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Harnessing the Power of Natural Products in Drug Discovery

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ABSTRACT

Background: Natural products and their structural analogues have historically played a crucial role in pharmacotherapy, especially in the treatment of cancer and infectious diseases. However, various challenges including screening, isolation, characterization and effectiveness contributed to a decline in natural product research within the pharmaceutical industry.

Purpose: This review explores the enduring use of natural compounds in folk medicine with special focus on drug discovery inspired by multifaceted molecular roles of small molecules from natural sources. The article also aims to elucidate how modern modifications of these compounds can lead to the development of innovative molecules with enhanced pharmacological potential & can have good pharmaceutics profile.

Methods: To accomplish these objectives, literature has been surveyed from PUBMED, MEDLINE, EMBASE etc. like search engines, for pinpointing detailed technological developments that empower natural product-based drug discovery. Various case studies are incorporated in terms of folklore usage, in process drug discoveries and small molecules scientifically founded with signalling pathway bio stimulation.

Conclusions: The journey of natural products from nature to clinic is very complex and time taking. In this pipeline, if attention can be drawn to some major aspects, it will lead to a paradigm shift in drug discovery processes. This can be witnessed by folklore usage of natural products and up laddering multifaceted concepts of small and lead molecules.

1. Introduction

In ancient times, people relied on nature's offerings for healing, using plants, herbs, animal parts and minerals as their primary medicines. These remedies steeped in tradition and cultural knowledge and formed the foundation for ancient healthcare systems, demonstrating humanity's deep connection with the natural world in seeking relief from ailments and illnesses (Atanasov *et al.*, 2021). The use of natural substances as therapeutic agents is deeply rooted in the history of medicine and the cultural traditions of diverse societies across the globe. Even today with remarkable advancements in synthetic chemistry and cutting-edge biotechnology, the enduring importance of natural products in drug discovery remains resolute (Zhang *et al.*, 2017).

Natural product drug discovery and design is a multidisciplinary approach for reshaping the way we develop medications. Traditional methods focused on single compounds, but now we understand that the synergy of multiple components in whole plant extracts can yield powerful therapeutic effects. Biological screening, using pharmacological and clinical methods, is crucial for identifying promising compounds (Grabowski *et al.*, 2008). To gain a deeper understanding, we employ technologies like genomics, proteomics, and metabolomics for precise identification and validation. Genomics involves the study of an organism's entire genome to identify genetic variations associated with diseases, aiding in the selection of potential drug targets (Seib *et al.*, 2009). Proteomics examines the complex world of proteins, essential in drug discovery. By characterizing the structure, function, and interactions of proteins, researchers pinpoint potential drug targets and unravel pathways critical to disease. This knowledge informs the design of drugs that selectively modulate specific proteins, minimizing off-target effects (Meissner *et al.*, 2022). Metabolomics, a powerful tool, facilitates the comprehensive analysis of complex metabolites in natural products (NPs). By leveraging metabolomics, researchers can efficiently identify and quantify bioactive metabolites, addressing issues of low solubility and chemical instability that often hinder the progression of NP-derived lead compounds in drug development. The integration of

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metabolomics with advanced technologies like nuclear magnetic resonance (NMR) and mass spectrometry databases significantly enhances the accuracy and efficiency of metabolite identification. These tools empower researchers to unravel the intricate structures of bioactive compounds, saving substantial time and labour during the extraction and isolation processes (Wishart. 2016). Big data analytics and machine learning are streamlining drug development, reducing errors, and making it more efficient (Ortholand & Ganesan., 2004). Computer-aided design optimizes compound properties, while precision medicine tailors treatments to individual genetics. This comprehensive approach is revolutionizing pharmaceutical development, offering new solutions to global health challenges (Qiao & Zhang., 2014, Koeberle & Werz., 2014).

Natural products (NPs) have long held a pivotal role in the field of drug discovery, serving as a wellspring of biologically active compounds with diverse structural and functional attributes (Katz *et al.*, 2016). In this review, multifaceted landscape of NPs and their undeniable impact on therapeutic advancements across a spectrum of medical disciplines have been explored. From combatting formidable foes like cancer and infectious diseases to addressing the subtleties of cardiovascular disorders and neurological conditions, NPs have emerged as an indispensable contributor to our pharmaceutical arsenal. However, despite the manifold advantages that NPs offer, their utilization in drug discovery has encountered a series of formidable challenges. The initial steps in NP-based drug research often involve screening libraries of crude extracts, a process that may not seamlessly align with traditional target-based assays. The acquisition of sufficient biological material for isolating and characterizing these bioactive NPs further compounds the complexity (Baltz *et al.*, 2016).

In the contemporary pursuit of enhanced therapeutic efficacy, researchers explore small molecules from natural sources for their multifaceted roles in modulating crucial cellular signalling pathways. By targeting intricate networks like AMPK and NFKB, these bioactive compounds offer tailored treatments, presenting a frontier in therapeutic intervention with reduced off-target effects (Li *et al.*, 2020). This review explores recent technological and scientific breakthroughs that promise to surmount the hurdles faced in NP-based drug discovery.

1.1. Natural Product

In pharmaceutical sciences, natural products refer to the chemical compounds or substances that are derived from natural sources, such as animals, plants, microorganisms, or minerals e.g. Morphine, Aspirin (Salicylic Acid), Artemisinin, Taxol (Paclitaxel), Digitalis (Digoxin), Quinine, Heparin, Insulin, Penicillin, Streptomycin, Cephalosporin, Lovastatin etc. (Najmi *et al.*, 2022). These substances are often used as a starting materials or lead compounds in the development of pharmaceutical drugs or therapeutic agents. Natural products can have a wide range of pharmacological activities and can serve as valuable sources of new drug candidates. They may be used as they are or modified through chemical synthesis to improve their properties, enhance their efficacy or reduce potential side effects. Natural products have historically played a significant role in drug discovery and continue to be a rich source of inspiration for the development of new medicines (Cragg & Newman, 2013). Table 1 provides comprehensive information about various natural products, including their scientific name, common names and sources of origin along with their diverse range of applications (Atanasov *et al.*, 2015).

