Introduction to Natural Products: State-of-the-Art of Drug Discovery

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**Abstract**

Natural products, and especially the active ingredients found in various plants used in the traditional medicine have a thousand-year-long history of clinical use and a strong theoretical basis in traditional medicine. As such, traditional remedies (plant extracts, concoctions, etc) provide shortcuts for the development of original new drugs in China and other parts of Asian countries with increasing numbers of natural products showing great therapeutic potential in various diseases and ailments. This paper reviews an up-to-date knowledge regarding the history and importance of historically important synthetic and natural plant-based natural products, their traditional medicinal usage, introduces the methods and newly emerging technologies used to identify and validate the targets of natural active ingredients, and summarizes the patterns of action of emerging technologies such as Metabolomics, dereplication, METLIN, etc to provide insights for the development of innovative natural product-based drugs. Our hope is that we can make use of advances in target identification of natural products to obtain a deeper understanding of mechanism of actions that will allow innovation and revitalization of traditional medicine and its swift industrialization.

1. **Introduction**

Natural products (NPs) are organic compounds with biological activity that are obtained from natural resources such as plants and animals (insects) [1, 2]. Cancer and other viral diseases have long relied on natural products (NPs) drugs, as have cardiovascular diseases (statins) and multiple sclerosis (fingolimod) [3-5]. Medicinal oils from *C. sempervirens* (Cypress) and *Commiphora* species (myrrh) were described on clay tablets in cuneiform from Mesopotamia (2600 B.C.) and are still used to treat coughs, colds, and inflammation [6]. Among the 700 plant-based remedies listed in the Ebers Papyrus (2900 B.C.) are tablets, infusions, gargles, and ointments. Shi Er Bing Fang (52 prescriptions), Shennong Herbal (365 medications), and Tang Herbal (100 medications) are all examples of the use of NPs in Chinese medicine dating back to 1100 BC [6]. Natural products, on the other hand, continue to provide distinct structural distinctions as compared to combinatorial chemistry, presenting prospects for the discovery of new low molecular weight lead molecules. Only 10% of the world's biodiversity has been examined for possible chemical and biological activity too far, and many important natural lead compounds are still waiting to be discovered, with the difficulty being how to access this natural chemical diversity. The collection and applications of medicinal plants were chronicled by Dioscorides (100 A.D.), and medicinal herbs were dealt with by Theophrastus (300 B.C.). The Western knowledge was retained in the monasteries of England, Ireland, France, and Germany throughout the Dark and Middle Ages while the Arabs preserved the Greco-Roman knowledge and extended its usage, along with Indian and Chinese plants that were new to the Greco-Roman civilization [6]. In the 8th century, the Arabs were the first to have their pharmacies. Avicenna, a Persian physician, pharmacist, poet, and philosopher, made significant contributions to the fields of pharmacy with works like the Canon Medicinae [6].

NPs have distinct features from synthetic molecules, which can aid or hinder the drug development process. NPs have huge scaffold variation and structural complexity. They have higher molecular mass, more sp3 carbon and oxygen atoms with less nitrogen and halogen atoms, more H-bond acceptors and donors, lower estimated octanol-water partition coefficients (stronger hydrophilicity), and higher molecular stiffness [7-10]. These distinctions can be useful; for example, the increased stiffness of NPs can be beneficial in medication development for protein-protein interactions [11]. Beyond Lipinski's rule of five [12], NPs are a key source of oral medicines. The growth in molecular mass of approved oral medications over the last 20 years demonstrates the growing importance of drugs that do not follow this norm [13]. Evolution has structurally optimized NPs to fulfil specific biological roles [1], such as the regulation of endogenous defence mechanisms and the interaction with other species, which explains their importance to counter infectious diseases and cancer. In addition, their usage in conventional medicine may reveal information about efficacy and safety. In comparison to normal synthetic small-molecule libraries, the NP pool is enriched with 'bioactive' molecules that cover a larger chemical space [14].

