimicrobianos(Rf-s572478).

Also, the marine biota has become a rich source of new compounds with unique chemical structures and with great therapeutic potential. Sponges were the starting point for the development of antiviral drugs, the first nucleoside analog spongothymidine inspired the synthesis of other synthetic analogs. Metabolites from algae are reported to have anti-inflammatory and antimicrobial activities, which adds diversity to the therapeutic potential of marine organisms. Marine bacteria have provided toxins and secondary metabolites with anticancer and anti-resistant activities, which lead to the inclusion of several compounds in preclinical and clinical trials for diseases that include infections and tumors (Banday et al., 2024). The Patent growth and the drug development correspond to the great biomedical potential of marine organisms. Above all, this highlights the importance of the search for new marine compounds and the development of marine biomaterials as new drug sources (Shinde et al., 2019).

Furthermore, natural products of animal origin represent a particular field of drug discovery, through bioactive molecules (peptides and venoms) applicable to therapeutics with more specific pharmacological activities. Some peptide toxins from snake and insect venoms have been exploited to design drugs for a range of cardiovascular and pain diseases, as seen in the case of captopril, the first drug targeting hypertension developed from the venom of the Brazilian viper Bothrops jararaca (Calixto, 2019). Like their plant-derived counterparts, animal toxins are highly selective for specific enzymes or receptors, thereby providing the basis for the development of drugs that exert particular effects and minimize their systemic toxicity. Even though scientific and technical barriers hinder the extraction and production of compounds from animal origin, advances in biotechnological methods have addressed their synthesis and modifications to enhance therapeutic properties. Thus, remarkable achievements in this field put animal natural products as a promising class able to

propose new approaches to still unmet medical needs, therefore, there is a great potential for drug discovery and development in this area (Calixto, 2019).

Mechanisms of Action and Therapeutic Applications

Natural products produce their pharmacological activities through an extensive variety of biological mechanisms, justifying their importance in drug development and clinical use. The most representative mode of action involves the inhibition of a specific enzyme crucial for the development and progression of a disease. This inhibits metabolic routes in pathogens or cancer cells and induces direct pharmacological effects. Furthermore, natural products frequently bind to cellular receptors and modulate signal transduction pathways implicated in inflammation, immunity, and cellular signaling, which justifies their target effects on a number of chronic and acute diseases. Most of these natural products also routinely present antimicrobial mechanisms that act upon processes like cell wall synthesis or protein function in bacteria, fungi, and viruses. This capacity is key to the continued search for answers to antimicrobial resistance (Atanasov et al., 2021). In summary, there is a wide variety of mechanisms employed by natural products. This is key not only to their extensive therapeutic range, but also to provide options for promoting the discovery of new candidates throughout the innovation process. (Atanasov et al., 2021).

Examples include taxol (paclitaxel), a natural product from the bark of the Pacific yew tree that stabilizes microtubules and prevents their depolymerization during mitosis, thereby blocking proliferation of cancer cells. The mechanism of action of taxol disrupting mitosis differs from other chemotherapeutic agents, making it an important drug in the treatment of ovarian and breast cancers. Another example is artemisinin, a natural product from Artemisia annua, exhibits strong antimalarial properties because free radicals were produced after the cleavage of the endoperoxide bridge when artemisinin comes in contact with iron in red blood cells infected with malaria. Free radical-induced cellular damage targets only certain types of Plasmodium, making artemisinin unique relative to conventional antimalarial agents. These examples highlight the uniqueness of compounds derived from plants showcasing mechanisms largely unexplored by conventional drugs (Chaachouay & Zidane, 2024). Novel mechanisms made possible by natural product scaffolds will add to the growing value of these compounds in drug discovery and continue to make the case for those efforts.