Table 1: Various pharmaceutical drugs obtained from natural sources.

Natural Product	Scientific Name	Common Name	Source	Uses	Reference
Morphine	Papaver somniferum	Morphine	Opium poppy	Pain relief, analgesic	(Laux *et al.*, 2011)
Aspirin	Acetylsalicylic acid	Aspirin	Willowbark (originally)	Pain relief, anti-inflammatory	(Desborough *et al.*, 2017)
Artemisinin	Artemisia annua	Artemisinin	Sweet wormwood plant	Antimalarial agent	(Hu *et al.*, 2022)
Taxol	Paclitaxel	Taxol	Pacific yew tree	Anticancer agent	(Yang *et al.*, 2017)

Streptomycin	Streptomyces griseous	Streptomycin	Bacteria (microorganism)	Antibiotic for tuberculosis	(Zhang *et al.*, 2012)
Digitalis (Digoxin)	Digitalis purpurea	Digitalis	Foxglove plant	Treatment of heart conditions	(Patocka *et al.*, 2020)

1.2. Historical Perspective

Ethnopharmacology served as the foundation for all medicines and plant based products whose knowledge about medicinal properties of various substances was gathered and refined over the years. It is estimated that only fraction, less than 10% of the earth's biodiversity has been explored as potential sources of medicines (Taylor & Werneke 2018). Even few vitamins and minerals found abundantly in nature are used to treat chronic ailments in the form of food supplements. For instance, Biotin, a water-soluble vitamin, plays a vital role as a coenzyme for five carboxylases in mammals. This essential nutrient naturally occurs in certain foods. Its deficiency can result in conditions such as alopecia, eczematous skin rashes, conjunctivitis, and candidiasis (Pirintsos *et al.*, 2022).

Use of natural products dates back to ancient civilizations in Mesopotamia (2600 B.C) in the form of clay tablets with cuneiform writing mentioned the use of oils from plants like Cypress and myrrh, which are still employed today for treating conditions such as coughs, colds, and inflammation. In Egypt, the Ebers Papyrus (2900 B.C), recorded over 700 plant-based remedies, including gargles, pills, infusions, and ointments. Greek physician Dioscorides (100 A.D.) detailed the collection, storage, and applications of medicinal herbs, while philosopher and natural scientist Theophrastus (~300 B.C.) focused on medicinal herbs (Dias *et al.*, 2012). During the dark and middle Ages, monasteries in Europe, England, Ireland, France, and Germany preserved western knowledge of herbal medicine. Simultaneously, Arab scholars preserved and expanded upon Greco-Roman knowledge and incorporated herbs from China and India, previously unknown to the Greco-Roman world. In the 8th century, the Arabs pioneered the concept of privately-owned pharmacies, with figures like Avicenna, a Persian pharmacist, physician, philosopher, and poet, making significant contributions to the fields of pharmacy and medicine through works like the Canon Medicinae (Chamorro-Cevallos *et al.*, 2022).

1.3. Folklore Medicine

Traditional medicine also referred to as indigenous or folk medicine. It encompasses the medical knowledge and practices that have evolved over generations within various societies and cultural beliefs. This knowledge is based on theories, beliefs and experiences unique to different cultures. It is utilized for maintaining health and addressing physical and mental illnesses (Graham-Brown & Healsmith., 2018). In several Asian and African nations, 80% of the population relies on traditional medicine as their primary healthcare. Examples of traditional medical systems include traditional European, Chinese, Korean, African, Ayurveda, Siddha, Unani, Iranian etc. Scientific fields dedicated to studying traditional medicine encompass herbalism, ethno medicine, ethno botany and medical anthropology (Yuan *et al.*, 2016).

The fungus Piptoporus betulinus, which grows on birch trees, was subjected to steam treatment to create charcoal, highly valued for its antiseptic and disinfectant properties. Strips of P. betulinus were cut and used to stop bleeding and they were also discovered to make excellent corn pads (Pleszczymska *et al.*, 2016). Another example is the fungus Agaricus campestris Linnaeux, also known as the field mushroom, found in various temperate regions was reportedly simmered in milk to provide relief for throat cancer (Prescott *et al.*, 2023). As far back in the 17th and 18th centuries, lichens were employed as dyes and held greater value than exotic species. Although no lichen-based drugs have been officially approved in the market, their applications in folklore have been extensively documented. Lichens have served as raw materials for perfumes, cosmetics and medicines dating back to early Chinese and Egyptian civilizations. In the Highlands, it was traditionally sprinkled on stockings before journeys to prevent foot inflammation and in Ireland; it was employed as a remedy for chin sores, burns and cuts (Ren *et al.*, 2023). In contrast, the marine environment has relatively few reported applications in traditional medicine. Red algae like Chondrus crispus and Mastocarpus stellatus were used to make a beverage popular as a folk remedy for colds, sore throats, chest infections, including tuberculosis. The algae were also boiled in milk or water and used for kidney issues and burns (Malve H., 2016). Based on the WHO report, nearly 65% of the global population relies on natural bioactive substances as their primary means of defence against various illnesses. Traditional medicinal practices in countries such as China and India have long incorporated a significant array of natural ingredients. In today's world, these natural compounds continue to be highly regarded as a valuable reservoir of potential drug candidates, actively explored by

the pharmaceutical industry (Newman & Cragg 2020). Figure 1 outline the isolation steps and a few associated problems along with a solution for bioactivity-guided drug discovery.

