

# INTRODUCTION TO NATURAL PRODUCTS: STATE-OF-THE-ART OF DRUG DISCOVERY

## Abstract

Natural products, particularly the bioactive constituents derived from diverse botanical sources used in traditional medicine, has a rich historical background spanning thousands of years in clinical application, supported by a robust theoretical foundation within traditional medicinal practices. Therefore, traditional medicines, such as plant extracts and concoctions, provide expedited pathways for the discovery of novel pharmaceuticals in China and other regions of Asia. These natural items have shown significant therapeutic promise in treating a wide range of illnesses and maladies. This paper provides a comprehensive review of current knowledge pertaining to the historical significance and relevance of both synthetic and natural plant-based natural products. It explores their traditional medicinal uses and introduces the methodologies and emerging technologies employed in the identification and validation of targets for natural active ingredients. Additionally, it summarizes the mechanisms of action observed in emerging technologies such as Metabolomics, dereplication, and METLIN. The aim is to offer valuable insights for the advancement of innovative drugs based on natural products. It is anticipated that leveraging advancements in the identification of natural product targets would provide a more comprehensive comprehension of their mechanism of action, hence enabling the innovation and rejuvenation of traditional medicine and their expedited industrialisation.

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## I. INTRODUCTION

Natural products (NPs) refer to organic chemicals that possess significant biological activity and are derived from various natural sources, including plants and animals [1, 2]. Cancer, cardiovascular diseases, multiple sclerosis, and other viral diseases have long relied on natural product (NP) drugs [3-5]. The clay tablets inscribed in cuneiform from Mesopotamia (2600 B.C.) provide descriptions of medicinal oils derived from Cypress and myrrh species. These oils have persisted in their use to address several prevalent health conditions such as coughs, colds, and inflammation [6]. Among 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. So far, 10% of the world's biodiversity has undergone scrutiny in search of potential chemical and biological properties. Numerous significant lead compounds of natural origin remain undiscovered, posing a challenge in terms of accessing this extensive reservoir of chemical variety. 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.). During the Dark and Middle Ages, Western knowledge was conserved inside the monastic institutions of England, Ireland, France, and Germany. Simultaneously, the Arabs safeguarded and expanded upon Greco-Roman knowledge, incorporating new botanical discoveries from India and China into the existing Greco-Roman civilisation [6]. In the 8<sup>th</sup> century, the Arabs were the first to have their pharmacies. Avicenna, a Persian physician, pharmacist, poet, and philosopher, made significant contributions to the field of pharmacy (Canon Medicinæ) [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 are high molecular weight molecules with more sp<sup>3</sup> carbon and oxygen atoms, less nitrogen and halogen atoms, having the ability of H-bonding, lower octanol-water partition coefficients (stronger hydrophilicity), and higher stiffness [7-10]. These characteristic features can be useful for the development of protein-protein interactions [11]. Beyond Lipinski's rule of five [12], NPs are the key sources of oral medications. However, the last 20 years demonstrate a huge rush in the use of high molecular mass oral medications [13]. Evolution has structurally optimized NPs to fulfill specific biological roles/functions [1], such as the regulation of endogenous defense mechanisms which explains their importance to counter diseases and cancer. Furthermore, the use of these compounds in traditional medical practices might provide insights on their effectiveness and potential risks. When comparing the NP pool to conventional synthetic small-molecule libraries, it is evident that the former exhibits a higher concentration of 'bioactive' molecules, including a broader range of chemical diversity [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 exhibit limited efficacy when used in conjunction with NP screens, which typically include a collection 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]. Gaining intellectual property rights for NPs with specific biological activities might become a limiting factor for the full exploration of natural products [17]. The benefit-sharing of marine genetic resources has been facilitated by recent advancements after the endorsement of the UN 1992 Convention on Biological Diversity and the implementation of the Nagoya Protocol, which became operational in 2014 [18, 19]. Although the complexity of NP structures might provide some benefits, the task of synthesizing structural analogs to investigate correlations between structure and activity, as well as to optimize NP leads, can be hard when the synthetic pathways are lengthy and environmentally impractical. Deconvolution of molecular mechanisms is time-consuming and is often identified by phenotypic assays [20]. Significant advancements have been achieved via the utilization of induced pluripotent stem cells, gene editing technologies, and persistent endeavors to elucidate pharmacological mechanisms of action [21, 22]. In this paper, we provide a comprehensive overview of the current understanding of the historical significance and relevance of synthetic and natural plant-based natural product molecules. We discuss their traditional medicinal uses and introduce the methodologies and emerging technologies employed in the identification and validation of the targets. Additionally, we summarize the mechanisms of actions via the usage of emerging technologies such as metabolomics, dereplication, METLIN, and others, which offer valuable insights for the development of novel drugs based on natural products.