Besides, drugs originating from natural products are essential for a diverse range of diseases, demonstrating the extensive therapeutic potential of biocompounds derived from natural sources. In this context, taxol highlights the importance of natural products in anticancer therapies, while artemisinin shows its relevance to infectious diseases. Likewise, the list of natural products as drugs employs also incorporates cardio-vascular diseases, being captopril based on a peptide structure, initially found in snake venom and the first drug to be used as a preferred therapy for hypertension and heart failure (Calixto, 2019). Besides these examples, natural products also figure in the therapy of inflammatory diseases, metabolic syndrome or neurologic pathologies, among others, evidencing their wide clinical usage. Consequently, this disease range correlates with the major market share that naturally derived pharmaceuticals hold due to their capacity to cover unmet medical needs in the major therapeutic areas (Calixto, 2019).

Moreover, the global threat of antibiotic resistance and the emergence of new pathogens make the promising role of natural products as a key weapon in the global health agenda. Natural products derived from plant, bacteria, fungi or animals exhibit wide spectrum of antibacterial activities with complex mechanisms of actions that disrupt membranes, metabolic pathways, interfere with quorum sensing, biofilm formation and other important processes (Ng et al., 2021). These complex mechanisms allow natural products to be effective against antibiotic-resistant bacteria, and they are also less likely to induce resistance because of their diversity of chemistry (Álvarez-Martínez et al., 2020). Additionally, several plant-derived compounds and polyphenols have antibacterial synergism with current antibiotics and are capable to restore or enhance antibiotic activity in resistant strains. The recently developed technologies, particularly the emerging -omics and informatics tools, also help to further accelerate the search and characterization of new natural antimicrobials, represent the promising role to tackle existing and future infectious threats (Álvarez-Martínez et al., 2020).

Advances in Natural Product Discovery

Natural product discovery has witnessed a growing trend of convergence through the use of the newest technologies in high-throughput screening, genome-based research, and informatics-driven methods. High-throughput screening approaches allow assessing vast chemical libraries originating from natural sources in a fast, and efficient manner to boost the discovery of bioactive natural products with specificity or biological potential for drug discovery. Likewise, advances in genomics enable a thorough characterization of the biological pathways for the biosynthesis of metabolites in microorganisms and provide access to uncharacterized natural products with unexplored therapeutic potential (Hobson et al., 2021). Genomic-based methods can help identify new chemical entities while revealing potential resistance mechanisms and rational designs to alter the natural product core. These technological advances provide new overhaul discovery platforms to conduct systematic screening on known and lesser-known biological resources for prospective drug agents (Hobson et al., 2021).

Also, the combination of bioinformatics, metabolomics and synthetic biology further improved the efficiency and productivity of pipelines for the discovery of natural products. The use of databases and bioinformatics tools contributes to the rational organization and processing of information, identification and annotation of biosynthetic gene clusters and design of compound libraries, although the problems of curation and standardization of natural product databases are still unresolved (Simoben et al., 2023). Metabolomics approaches allow the comprehensive profiling of metabolites in heterogeneous biological samples, facilitate the detection of low-abundance bioactive metabolites or their new forms, which would be impossible exclusively using standard methods. Synthetic biology offers genetic and biochemical solutions for the reconstruction or optimization of more efficient biosynthetic pathways in heterologous (non-native) producers of natural products, which solves problems of limited supply and low yields of target compounds. Together, these sciences contain protocols and strategies that not only speed up the process of research, but also help to overcome its bottlenecks, such as low yields of compounds, acquisition of samples needed for biological testing, etc (Simoben et al., 2023).