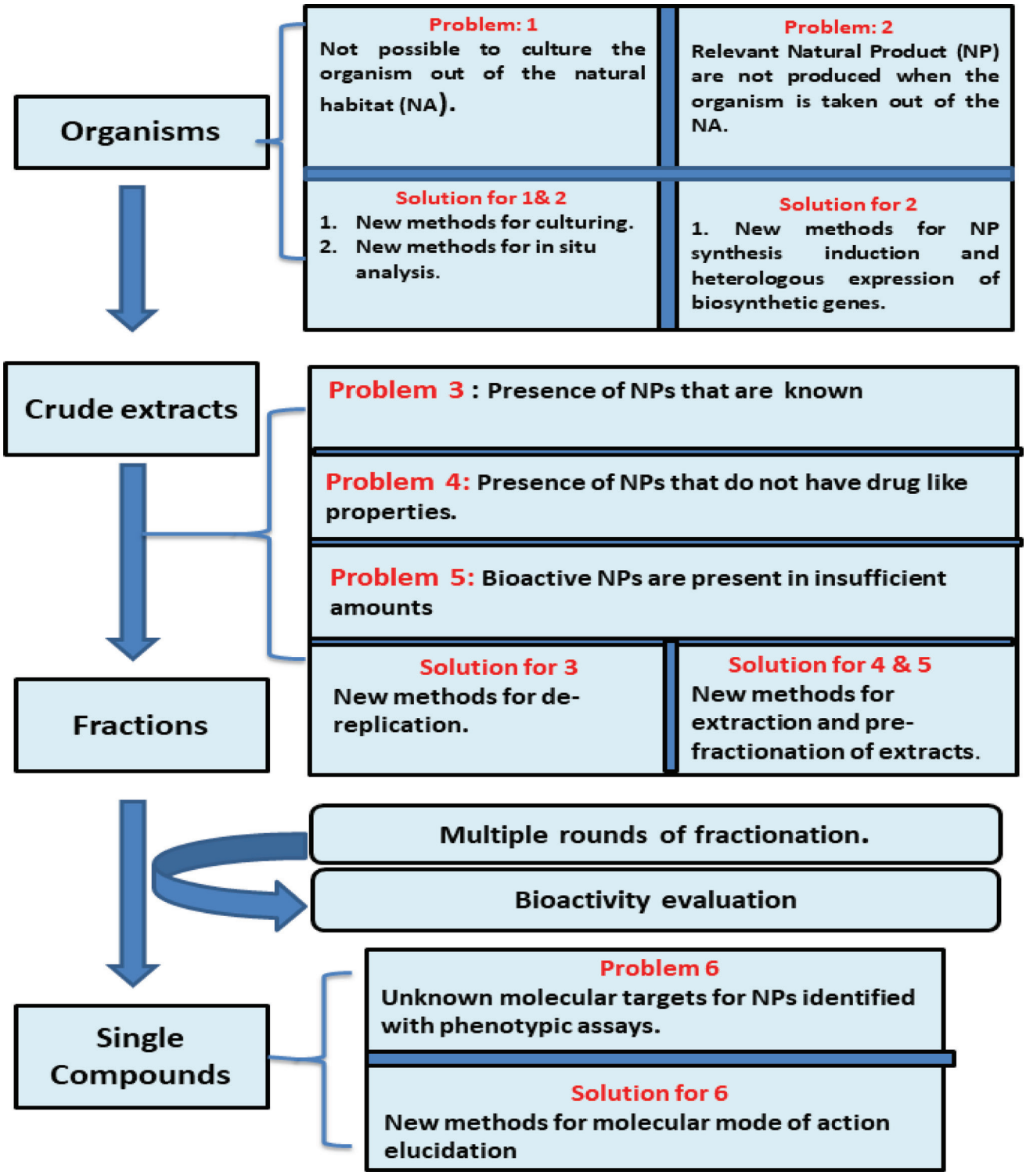

Figure 1: Outline of traditional bioactivity-guided isolation steps in natural product drug discovery.

2. Drug Discovery Processes from Natural Resources

In drug development, lead identification and optimization are pivotal steps for identification of a biological target. These stages involve modifying a drug's chemical structure to enhance properties like efficacy, potency, selectivity, and pharmacokinetics (Ebob *et al.*, 2021). The chemical structure serves as the foundation for identifying lead compounds. Once a promising lead compound is found, the next step involves studying ADMET (absorption, distribution, metabolism, excretion, and toxicology) (Xu *et al.*, 2015). Positive results confirming its non-toxic and non-mutagenic nature indicate its potential. These lead compounds are the starting point for new drug development, facilitated by advanced techniques to improve their pharmacological properties, ultimately leading to the creation of innovative, safe, and effective medications (Gajula *et al.*, 2021).

There has been a growing interest in the field of natural product research due to the limitations of traditional drug discovery methods, especially in areas like immunosuppression, anti-infective, and metabolic diseases (Hon & Lee, 2017). Natural product research aims to identify novel chemical compounds that can serve as a foundation for developing new drugs within the pharmaceutical industry. It is evident that innovative approaches are needed to improve the overall drug discovery and development process, with a focus on both understanding drug targets and discovering promising lead compounds (Shah *et al.*, 2021).New technologies such as automated separation techniques, high-throughput screening, and combinatorial chemistry have emerged as powerful tools that are transforming the landscape of drug discovery (Fattori *et al.*, 2008).

2.1. Screening Approaches

Screening approaches for natural products in drug discovery are critical for identifying potential therapeutic compounds from plant sources. Ethno pharmacology and chemotaxonomy offers valuable insights into medicinal plants by studying traditional uses and classifying plants based on chemical constituents (Dzobo, 2022). However, relying solely on these methods can lead to overlooking intriguing chemicals. To reduce bias, a random sampling of plants is employed, where plant components undergo standard extraction and systematic bioassays without prior selection based on chemotaxonomy or ethno-botanical information. This approach ensures a more comprehensive evaluation of the local flora, increasing the chances of discovering novel bioactive compounds (Fu *et al.*, 2019). Procedures for obtaining active principles from plants based on various screening approaches have been represented in Figure 2.