Due to many various limitations, pharmaceutical companies have limited their NP-based medication research efforts, even though many successful drug discoveries have been done to date. Target-based assays may not work with NP screens, which generally involve a library of natural extracts [15]. To prevent rediscovering previously found compounds, dereplication approaches must be utilized to find the bioactive molecules of interest. Enough biological material may also be difficult to get [16]. Furthermore, gaining intellectual property (IP) rights for NPs with relevant bioactivities might be problematic since naturally occurring compounds are not typically copyrighted [17]. Complicating matters is the UN 1992 Convention on Biological Diversity and the Nagoya Protocol, both of which came into effect in 2014, as well as recent developments relating to benefit-sharing related to the utilization of marine genetic resources [18, 19]. While NP structure complexity may be advantageous but synthesizing the structural analogs to examine structure-activity correlations and optimize NP leads may be challenging if the synthetic routes are difficult. Deconvolution of molecular mechanisms is time-consuming which are often identified by phenotypic assays [20]. Fortunately, both screening tests (using induced pluripotent stem cells and gene editing technologies) and attempts to find important pharmacological mechanisms of action have made great progress [21, 22]. Herein, we present an up-to-date knowledge regarding the history and importance of historically important synthetic and natural plant-based natural products, their traditional medicinal usage, introduces the methods and newly emerging technologies used to identify and validate the targets of natural active ingredients, and summarizes the patterns of action of emerging technologies such as Metabolomics, dereplication, METLIN, etc to provide insights for the development of innovative natural product-based drugs.

1. **Natural Products (NPs) in traditional medicine**

Traditional medicines, potions, cures, and oils, all made from natural ingredients, have been used as medicines for centuries. However, the bioactive components of many of these natural items remain unknown. Medicinal plant applications have mostly been discovered by human experimentation throughout hundreds of years, whether it be through tests of taste or tragically early deaths in the quest for cures for sickness [23, 24]. The plant genus *Salvia*, which grows across the southwest United States and north-western Mexico, was utilized by the Indian tribes of southern California to help with birthing [23]. It was thought that by "cooking" male newborns in hot Salvia ashes, these infants would grow up to be the strongest and healthiest members of their tribes, immune from any respiratory diseases for the rest of their lives [23]. *S. sclarea* is commonly referred to as the clear eye or eye brilliant since the fresh plant's juice was used to heal eye ailments [25]. It was also used in Germany in the 19th century to flavour wine and beer. *S. sclarea* is still employed in the production of muscatel wine, even though it has been outlawed. As a remedy for rheumatism, infusions or decoctions of the plant have been and continue to be used in baths [25]. Apart from this, aqueous extracts of *S. sclarea* were utilized to treat a variety of digestive. The aqueous extract also functions as a deodorant and an anti-catarrhal agent. *S. Sclarea* is used in the form of a throat wash to treat oral cavity infections. Symptoms of several CNS illnesses have been successfully treated with the plant's extracts in clinical trials. *S. sclarea* was used to treat amenorrhea and dysmenorrhea because of its emmenagogic qualities [26-28].

It has been documented and claimed by Ayurvedic people that *Alhagi maurorum* Medik (Camel's thorn) helps treat anorexia, dermatosis, constipation, epistaxis, leprosy, fever, obesity, and other ailments by releasing a gummy and sweet material from its stems and leaves known as "manna," which is composed of sucrose, melezitose, and invert sugar. Roots of the Camel thorn plant were cooked and used as an antidote to bloody diarrhea in Israel, according to folklore. The Romans and Konkani people utilized the same herb to cure nasal polyp illness [24]. Eating the raw root of the plant *Ligusticum scoticum* L. in the morning is considered to prevent a person from everyday infections. The root was also used as a treatment for flatulence and as an erectile dysfunction remedy [29-32].