## II. 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]. *Salvia*, a plant species that thrives in the southwestern region of the United States and northern Mexico, has been documented as being employed in child birth [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 flavor 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].

Ayurvedic practitioners have recorded and asserted that *A. 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

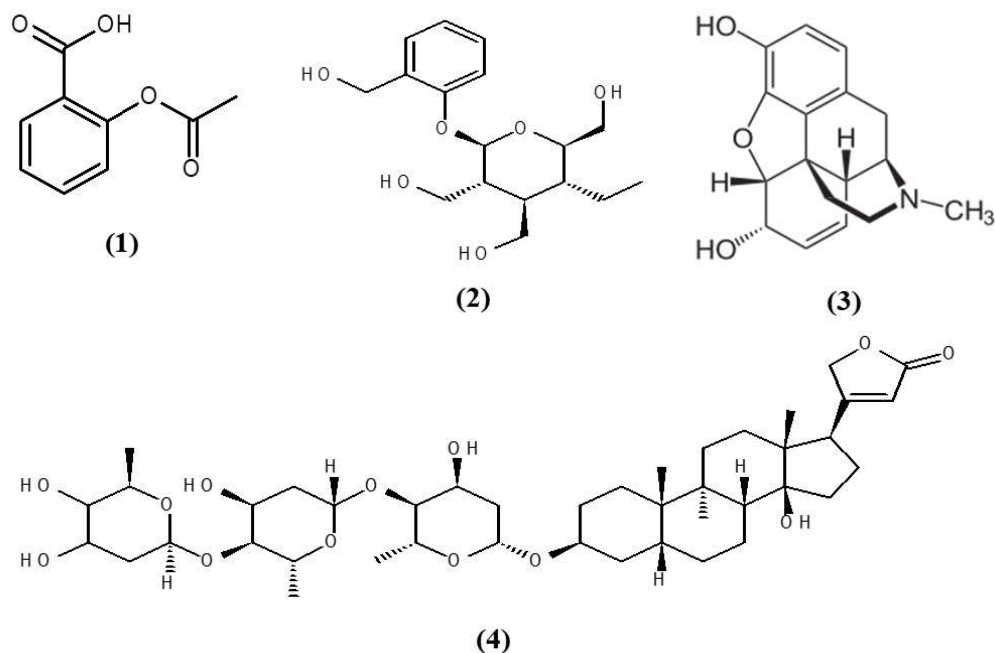
[24]. Eating the raw root of the plant *Ligusticum scoticum* L. in the morning is considered to prevent a person from everyday infections. The root was also used as a treatment for flatulence and as an erectile dysfunction remedy [29-32].

### III. PRIMARY AND SECONDARY METABOLITES

Primary metabolites refer to the macromolecules, including lipids, proteins, nucleic acids, and carbohydrates, that play crucial role in the sustenance of all living organisms [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 defense strategy against predators. Biological intermediates and secondary metabolites (natural products) are produced in biosystems via the basic processes of photosynthesis and glycolysis [33, 35]. While the availability of building blocks may be limited, the generation of secondary metabolites exhibits a vast and unrestricted diversity. Acetyl coenzyme A (acetyl-CoA), shikimic acid, mevalonic acid, and 1-deoxyxylulose-5-phosphate are notable substrates implicated in the production of secondary metabolites. Decarboxylation, aldol, claisen, and schiff base synthesis are a few of the processes and reactions involved [33]. It is widely believed that secondary metabolism mostly utilizes amino acids through the acetate and shikimate routes to generate intermediates that have undergone alternative biosynthetic pathways, ultimately resulting in the biological production of NP molecules. Various factors, including both natural such as viruses or environmental changes, and manmade factors such as chemical or radiation exposure, result in biosynthetic pathway adjustments for the organism to adapt or give immunity [36]. Thus, the characteristic chemical structures with a wide range of biological activities are generated through unique biosynthetic pathways using of the secondary metabolites.