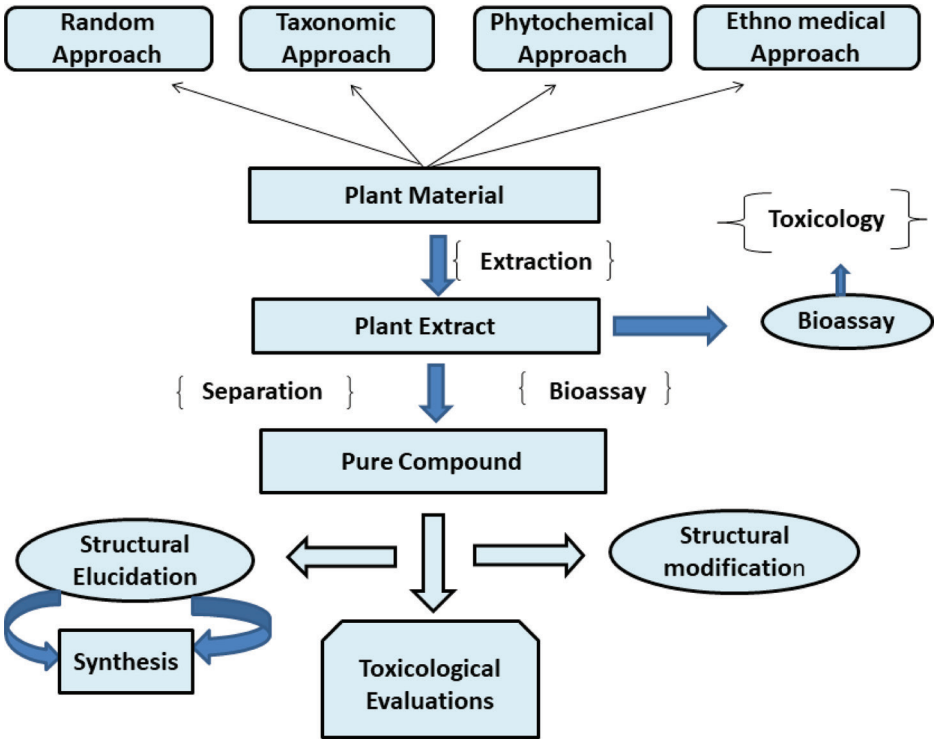

Figure 2: Schematic representation of general procedure for obtaining active principles from plants.

2.2. Lead Identification

Rationale for lead discovery is to identify potential new chemical compounds that can be further developed into effective drugs for clinical use. Lead compounds should exhibit the desired level of potency along with the specificity for their intended target and should be easy to synthesize and amenable to chemical modifications. Their formulation should not present challenges, and they should be readily adaptable into various forms such as pills, gels, or creams for treatment. It's crucial to avoid structural elements that may cause toxicity, such as alkylating agents (Guido *et al.*, 2011). Identifying a lead compound can occur through various routes: serendipitous discovery during research (e.g., penicillin), improving the side effects of existing compounds, drawing insights from herbal or folk remedies, screening metabolites from natural sources, high-throughput screening of compound libraries, rational drug design, designing drugs based on knowledge of natural substrates (Hefti, 2008).

Converting a lead compound into a viable drug candidate is a very labour-intensive process which involves the process of lead optimization. If a lead compound doesn't meet the necessary distribution parameters, it can be refined through lead optimization. Key physicochemical and biochemical properties, such as solubility, permeability, and metabolic stability, play a crucial role in determining a drug's pharmacokinetics (Honorio *et al.*, 2013). These properties guide the structural modifications required to enhance a compound's drug-like characteristics. It's essential to focus on optimizing these properties to ensure that the final drug candidate possesses all the attributes of a successful drug. It's worth noting that approximately 39% of drugs fail during the development process due to issues related to poor bioavailability and pharmacokinetic properties (Zhang *et al.*, 2018).

2.3. Lead Optimization

1. After the identification of a potential lead compound, the Lead Optimization process involves various activities. These include refining the synthesis and characterization of the promising compound and examining its different properties. Modifying the chemical structure of the molecules slightly can help minimize potential future adverse events. One crucial aspect is evaluating the molecule's selectivity and specificity to the target of interest and assessing its binding properties (Iao *et al.*, 2016).
2. Another essential aspect of Lead Optimization is the identification and quantification of drug metabolites. This is a crucial step as it can reveal potential toxic effects that may arise during subsequent clinical trials. Any safety concerns associated with lead compounds can be addressed by making structural modifications (Khalaf, 2016). It's important to maintain other favourable properties during this phase through advanced tools such as mass spectrometry (MALDI) and nuclear magnetic resonance (NMR), fragment-based screening (FBS) are employed to study metabolites found in tissues. Pharmaceutical companies often utilize these modern automated screening systems in the Drug Discovery process (Zhao *et al.*, 2010 & Sukmarini, 2021).
3. During the final stages of Lead Optimization, several key factors are thoroughly investigated before advancing to Clinical Trials. These include efficacy, potency, toxicity, stability, bioavailability, and the optimization of chemical compounds. In vitro and in vivo studies are conducted to gain insights into metabolic processes using pharmacokinetic and pharmacodynamics approaches. However, cell-based and biochemical screens may miss some important effects related to toxicity or in vivo drug responses (Sun *et al.*, 2022).
4. In vivo models can reveal how a drug affects a cell niche, not just the target cell type itself. Zebrafish screening offers a straightforward and cost-effective alternative animal model that considers all these factors simultaneously, providing a more accurate prediction of drug efficacy. Zebrafish's high genetic similarity to humans, along with its easy handling, small size, and transparent larvae, make it an excellent model for phenotypic Screening in a High Content Screening (Wiley *et al.*, 2017).

3. Strategies and Techniques of Drug Discovery from Natural Products

Bioassay-guided isolation methods have become less effective due to the repetitive rediscovery of known compounds. Consequently, the search for novel and complex metabolites has shifted towards less explored sources, focusing on untapped resources such as endophytes, uncultivable microorganisms, and extremophiles found in harsh environments (Erenler *et al.*, 2017). Recent advancements in genomics have revealed that microorganisms possess a remarkable capacity to produce novel and intricate secondary metabolites. Through genome mining techniques, previously dormant biosynthetic gene clusters in microbes can be activated, leading to the discovery of cryptic natural products that remain hidden under standard laboratory conditions (Kim *et al.*, 2021).