1. **Primary and secondary metabolites**

The synthesis and breakdown of biomolecules that are essential to all living creatures (lipids, proteins, nucleic acids, and carbohydrates)are known as fundamental metabolism and the molecules involved are known as primary metabolites [33]. The process through which bacteria, plants, and animals biosynthesize chemicals is called secondary metabolism, and the compounds are known as secondary metabolites (natural products) which are unique to each organism or a manifestation of a species' identity [33,34]. Environmental adaption of different organisms resulted in the production of chemicals/natural products as a defence strategy against predators. Biological intermediates and secondary metabolites (natural products) are produced in biosystems via the basic processes of photosynthesis and glycolysis [33, 35]. Although the number of building blocks is restricted however, the secondary metabolite production is unlimited. Among the important substrates involved in secondary metabolite biosynthesis isacetyl coenzyme A (acetyl-CoA), shikimic acid, mevalonic acid, and 1-deoxyxylulose-5-phosphate. Decarboxylation, aldol, claisen, and schiff base synthesis are a few of the processes and reactions involved [33]. Secondary metabolism is thought to primarily employ amino acids and the acetate and shikimate pathways to create intermediates that have taken a different biosynthetic route, leading to the biological synthesis of natural products [36]. Natural (e.g., viruses or environmental changes) and unnatural (e.g., chemical or radiation) causes result in biosynthetic pathway adjustments for the organism to adapt or give immunity [36]. Thus, the characteristic chemical structures with a wide range of activities are formed by the unique biosynthesis of these secondary metabolites which are produced by a huge number of terrestrial and marine species.

1. **Historically important synthetic and plant-based natural products**

Traditional therapeutic techniques were used by people in ancient times, followed by clinical, pharmacological, and chemical studies [37]. The synthesis of the anti-inflammatory drug aspirin **(1)** from the natural substance salicin **(2)** extracted from the bark of *Salix alba* L. is a notable example of the use of plant natural products as therapeutic agents [38]. The opium poppy, *Papaver somniferum* L., produces a variety of alkaloids including morphine **(3)**, a commercially important narcotic drug discovered in 1803. It wasn't until the 1870s that morphine was discovered to produce diacetylmorphine (heroin) when treated with acetic anhydride and easily converted to codeine (painkiller). Poppy extracts were considered to have been used medicinally by the Sumerians and ancient Greeks, while the Arabs portrayed opium as addictive [38]. Digitoxin (a cardiotonic glycoside) **(4)** (**Fig. 1**) was discovered in the 1700s to promote cardiac conduction, thus enhancing the strength of cardiac contractibility. Digitoxin and its derivatives have long been used to treat congestive heart failure, but because of their long-term side effects, they have been superseded by other drugs for the treatment of "heart deficiency" [38].

Diagram

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**Fig. 1: Structure of Acetylsalicylic acid (1); Salicin (2); Morphine (3); and Digitoxin (4)**

The antimalarial drug quinine **(5)**, derived from the bark of *Cinchona succirubra* Pav. Ex Klotsch and licensed by the US FDA in 2004, has long been used to treat malaria, fever, mouth and throat infections, and cancer. Cinchona bark has been used to cure malaria since the mid-eighteenth century when the British initiated widespread cultivation [38]. Pilocarpine **(6)**, an L-histidine-derived alkaloid isolated from *Pilocarpus jaborandi* (*Rutaceae*), has been utilized for over ten decades as a therapeutic medication in the treatment of glaucoma. Pilocarpine was licensed by the FDA in 1994 for the treatment of Xerostomia (side effect of radiation therapy). Pilocarpine is also used to cause sweat glands to record sodium and chloride ion concentrations [39]. In 1998, an oral preparation of pilocarpine was licensed for the treatment of Sjogren's syndrome, an autoimmune disease that destroys the salivary and lacrimal glands.

Medicinal uses of plants have been widely recorded for time immemorial. The plants have adapted themselves over some time to combat bacteria, insects, and fungi, resulting in the synthesis of unique but structurally distinct secondary metabolites (NPs). Plant ethnopharmacological qualities have served as the main source of medications in the early stages of drug discovery [40, 41]. Plant-based medicines are used by about 80% of the world's population, according to the WHO, whereas 80% of 122 plant-derived remedies were shown to have an ethnopharmacological function [42, 43]. Traditional medicine's expertise (complementary or alternative herbal products) has prompted more research into medicinal plants as possible medications, resulting in the isolation of large amounts of natural compounds that have gone on to become well-known pharmaceuticals. Paclitaxel (**7**) (Taxol® from the bark of the Taxus brevifolia tree)is one of the most often used breast cancer medications[44]. A course of treatment may require 2 grams of Taxol, which is typically produced from three mature 100-year-old trees. Taxol is being generated in synthetic laboratories at a rate of 100-200 kg per year (i.e. 50,000 treatments per year) to meet market demand [33]. Taxol® received the first of multiple FDA clearances for diverse applications in 1992 [45]. Because Taxol® **(7)** is found in smaller levels in nature, it has been synthesized (albeit it is difficult and expensive) [46]. Baccatin III **(8)** (**Fig. 2**) which is found in larger concentrations and is readily available from *T. brevifolia* and its derivatives, is an example of a structural counterpart that can be converted into Taxol [33].