### IV. HISTORICALLY IMPORTANT SYNTHETIC AND PLANT-BASED NATURAL PRODUCTS

Traditional therapeutic techniques were used by people in ancient times to treat various diseases and ailments, followed by clinical, pharmacological, and chemical studies [37]. The use of plant-derived natural products as therapeutic agents was shown by the production of aspirin (**1**), one of the first anti-inflammatory medications, synthesized from salicin (**2**) obtained from the bark of *S. alba* L [38]. The opium poppy, scientifically known as *Papaver somniferum* L., is responsible for the synthesis of many alkaloids, among which is morphine (**3**), a very significant narcotic substance, was first identified in 1803 and has since gained immense economic value. 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]. The cardiotoxic glycoside known as digitoxin (**4**) (**Fig. 1**) was first isolated in the 1700s and has since been used to strengthen cardiac contractibility by promoting cardiac conduction. Congestive heart failure has long been treated by digitoxin, and its derivatives which are now no longer utilized to treat "heart deficiency" due to their long-term negative effects [38].

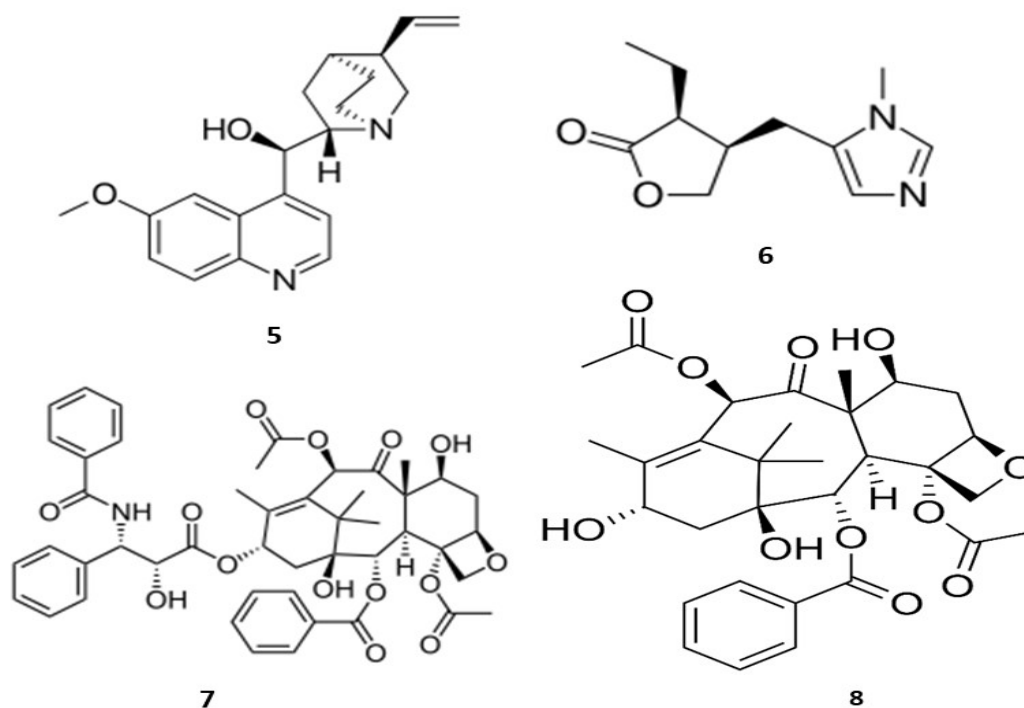


**Figure 1:** Structure of Acetylsalicylic acid (1); Salicin (2); Morphine (3); and Digitoxin (4)

The antimalarial drug quinine (5), is derived from the bark of *C. succirubra* Pav. Ex Klotsch and licensed by the US FDA in 2004, has long been used for many throat infections in addition to malaria, fever, mouth, and cancer. Cinchona bark has been used to cure malaria since mid 18<sup>th</sup> century [38]. Pilocarpine (6), an L-histidine-derived alkaloid isolated from *P. jaborandi* (*Rutaceae*), has been utilized for over ten decades as a therapeutic medication in the treatment of glaucoma. The Food and Drug Administration (FDA) granted licensure to pilocarpine in 1994 for the therapeutic management of Xerostomia, a condition that arises as a consequence of radiation therapy. Pilocarpine is further used for the purpose of regulating the amounts of sodium and chloride ions inside sweat glands [39]. The licensing of an oral pilocarpine formulation for the treatment of Sjogren's syndrome, an autoimmune disorder characterized by the destruction of salivary and lacrimal glands, occurred in 1998. 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].