Finally, combining ancient medicinal practices with modern scientific techniques has facilitated a more efficient and expansive natural product drug discovery development process. By employing the empirical evidence gained through centuries, researchers are able to identify and focus on select plants and preparations in subsequent chemical and pharmacological studies, guiding research efforts toward the sources most likely to produce therapeutically active agents. This practice is becoming increasingly achievable through the cutting-edge techniques of rational drug discovery, such as bioactivity-guided fractionation, molecular modeling, virtual screening, etc. (Najmi et al., 2022). They allow for a more selective employing of resources in the bioactive compound discovery process to rationalize the drug development of bioactive compounds. Interdisciplinary approaches that incorporate fields such as ethnobotany, molecular biology, and chemistry are bringing together historic knowledge and modern understanding to expedite the process of identifying, characterizing, and drug-candidate optimizing. As such, the agglomeration of historically gained therapeutic knowledge with current methodologies translates into a more focused natural product pathways that minimizes investments in time and resources, as well as renders the process more adaptable to current circumstances (Najmi et al., 2022).

Challenges in Natural Product Drug Development

While drug discovery from natural products has had some notable accomplishments, there remain a number of critical challenges (including issues of supply, structural complexity, and reproducibility) that continue to limit their development. As many bioactive compounds may be found in minute quantities in the organisms producing them, obtaining them in large quantities is often not feasible. Further, sourcing a single compound from a rare or endangered species raises questions over sustainability (Bano et al., 2023). The structural complexity and variability posed by many natural products complicates the synthesis of adequate quantities for preclinical and clinical studies, often necessitating sophisticated synthetic chemistry or biosynthetic techniques that are time- and resource-intensive (Bano et al., 2023). The quality of the starting material may further vary depending on the season or environmental changes; thus, ensuring uniformity in preparations may prove difficult, complicating efforts to clearly characterize and establish their efficacy and safety. These factors have long been implicated in the high cost and long timeframes required in natural product drug discovery, processes that may entail over a decade of work and investment to bridge the gap between a promising compound and a successful therapeutic (Bano et al., 2023).

Table 2: Key Challenges in Natural Product Drug Discovery.

Challenge	Description	Impact on Development	References
Supply Limitations	Active compounds often available in minute quantities; source species may be rare or endangered	Limited scalability; sustainability concerns	Bano et al. (2023)
Structural Complexity	Complex chemical structures make synthesis and modification difficult	Increased cost, time, and technical difficulty	Bano et al. (2023)
Variability & Reproducibility Issues	Chemical composition varies with environment, season, genetics	Difficult to standardize; inconsistent clinical results	Atanasov et al. (2021)
Regulatory & Ethical Barriers	Strict quality/safety requirements; IPR and fair-benefit issues	Delays in approval; challenges in commercialization	Ali (2023)
Sustainability & Environmental Concerns	Overharvesting threatens biodiversity; climate impact	Loss of potential species and bioactive compounds	Ali (2023)

In table-2 explore the significant potential, natural product drug discovery faces several challenges. Limited supply and scarcity of bioactive compounds restrict scalability, especially when species are rare or endangered (Bano et al., 2023). Complex molecular structures further complicate extraction, synthesis, and

modification, increasing time and cost (Bano et al., 2023). Variability in chemical profiles due to environmental and genetic factors creates reproducibility issues that hinder standardization (Atanasov et al., 2021). Regulatory hurdles and ethical concerns related to access and benefit-sharing also slow down development and commercialization (Ali, 2023). Additionally, unsustainable harvesting practices threaten biodiversity and future drug prospects (Ali, 2023).Moreover, regulatory, ethical, and sustainability challenges are complex issues hindering the sourcing and commercialization of natural products for drug formulation. Regulating laws demand rigorous quality assurance, safety, and therapeutic efficacy data and often become a hindrance to the consistent availability and market approval of phytopharmaceuticals (Ali, 2023). Ethical challenges emerge when sources use indigenous knowledge without appropriate eco- and end-benefits arrangements; this issue raises intellectual property rights (IPR) and the fairness of commercial profits distribution among different parties. Sustainability imparts additional challenges such as excessive and unsustainable harvest of wild species for pharmaceutical purposes and the potential risk of enhancing biological diversity and eradicating endangered species. Meeting these challenges demands the collaborative approach of researchers, regulatory authorities, industries, and native people to guarantee responsible use and compliance with legal and ethical frameworks and promote biological diversity conservation for trillions of years to come (Ali, 2023).