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**Fig. 2: Structure of Quinine (5); Pilocarpine (6); Taxol® (7); and Baccatin III (8)**

Ingenol-3-O-angelate **(9)** is a derivative of diterpenoid ingenol isolated from *Euphorbia peplus*, is a potent chemotherapeutic agent for skin cancer, and is currently being studied for clinical trials by Peplin Biotech [47, 48]. Similarly, PG490-88 (14-succinyl triptolide sodium salt) **(10)**, the derivative of triptolide found naturally in *Tripterygium wilfordii* is used to treat autoimmune and inflammatory illnesses [49, 50]. Similarly, Combretastatin A - 4 phosphate **(11)** is a stilbene compound extracted from *Combretum caffrum,* is currently in Phase II clinical studies in China [51, 52]. AIDS (Acquired Immune Deficiency Syndrome) compelled the NCI and other institutions to look at natural compounds as sources of prospective AIDS therapeutic candidates. A total of over 60,000 extracts were evaluated against lymphoblastic cells infected with HIV-1. The discovery of the important class of natural chemicals known as calanolides was based on this approach. As a result, calanolides such as calanolide A **(12)** and calanolide B **(13)** from *Calonphyllum* species, as well as prostratin **(14)** (**Fig. 3**) from *Homalanthus nutans* lead to clinical and preclinical development [53-55].

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# Fig. 3: Structres of Ingenol 3-*O*-angelate (9); PG490-88 (10); Combretastatin A - 4 phosphate (11); calanolide A (12); calanolide B (13) and prostratin (14)

Sarawak Medichem Pharmaceuticals had licensed and approved Calanolide A for Phase II clinical studies, but it could not be pushed forward for further therapeutic development. For the first time, prostratin was tested on humans in 2010 by the AIDS Research Alliance in Los Angeles, California. Artemisinin (**15**) introduced as Artemisin was isolated from *Artemisia annua* and was among the approved antimalarial drugs [56]. Arteether was introduced in 2000 as Artemotil, a synthetic derivative of artemisinin **(16)** which was isolated from *Artemisia annua* **(Fig. 4)**. *Artemisia annua* was previously used in traditional Chinese medicine to cure fevers and chills. Other antimalarial medications based on synthetic artemisinin analogs are in different stages of clinical development in Europe [6, 33]. Piperaquine (synthetic bisquinoline drug), based on the 16 pharmacophoresin conjunction with a synthetic trioxolane is now being explored in tandem to treat malaria [57]. Grandisine A **(17)** and Grandisine B **(18)**, are the indole alkaloids isolated from *Elaeocarpus grandis* leaves. Grandisine A has a tetracyclic skeleton whereas Grandisine B has both isoquinuclidinone and indolizidine rings in its structure. Both of these alkaloids bind to the opioid receptor in humans and are potent analgesics [58]. Similarly, galantamine hydrobromide **(19)**, an amaryllidaceae alkaloid derived from *Galanthus nivalis*, is widely used in Turkey and Bulgaria to treat neurological illnesses, including Parkinson's and Alzheimer's disease [59, 60]. Apomorphine **(20)**, a synthetic derivative of morphine, is a dopamine D1 and D2 receptor agonist as well as a powerful dopamine agonist for Parkinson's disease treatment. Tubocaurarine **(21)** is an active ingredient found in *Chondrodendron tomentosum* (Menispermaceae) that is utilized as a muscle relaxant in surgical procedures, reducing the requirement for deep anesthesia. The availability of tubocaurarine **(21)** in trace amounts has led to the development of several synthetic derivatives that are currently favoured over natural substances [33].