More than half of legally prescribed small-molecule medications between 1981 and 2014, including unmodified natural compounds, chemically altered derivatives, and synthetic mimics are derived from natural product templates or pharmacophore (Chen & Kirchmair., 2020).

Remarkably, over one-third of the new molecules approved by the U.S. Food and Drug Administration (FDA) also originate from natural products. This trend is particularly pronounced in the domains of antibiotics and anticancer agents, highlighting the significant enrichment of these fields through natural product-based research (Patridge *et al.*, 2016).

4. Natural Product Discovery Program

The era known as the 'Golden Age of Antibiotics' and the global push to find new antibiotics, major pharmaceutical companies launched Natural Product Discovery (NPD) programs. These initiatives aimed not only to discover antibiotics and antifungal agents but also to tackle infectious diseases (Hornburg *et al.*, 2018). These programs yielded promising compounds for treating cancer, microbial infections, and hypercholesterolemia and tissue rejection in organ transplants. However, in the 1990s and early 2000s, many large pharmaceutical firms dismantled their NPD programs (Dong & Ming 2023). The introduction of automated High Throughput Screening (HTS) brought a significant shift in biological testing and Combinatorial Chemistry which gained prominence as a more attractive method for generating "drug-like" compounds for HTS. Consequently, numerous pharmaceutical companies discontinued or sold their collections of screening extracts. Moreover, the time required to develop a pharmaceutical product from an extract hit was considered too lengthy. HTS technologies leaned towards combinatorial chemistry to create extensive compound libraries (Klebe *et al.*, 2006, Szymanski *et al.*, 2012).

Over the past two decades, "classical natural product chemistry" has largely given way to molecular target-based drug discovery, which relies on large combinatorial libraries to identify effective "hits." Nevertheless, advancements in technology and sensitive instrumentation have continued to enhance the natural product discovery process (Mishra *et al.*, 2011). Starting in the 1980s, there was an expectation that combinatorial chemistry would be a prolific source of new carbon structures and drug leads, but this prediction has not materialized as only one combinatorial New Chemical Entity (NCE), the kinase inhibitor 'sorafenib' (FDA-approved in 2005 for renal carcinoma), has been approved by the U.S. Food and Drug Administration (FDA) during this period (Kane *et al.*, 2006).

5. Drug Discovery: Natural Product Chemistry versus Combinatorial Chemistry

Natural product chemistry (NPC) and combinatorial chemistry (CC) represent two distinct approaches within the field of chemistry, each with its unique characteristics and applications. Natural product chemistry is fundamentally rooted in the exploration of compounds derived from natural sources such as plants, microorganisms, animals and marine life (Bauer& Bronstrup., 2014). Natural product chemists isolate and characterize these compounds often focusing on their medicinal, biological, or ecological significance. These compounds may serve as a valuable leads for drug development or find applications in various fields beyond pharmaceuticals (Molinski, 2014). In contrast, CC takes a more synthetic and systematic approach, it involves the creation of extensive libraries of compounds through automated and parallel synthesis techniques in the laboratory. These compounds are not found in nature and are often simpler in structure compared to natural products. CC is primarily employed in the pharmaceutical industry for drug discovery and development. Its primary goal is to rapidly generate a large number of compounds for high-throughput screening (HTS), with the aim of identifying potential drug candidates efficiently (Liu *et al.*, 2017).

The discovery processes in these two approaches differ significantly like; NPC relies on traditional methods of compound isolation, purification, and structural elucidation, which can be time-consuming and resource-intensive. This approach requires expertise in organic chemistry and biology to navigate the complexity of natural products. CC on the other hand, leverages automation and well-established synthetic protocols to create compounds systematically, making it a highly efficient method for generating compound libraries. These two approaches complement each other in the broader landscape of chemical research and drug development (Ortholand & Ganesan., 2005).

Although combinatorial chemistry has brought about a significant transformation in the development of new active chemical compounds, leading to the creation of structural analogues, however, in the late 1990s, synthetic chemists recognized that these libraries lacked the intricate complexity seen in natural products synthesized by nature. This realization led to the adoption of diversity-oriented synthesis (DOS), where chemists aimed to produce compounds that mimicked natural products or were based on natural product structures. These synthesized compounds are currently undergoing extensive testing in various biological screens to determine their potential as starting points for new drug development (Kidd *et al.*, 2018).

6. Drug Discovery inspired by Multifaceted Roles of Small Molecules from Natural Sources

In modern era, researchers are looking for multifaceted amplification of any desired activity. The synthetic molecules having a distinct role can only have a single

cornered activity, thus sometime the effectiveness is compromised. Small molecules are coming in this zone with an instigation of multifaceted & multi-molecular approaches. If the membrane receptor and nuclear receptor of same circuit can be stimulated or inhibited as per the need, the effectiveness will be increased to several folds. The intricate interplay between cellular signalling pathways and human health stands as a cornerstone in understanding and combatting various diseases. Signalling pathways such as AMPK and NFKB orchestrate fundamental cellular processes, governing growth, proliferation, inflammation, and differentiation. Dysregulation within these pathways has been intricately linked to a myriad of diseases, encompassing cancer, metabolic disorders, inflammatory conditions, and more (Kim *et al.*, 2022). In recent years, research has unveiled a promising avenue in the utilization of small molecules derived from plant sources as potent modulators of these signalling pathways. These bioactive compounds possess the remarkable ability to fine-tune or inhibit the aberrant activation of signalling cascades, thereby holding immense therapeutic potential across diverse disease spectra. Understanding the pivotal roles of these signalling pathways in disease pathogenesis is imperative. TGFβ signalling, for instance, plays a dual role, acting as a tumour suppressor in early stages of cancer while promoting tumour progression in advanced stages (Ren *et al.*, 2021). The AMPK pathway, a central regulator of cellular energy homeostasis, influences metabolic disorders like diabetes and obesity. NFKB signalling governs inflammation and immune responses, implicated in chronic inflammatory conditions and autoimmune diseases (Srivastava *et al.*, 2012). The multifaceted approach of small molecules derived from plants in modulating these signalling pathways represents a frontier in therapeutic intervention. Their ability to selectively target specific nodes within these complex networks offers the prospect of tailored treatments with reduced off-target effects. By elucidating the mechanisms of action of these compounds and their interactions with signalling components, novel avenues for therapeutic development are emerged (Li *et al.*, 2022). Table 2 provides a concise catalogue of bioactive small molecule metabolites (Metabolite) derived from diverse natural products, specifying their biological targets and actions.