In addition, the use of natural product extracts in clinical interventions also raises major difficulties in the standardization of items associated with safety and effectiveness. In fact, variations in their chemical composition, associated with divergences in the environmental conditions, genetic background, and harvesting of the species, are also responsible for a lack of reproducibility of therapeutic results. Therefore, it makes it impossible to determine the correct dosage and establish reliable clinical protocols due to the variability in the action of the natural product in each patient based on the low diversity presented in the extract profile(Atanasov et al., 2021). Although significant advances have been made in analytical methods that allow the characterization and quantification of active components, the standardization of extracts from crop and harvest to harvest remains a challenge. However, the result of differences in clinical performance and safety caused by variations in the composition of natural extracts also restricts the acceptance and integration of these products into practices and health systems (Atanasov et al., 2021).

Future Prospects and Opportunities

Among the promising future trends that could improve the natural products drug discovery in drug development are bioprospecting, combinatorial biosynthesis, and personalized medicine. Bioprospecting involves exploring biodiversity-rich environments for unknown bioactive compounds. However, the recent revival of its application can be attributed to increased awareness of biodiversity and advancements in biosynthesis technologies. Combinatorial biosynthesis is a new approach to developing natural products using genetic technologies, through which scientists can now develop new chemical entities using existing biosynthetic genes from different organisms. Natural products often demonstrate an inherent limitation in structural diversity, which can now be increased using the combinatorial biosynthesis method. This method remains at the forefront of the natural products drug discovery because it has demonstrated developers a significant advantage over traditional combinatorial chemistry (Newman & Cragg, 2020). Personalized medicine is the last trend associated with natural product discovery methods. It describes a growing tendency to develop personalized drugs, which could be achieved by applying genetic and metabolomic screening results to natural product candidates. The aforementioned trends suggest a vibrant research environment filled with emerging concepts and guiding principles for the future of this promising research area (Newman & Cragg, 2020).

Lastly, climate change, biodiversity conservation, and international collaboration will closely determine the future accessibility and usability of natural products as therapeutics. Climate change potentially disrupts the habitats of terrestrial and marine organisms, leading to decreased accessibility of biologically active sources that are unique from the natural ecosystem even before their therapeutic usage is explored. Biodiversity conservation must be done effectively in order to ensure the sustainability and accessibility of unique natural products, as well as their chemical diversity that is highly needed for isolating novel therapeutic agents. This is especially true for marine organisms found in reefs or land-dwelling plants endemic to specific locations, such as rainforests (Shinde et al., 2019). International collaboration can help harmonize research ventures across nations, uphold fairness and equity in access and sharing of scientific knowledge, and allow sustainability in controlled resources and accessibility despite geographical barriers. Combining climate change efforts with sound conservation policy practices nationally and internationally will help promote sustainability of natural products as long-term sources of novel drugs through their biologically active compounds, to which innovations in their application on drug invention will definitely benefit (Shinde et al., 2019).

CONCLUSION

Natural products have been and will continue to be an invaluable source for drug discovery. Historically, natural products have been a reliable source of biologically active compounds with unique structural diversity. The devastating impact of natural products—despite their accessibility—can be seen in traditional medicine and the practice of modern drug discovery and development

today, where these compounds have left a clear mark in the therapeutic approach to several diseases across different therapeutic areas. Although several hurdles such as sustainability, standardization, and regulatory-related issues have hampered their entry into the pharmaceutical development process, the evolution of technology and interdisciplinary approaches have been continuously working to overcome these challenges. Furthermore, novel techniques like bioprospecting, combinatorial biosynthesis, and nature conservation-based partnerships are regaining the lost urge for tapping the unexplored chemical diversity concealed within nature. In conclusion, the role of natural products in drug discovery will continue being crucial, especially in illuminating the path for next-generation drugs that will contribute to the further progress of global health and drug development.

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