# Diagram, schematic Description automatically generated

# Fig. 4: Structures of Artemisinin (15); Artemisinin (16); Grandisine A (17); Grandisine B (18); Galantamine hydrobromide (19); Apomorphine (20); Tubocaurarine (21)

1. **Current status of natural products: Drug discovery and analytical methods**

Conventional drug research uses biological screening of crude extracts to select a bioactive hit extract, which is then fractionated to isolate the active NPs. Many limitations are associated with bioactivity-guided isolation however, these can be solved using several techniques and technology. For example, the crude plant extracts can be pre-fractionated into various sub-fractions that will be more appropriate for automated liquid handling systems to build libraries that are compatible with high-throughput screening. Furthermore, the fractionation procedures can be modified to ensure that sub-fractions contain molecules with drug-like characteristics. Such When techniques help to improve the number of hits [61].

Metabolomics is a technique used to analyze various metabolites in the same sample (plant extract) at the same time. Due to improvements in chromatographic and spectrometric techniques, metabolomics was employed in various fields including biomedical and agricultural sciences [2]. The use of metabolomics in drug discovery has helped researchers to a great extent for searching active ingredients with the help of different NP analytical instruments and computational approaches that can generate convincing NP analogs and their simulations spectra [62-64]. It is possible to use metabolomics to identify novel NP scaffolds and annotate unknown analogs and new metabolite composition from crude extracts, all of which can aid in the separation of different NPs [65, 66]. It is also possible to use metabolomics to discover changes in metabolite compositions in distinct physiological states of the organism producing them and provide hypotheses to explain them, and metabolite profiles to support phenotypic characterization at the molecular level [67]. To better comprehend the chemical mechanisms of action, one can adopt either strategy. Metabolite profiling involves the use of various basic spectroscopic techniques such as NMR or HRMS or a combination of two or more techniques such as ULC for separating the mixture of two or more isomers present in crude NP extract [68-70]. The result of combined methods such as NMR and HRMS is much better compared to the use of single methods [71, 72]. Even while NMR extraction of NP extracts can be done easily with a high degree of repeatability and enough structural information of major components, it lacks sensitivity and can only be used to identify the major components only [70]. NMR instrumentation is a versatile spectroscopic technique that can be used to identify the chemical components in both unfractionated or LC fractionated samples [73]. HRMS is the gold standard for both qualitative and quantitative metabolite profiling which is often used in conjunction with LC [70]. Direct infusion mode (DIMS), whereby materials are directly profiled by MS without a chromatography stage or MS imaging (MSI), which permits the spatial distribution of NPs inside live organisms, may also be employed with HRMS [74, 75]. HRMS routinely acquires precise molecular mass information, which along with adequate heuristic filtering may allow unambiguous assignment of molecular formulas for hundreds to thousands of metabolites in a single extract across a dynamic range that may exceed five orders of magnitude [68, 76]. There are, however, significant problems in data mining and the identification of the metabolites utilizing open web-based procedures [77].

Dereplication of secondary metabolites involves determining the molecular mass and formula as well as checking the literature or structural NP databases with taxonomic information which substantially aids the identification procedure. Such metadata are typically gathered in private databases, such as the Dictionary of Natural Products (DNP), which includes all documented NP structures with linkages to their biological origins. Nevertheless, there is no complete experimental tandem mass spectrometry database of all NPs published to date, and the absence of uniform collision energy parameters for fragmentation in LC-MS/MS hinders a search for experimental spectra across multiple platforms [62].A new molecular networking platform created in the Dorrestein laboratory is an essential contribution to the toolset in this regard [78]. MS/MS data captured from a single set of extracts may be organized and shown as a cluster of structurally linked molecules using molecular networking. Dereplication is facilitated by the ability to annotate isomers and analogs of a particular cluster metabolite [79]. An MS/MS spectra predicted by methods like competitive fragmentation modelling may be compared to the experimental spectra obtained during the experiment (CFM- ID) [80]. Massive theoretical NP spectrum databases were built and put to use in dereplication as a result of these kinds of techniques. But there are several issues with this technique, such as the fact that certain NPs are more suited to it than others, and the difficulty in assigning a structure to a particular NP [81]. GNPS molecular networking strategy has many drawbacks such as non-specificity as some classes of NPs show better results compared to other extracts and uncertainty in structural assignment among possible predicted candidates. Efforts to overcome these difficulties are in the process such as by overlaying molecular networks of large NP extract libraries with taxonomic information to improve the confidence of annotating them [82-85]. In general, molecular networking helps scientists prioritize the isolation of unknown compounds by strengthening the process of getting rid of duplicates and figuring out how NP analogs are related to each other. Structure elucidation for NPs of interest should not be overlooked.