Table 2: List of bioactive small molecule metabolites derived from NPs.

Metabolite	Sources	Target	Action	References
Silymarin	Milk thistle	P-glycoprotein, estrogenic and nuclear receptors.	Hepatoprotective, antioxidant.	(Gazak *et al.*, 2007)
Resveratrol	Grapes, red wine, peanuts	SIRT1 (Sirtuin 1), AMP-activated protein kinase (AMPK).	Antioxidant, anti-inflammatory, cardioprotective.	(Bhullar *et al.*, 2015)
Quercetin	Fruits, vegetables, red onions	Histamine receptors, various inflammatory signalling pathways (e.g., NF-κB, MAPK).	Antioxidant, anti-inflammatory, antihistamine.	(Rakheja *et al.*, 2022)
Morphine	Opium poppy	Opioid receptor.	Analgesic	(Lam *et al.*, 2018)
Artemisinin	Sweet wormwood	Ankyrin type 1 receptor-channel	Antimalarial	(Li *et al.*, 2017)
Capsaicin	Chili peppers	TRPV1 (Transient Receptor Potential Vanilloid 1)	Analgesic, thermogenic	(Ludy *et al.*, 2012)
Taxol (Paclitaxel)	Pacific yew tree	Binds to beta-tubulin within microtubules	Anticancer	(Cao *et al.*, 2022)
Caffeine	Coffee beans	Adenosine receptors (A1 and A2A), phosphodiesterase (PDE)	Central nervous system stimulant	(Van der Walt *et al.*, 2009)
Cannabidiol	Cannabis	CB1 and CB2 cannabinoid receptors, transient receptor potential (TRP) channels.	Anxiolytic, anti-inflammatory	(Van Breemen *et al.*, 2022)
Salicin	Willow bark (Salix species)	Inhibits cyclooxygenase (COX) enzymes	Analgesic, anti-inflammatory	(Lin *et al.*, 2023)
Allicin	Garlic	DNA gyrase, thiol-containing proteins and enzymes of microorganisms	Antimicrobial, cardiovascular benefits	(El-Saber Batiha *et al.*, 2020)

Epigallocatechin gallate	Green tea	Inhibition of EGFR (Epidermal Growth Factor Receptor)	Antioxidant, anti-cancer	(Musial *et al.*, 2020)
Ginkgolides	Ginkgo biloba	Platelet-activating factor (PAF) receptors	Antiplatelet, Cognitive enhancer	(Sarkar *et al.*, 2020)
Betulinic acid	Birch tree bark	Induction of apoptosis via mitochondrial pathways	Anticancer	(Saneja *et al.*, 2018)
Berberine	European barberry, Oregon grape	AMP-activated protein kinase (AMPK)	Antimicrobial, Anti-inflammatory.	(Wang *et al.*, 2017)
Thymoquinone	Black cumin	Modulation of NF-κB and other inflammatory pathways	Antioxidant, anti-inflammatory.	(Hannan *et al.*, 2021)
Gallic acid	Plants, fruits, and vegetables	Inhibition of xanthine oxidase	Antioxidant, anti-inflammatory	(Tuli *et al.*, 2022)
Ursolic acid	Apple peels, rosemary, basil	Various signalling pathways, including NF-κB.	Antioxidant, anti-inflammatory.	Ramos-Hryb *et al.*, 2017)
Picroside II	Picrorhiza kurroa	Activation of farnesoid X receptor	Hepatoprotective, anti-inflammatory	(Ma *et al.*, 2020)
Lycopene	Tomatoes, watermelon, pink grapefruit	Activating the peroxisome proliferator -activated receptor gamma (PPARγ)-liver X receptor alpha (LXRα) -ATP -binding cassette transporter 1 (ABCA1) pathway	Antioxidant, anti-cancer	(Khan *et al.*, 2021)

As reported in recent literatures, distinct roles of nature derived small molecules are emphasized specially in modulating signalling pathways pertinent to diabetes pathogenesis. DAQ-B1, an insulin receptor tyrosine kinase (IRTK) activator, exhibits promise in lowering blood glucose levels but necessitates caution due to potential off-target effects at higher concentrations (Boucher *et al.*, 2014). Conversely, UA0713, a derivative of ursolic acid, selectively inhibits protein tyrosine phosphatase 1B (PTP1B), enhancing insulin receptor phosphorylation and subsequent glucose uptake (Zhang *et al.*, 2006). NPLC441, derived from oleanolic acid, demonstrates multi-target inhibitory action against PTP1B, thereby enhancing insulin signalling through varied pathways (Lin *et al.*, 2008). Furthermore, corosolic acid, oleanolic acid and maslinic acid act as inhibitors of glycogen phosphorylase, potentially offering anti-hyperglycaemic effects (Oboh *et al.*, 2021). Berberine (BBR) activates AMPK, contributing to insulin sensitization and metabolic regulation (Geng *et al.*, 2016). These molecules, each with distinct mechanisms of action and targets within intricate signalling pathways, represent potential therapeutic avenues in diabetes management.