METLIN is another good platform for metabolite identification. This platform has a high-resolution MS/MS database that can be used to find unknown compounds [86]. Compound Structure Identification (CSI): FingerID and Input-Output Kernel Regression (IOKR) can be used to search fragment ion spectra that are available, as well as to predict the spectra that aren't in the databases [87]. A new computer program that can predict the structural identity of metabolites that come from any known compound has also been reported, which should make NPs easier to find [88]. To speed up the process of finding bioactive NPs in extracts, data from metabolomics can be matched to the biological activities of these extracts [89]. There are many types of chemometric methods that can help you figure out which compounds are active in complex mixtures without having to do more bioassays [90-92]. For example, multivariate data analysis can help you figure out which compounds are active in complex mixtures without having to do more bioassays. Several analytical modules can be linked together to allow the simultaneous bioactivity evaluation and identification of compounds in small amounts (analytical scale) and complex compound mixtures [71, 72]. We can combine the results of metabolomics screenings with those from transcriptome and proteome analyses or imaging-based screens. NP-mediated interactions between *Micromonospora* and *Rhodococcus* were studied by *Acharya et al.* using the same procedure [93]. *Kurita et al.* used untargeted metabolomics data from an extract library in conjunction with cytological profiling to develop a compound activity mapping platform for the prediction of constituent identities and mechanisms of action and identified the quinocinnolinomycins as a new family of NPs that cause endoplasmic reticulum stress [94, 95] (**Fig. 5**).

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**Fig. 5: Applications of advanced analytical technologies empowering modern natural product-based drug discovery (LC-HRMS profiling of NPs)**

NP-based drug development may be accelerated by analytical improvements that allow for the tracking of responses to bioactive compounds at the single-cell level. One of the most efficient ways to study bioactivity using single cells is through the use of high-throughput platforms developed by Irish, Bachmann, Earl, and colleagues, which incorporate phosphor-specific flow cytometry as well as single-cell chemical biology and cellular barcoding as well as other techniques from the field of metabolomic arrays. Biopsies from individuals with acute myeloid leukemia were analyzed using this technology, which allowed the researchers to identify novel bioactive polyketides after analyzing the single-cell responses of bone marrow biopsy samples [96]. The advancement of higher-field NMR instruments and probe technology [97, 98] has made it possible to determine the structure of NPs from extremely small quantities (below 10 g) [99, 100], which is crucial because NP quantities are often constrained. Microcrystal electron diffraction (MicroED) is a cryo-electron microscopy-based approach for unambiguous structural identification of tiny compounds that have already found substantial uses in NP research [101, 102].Isolated NPs may also suffer from an issue known as 'residual complexity' which occurs when physiologically powerful but undiscovered contaminants (which include structurally similar conformers) in an isolated NP sample lead to inaccurate attribution of structure or activity. It was advised by *Pauli et al.* that lead NPs to undergo advanced purity analysis utilizing quantitative NMR and LC-MS at an early stage [103-104].

1. **Outlook for NPs in drug discovery**

Natural Products based medication research may be resurrected in both established and emerging sectors because of the developments highlighted above. Long have NPs served as a primary source of new antibiotics and other drugs for treating various infectious diseases [105, 106]. Fig. 5 shows the NPs with antimicrobial properties that were found by leveraging discoveries in the prior sections, such as strategies to use the human microbiome for novel NPs [107, 108]. Additionally, researchers are looking for new NPs with antibacterial properties by using biosynthetic engineering, fully synthetic, and semi-synthetic approaches (**Fig. 6**) [109-112]. Biosynthetic engineering, which modifies the producing organism's biosynthetic pathways, and total chemical synthesis will be very important in this context (**Fig. 7**). NPs targeting bacterial quorum sensing might also be used as an antiviral method to fight infections [113, 114]. Several studies have already discussed the success NPs being served as potential cancer therapeutics [115-118]. NPs have the potential to trigger an immune response against cancer cells that is both selective and potent. This is a new opportunity in this field, given the current interest in strategies that could improve response rates to immune checkpoint inhibitors by turning "cold" tumors "hot" [119]. As an example, the production of damage-associated molecular patterns (DAMPs) by stress and dying cancer cells might enhance their immunogenicity, which could lead to new paths for drug development or repurposing [120-123]. Because of the potential for synergistic therapeutic effects of components in the plant extracts, botanical treatments involving complex mixtures of NPs have long been of interest [124, 125].