7. Case Studies

7.1. Artemisinin: A Malaria Miracle of Traditional Chinese Medicine

Youyou Tu, a senior pharmacologist at the China Academy of Traditional Chinese Medicine, was awarded Nobel Prize for her significant role in the discovery of 'Artemisinin', which ultimately led to a family of potent antimalarial drugs. The artemisinin discovery has gained global attention from the academic, industrial, and political communities. This recognition marks the first time a Chinese scientist has received a Nobel Prize in the natural sciences for ground-breaking work conducted in china in collaboration with her Chinese colleagues (Kong *et al.*, 2015).

Artemisinin, an annual wormwood extract derived from Artemisia annua L., is a sesquiterpene lactone endoperoxide that effectively inhibits the replication of the malaria parasite. Within this group of compounds, artemether, arteether and sodium artesunate have also received approval as drugs for treating severe malaria. Even though four decades have passed since its discovery, artemisinin-based combination therapies (ACTs) continue to be the top recommendation by the World Health Organization (WHO) for treating malaria (Guo Z, 2016). During the Vietnam War, widespread malaria posed a serious threat. In response, China initiated the "523 Project" in 1967 to find new antimalarial solutions. Before Youyou Tu joined in 1969, they had screened 10,000 compounds with no success. Tu's crucial contribution was the use of ethyl ether for extracting an unstable antimalarial compound from wormwood, resulting in the discovery of artemisinin (Liu *et al.*, 2012).

7.2. Taxol: The Pacific Yew's Gift

Paclitaxel, a widely recognized cancer medication sourced from the Pacific yew tree's bark Taxus brevifolia, is employed

to combat various types of cancer, including breast, lung, and ovarian cancer. It is a cytoskeletal drug targeting tubulin, which disrupts cell division by stabilizing microtubules, preventing their disassembly. This leads to defects in mitotic spindle formation and chromosome segregation. High therapeutic concentrations of paclitaxel inhibit microtubule detachment from centrosomes, a process crucial during mitosis, by binding to beta-tubulin subunits, which ultimately triggers apoptosis or cell cycle arrest (Kohler *et al.*, 1994).

In 1962, researchers from the U.S. Department of Agriculture collected Pacific yew bark samples in pursuit of potential cancer cures. By 1977, Taxol (paclitaxel), extracted from this bark, exhibited promising antitumor activity in animal models, including melanoma, mammary, lung, and colon tumours. Dr. Susan Horwitz elucidated Taxol's mechanism of action by stabilizing microtubules, impeding cell division (Cragg, 1998). In 1984, National cancer institute (NCI) initiated phase I clinical trials, leading to a pivotal moment when Taxol showed substantial responses in advanced ovarian cancer patients. FDA approval in 1992 for ovarian cancer treatment marked a significant breakthrough. Subsequent trials confirmed Taxol's efficacy against advanced breast cancer, resulting in FDA approval for this indication in 1994. This discovery and subsequent clinical approvals revolutionized cancer treatment. Since then, on-going clinical trials have explored Taxol's effectiveness against various cancer types, solidifying its role as a cornerstone chemotherapy drug (Foa *et al.*, 1994).

7.3. Penicillin: An Accidental Discovery

Penicillin's are a class of β-lactam antibiotics originally derived from molds, primarily Penicillium species like P. chrysogenum and P. ruben. The majority of clinically utilized penicillins are produced through deep tank fermentation by P. chrysogenumand subsequently purified. Several natural penicillins have been identified, however only two purified compounds are employed in medical practice: penicillin G (administered via intramuscular or intravenous routes) and penicillin V (taken orally). Penicillins were among the earliest effective treatments for a wide range of bacterial infections caused by staphylococci and streptococci. Despite their continued usage for diverse bacterial infections, extensive use has led to the development of resistance in many bacterial strains (Lima *et al.*, 2020).

Penicillin marked a ground-breaking moment in medical history as the first true antibiotic, discovered by Alexander Fleming in 1928. Prior to its introduction, infections like pneumonia, gonorrhoea and blood poisoning were untreatable. Fleming stumbled upon penicillin's potential, when he noticed a mold clearing a bacterial culture, indicating its antibacterial properties. He found that this "mold juice" could kill various harmful bacteria. Despite challenges in isolating pure penicillin, he published his findings in 1929, initially emphasizing its use for distinguishing bacterial sensitivity. This discovery laid the foundation for the antibiotic era, forever changing the course of medical history and providing hope for countless patients (Bentley *et al.*, 2017 & Ligon, 2004).

7.4. Caffeine: The Universal Stimulant and Cognitive Enhancer

Caffeine is a small molecule classified as a xanthine alkaloid. It is naturally found in coffee beans, tea leaves, and cocoa plants. It is renowned for its stimulant properties, affecting the central nervous system. It acts as an adenosine receptor antagonist, preventing adenosine, a neurotransmitter that induces sleep and relaxation, from binding to its receptors. This leads to increased release of other neurotransmitters, such as dopamine and norepinephrine, resulting in heightened alertness and reduced perception of fatigue (Nehlig *et al.*, 1992). In 2016, a study published in the journal "Neuroscience and behavioural reviews" examined the cognitive effects of caffeine. The research indicated that moderate caffeine consumption enhanced memory, attention, and mood in participants. The case study highlighted caffeine's widespread use as a cognitive enhancer and its potential applications in managing fatigue-related conditions (McLellan *et al.*, 2016)

The discovery of caffeine as a potent stimulant traces back to ancient times when communities first noticed the invigorating effects of consuming beverages derived from the Coffea Arabica plant. Early civilizations in Ethiopia observed heightened energy levels and alertness after ingesting concoctions made from coffee beans. Over centuries, Arab scholars recognized its potential, with Avicenna documenting coffee's medicinal properties in the 11th century. Today, caffeine's role as a powerful stimulant is well-established, shaping its widespread use and exploration in drug discovery (Cappelletti *et al.*, 2015).