Diagram, timeline

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**Fig. 6: NP- derived antibiotics with semisynthetic and synthetic derivatives**

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**Fig. 7: The biosynthetic engineering approach for the generation bleomycin**

Botanical medicine development is hampered by the fact that the NP content in the beginning plant material is very variable due to variables such as environmental differences in the region where the plants are obtained [1]. When it comes to developing new medicines, it is becoming increasingly possible to combine many NPs rather than find and isolate a single active component [126]. Because NPs have been shown to influence the makeup of the gut microbiome, this is a promising area for NP-based medication development in the future [127-133]. Drug development efforts in this field are, however, only getting started, and there are still a lot of concerns [134]. Single microbiota-derived species for specific therapeutic applications may be a future area for research, and the above-discussed advancements in culture techniques, genome mining, and analytics will be critical. These developments are supplemented by computational tools and databases that may be used to analyze genetic information and predict chemical structures and pharmacological activities, as well as methods for integrating data sets containing different information (such as multi-omics analysis). Last but not least, NP-based drug discovery provides a unique niche for various types of academic–industry cooperation, but a fundamental difficulty is that scientific and technical knowledge is typically dispersed across several academic institutions and firms. To promote translational NP research in academia, which has grown increasingly challenging due to a decrease in the number of big corporations actively participating in NP research, focused efforts are required. To promote academic-industry ties, a common approach is to bring together all the required knowledge under one roof. One such initiative based in Austria's Innsbruck, the Phytovalley Tirol aims to speed up NP-based drug discovery by bringing together several research institutions and companies (including the Austrian Drug Screening Institute, the Michael Popp Research Institute for New Phyto-Entities, Bionorica Research, and Biocrates Life Sciences AG). The International Natural Product Sciences Taskforce (INPST), which was recently formed offers a forum for the integration of experience, technology, and materials from the participating academic and industry groups. Finally, NPs remain a promising source for discovering scaffolds with high structural diversity and diverse bioactivities that can be used as-is or as a starting point for developing novel drugs. While high attrition rates continue to hinder drug development, NPs face additional challenges due to issues like accessibility, supply sustainability, and IP restrictions.

1. **Future prospects of natural product research**

Natural occurring chemicals and their synthesized counterparts make up around 50% of all medications now in use. They have also given the chemical platform or conceptual insight for the synthesis of almost half of all bioactive molecules that have been synthesized. According to a statistical examination of natural-source chemicals used in drug development, roughly 90,000 known naturally occurring compounds account for about 40% of total probable novel therapeutic molecules, whereas the other 60% is made up of several million synthetic molecules [135]. This large disparity in productivity can be explained by the fact that only a small number of molecules are involved in, or have a useful effect on, various life processes, and that nature has been the best selector of molecules that affect certain metabolic processes in living things [136]. Natural products continue to be one of the primary sources of new chemical entities for medication development, despite the pharmaceutical industry's enormous investment in current drug-discovery techniques. New avenues into the mechanism of pharmacological action have been discovered by the investigation of isolated compounds from natural resources [137]. In this context, natural compounds such as heroin, nicotine, acetylcholine, penicillin, and others have made significant contributions to contemporary pharmacology. Natural products offer medicinal chemists a wealth of options since the molecular structure is directly connected to biological action. When a compound's mechanism of action is uncertain, manufacture and research of precisely designed analogs of the lead molecule can be utilized to fine-tune the drug's molecular target contact to generate the desired biological response. Finally, lead modification can be used to change a molecule's physical properties so that it can be formed (e.g., as an oral dosage form).

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