7.5. Quercetin: Health Benefits and Therapeutic Potential

Initially identified by Szent-Gyorgyi in 1936, quercetin has a chemical formula of $C_{15}H_{10}O_7$. Its structure comprises a common flavone nucleus composed of two benzene rings connected by a heterocyclic pyrone ring. Quercetin has been applied in the treatment of cancer, allergic reactions, inflammation, arthritis, etc. A diet enriched with quercetin offers numerous health-promoting advantages, acting to reduce coagulation, hyperglycaemia, inflammation, and

hypertension. Clinical studies have demonstrated the use of quercetin supplementation in preventing and treating chronic diseases, particularly cardiovascular disorders (Aghababaei, F., & Hadidi, M. 2023).

The flavonoid quercetin, denoted by the Latin term "Quercetum," belonging to the flavonol class, is not endogenously synthesized in the human body. The term "quercetum" in Latin refers to quercetin, signifying a yellow-coloured compound. In 1814, the French explorer Michael Eugene Chevrel identified the initial flavonoid, later named quercetin. The exploration of flavonoids in Russia commenced in 1873 under the guidance of the renowned botanist Ivan Borodin (Anand *et al.*, 2016). A pivotal moment in bioflavonoid research unfolded in 1936, when the American scientist of Hungarian descent, Albert Szent-Györgyi (later a Nobel Prize recipient in Medicine for contributions to biological oxidation, vitamin C, and fumaric acid catalysis), along with Istvan Rusniak, discovered that a complete cure for scurvy required combining vitamin C with another substance enhancing capillary resistance (Teixeira S. 2002).

7.6. Betulinic acid: A Natural Anticancer Compound with Ancient Roots

Betulinic acid is a naturally occurring tri-terpenoid found in the bark of certain trees, such as the white birch tree (Betula alba), and in various plant species like Syzigium claviflorum and Ziziphus mauritiana. This small molecule has garnered attention for its potential therapeutic properties, particularly its role as an anticancer remedy. Its anticancer mechanism involves mitochondrial disruption, triggering apoptosis through the release of cytochrome C and activation of Apaf-1. It selectively targets death receptors like TNFR1 and Fas receptor on the cell surface, initiating extrinsic apoptotic pathways. It also inhibits angiogenesis by interfering with VEGFR signalling and induces cell cycle arrest through modulation of cyclins and CDKs. This multifaceted action, interacting with both mitochondrial components and specific receptors, showcases betulinic acid's sophisticated approach to inducing apoptosis in cancer cells, making it a promising candidate for receptor-specific anticancer therapy (Mukherjee *et al.*, 2006).

The journey of betulinic acid's discovery can be traced back to traditional medicine practices, where indigenous communities recognized the medicinal properties of plants containing this compound. In various cultures, extracts from betulinic acid-rich sources were used to address ailments and promote overall well-being. However, it was not until modern scientific research that the compound's specific anticancer properties were uncovered. In recent decades, scientists have explored the molecular mechanisms underlying betulinic acid's effects, particularly its ability to induce apoptosis (programmed cell death) in cancer cells (Cichewicz, R. H., 2004) Research studies, including a notable investigation published in the "Journal of biochemical and molecular toxicology " in 2022, highlighted betulinic acid's potential as a selective cytotoxic agent against certain cancer cell lines (Aswathy *et al.*, 2022).

Conclusion

Plants serve as natural laboratories for synthesizing diverse molecules, surpassing randomly created compounds in biological and pharmacological potency. Natural products (NPs) continue to hold great potential for uncovering unique molecular frameworks with diverse structures and valuable biological properties. These NPs can serve as valuable candidates for direct development or as initial templates for creating new drugs. Despite the persistent challenges faced in drug development, including high failure rates, NPs encounter additional obstacles related to accessibility, maintaining a sustainable supply, and intellectual property constraints. In drug discovery, the multifaceted potential of small molecules derived from plants stands out as potent modulators of cellular signalling pathways, offering tailored therapeutic interventions with reduced off-target effects and promising avenues for disease treatment. Natural laboratories, synthesizing diverse molecules, showcase the superiority of natural products over randomly created compounds in biological and pharmacological potency. The scientific and technological advancements discussed here not only contribute to understand the signalling pathways but also provide a roadmap for harnessing the unique molecular frameworks within natural products for drug development. By bridging the gap between small molecules and natural products, this review underscores the promising trajectory of NP-based drug discovery in improving human health and extending lifespans.

Future Perspective

The process of discovering potential drug candidates with desired properties is a complex challenge. Utilizing natural compounds as initial leads and optimizing them can reduce the risk of drug failure during development. However, some medicinal plants are on the brink of extinction, necessitating international efforts for both their conservation and the screening of their chemical compounds. To enhance drug development, new physicochemical properties should be explored for optimizing the efficacy of lead compounds. Understanding drug mechanisms at the atomic level, whether they act as an agonists or antagonists, can inform the drug design process. Conducting more experimental

studies on the absorption, distribution, metabolism, and toxicity (ADMET) of drug molecules can generate valuable datasets for predictive models. It is crucial to study the metabolites of different drugs and their toxicity mechanisms comprehensively, cataloging their fate.

In drug design, factors like pharmacokinetics, pharmacodynamics, structure-activity relationships, and synthetic feasibility must be considered. Achieving site-specificity in drug targeting, which reduces toxicity, can be accomplished through various methods such as structural modifications, antibody-drug conjugates, and nanoparticle carriers. The accuracy of the native 3-D structure of the target protein is pivotal in drug design, and incorporating molecular dynamics simulation data can guide lead modifications. Other parameters influencing protein-ligand interactions under physiological conditions should be integrated into molecular dynamics simulations. Drug discovery requires a holistic approach, combining natural compounds, advanced research, and innovative strategies to optimize drug candidates and improve their effectiveness and safety.

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Kumar Anand: Conceived and designed the manuscript; Sayak Khawas: Collected data on on-going study; Apurva Singh, Puja Kumari, Neha Nupur: Contributed equally in writing, Figure conceptualisation, drafting the manuscript; Neelima Sharma: Critically reviewed and performed final approval of the version to be published, all authors read and approved the final manuscript.

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