The proficiency of traditional medicine has stimulated more investigation into the therapeutic potential of medicinal plants, leading to the extraction of substantial quantities of natural chemicals that have subsequently gained recognition as widely-used medicines. Paclitaxel (7), commercially known as Taxol®, is a frequently prescribed medicine for the treatment of breast cancer [44]. It is derived from the bark of the *Taxus brevifolia* tree. The administration of a treatment regimen may need the use of a dosage equivalent to 2 gm of Taxol, a pharmaceutical compound that is often derived from the extraction of resources

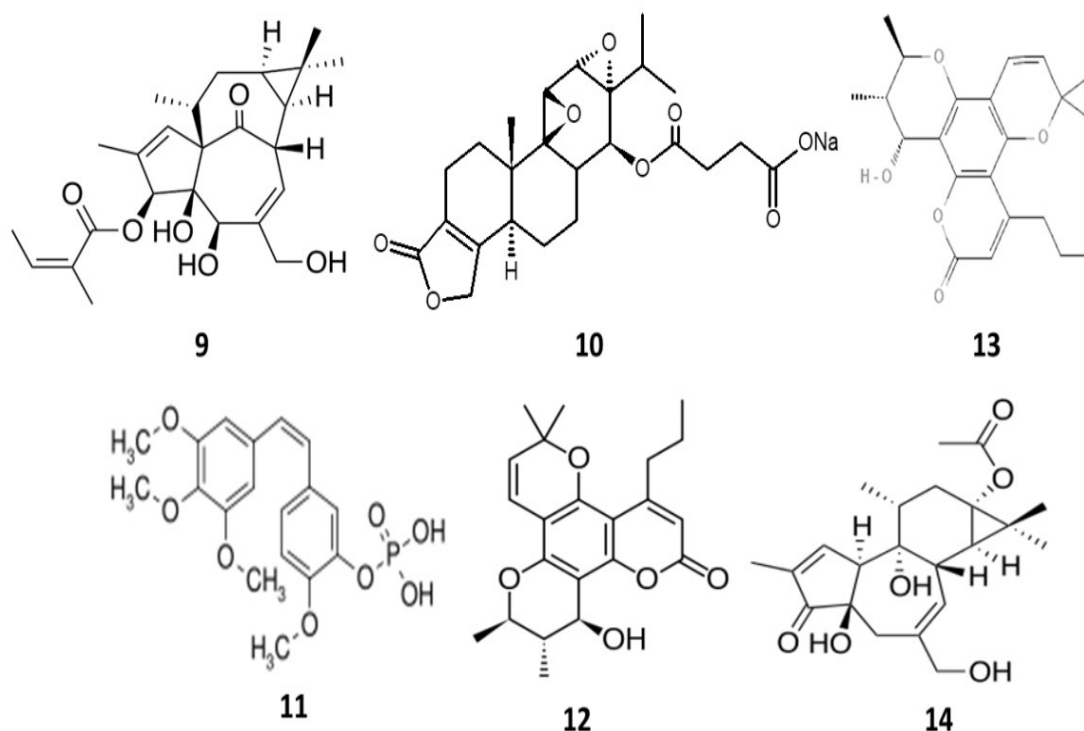
obtained from three fully developed trees with an average age of 100 years [33]. Taxol® (7) received the first of multiple FDA clearances for its diverse applications in 1992 [45]. Because Taxol® is found in smaller levels in nature, it is being synthesized in laboratories [46]. Baccatin III (8) (Fig. 2) which is found in larger concentrations and is readily available from *T. brevifolia* and its derivatives, serves as an illustrative example of a structural analogue that can be transformed into Taxol [33].



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

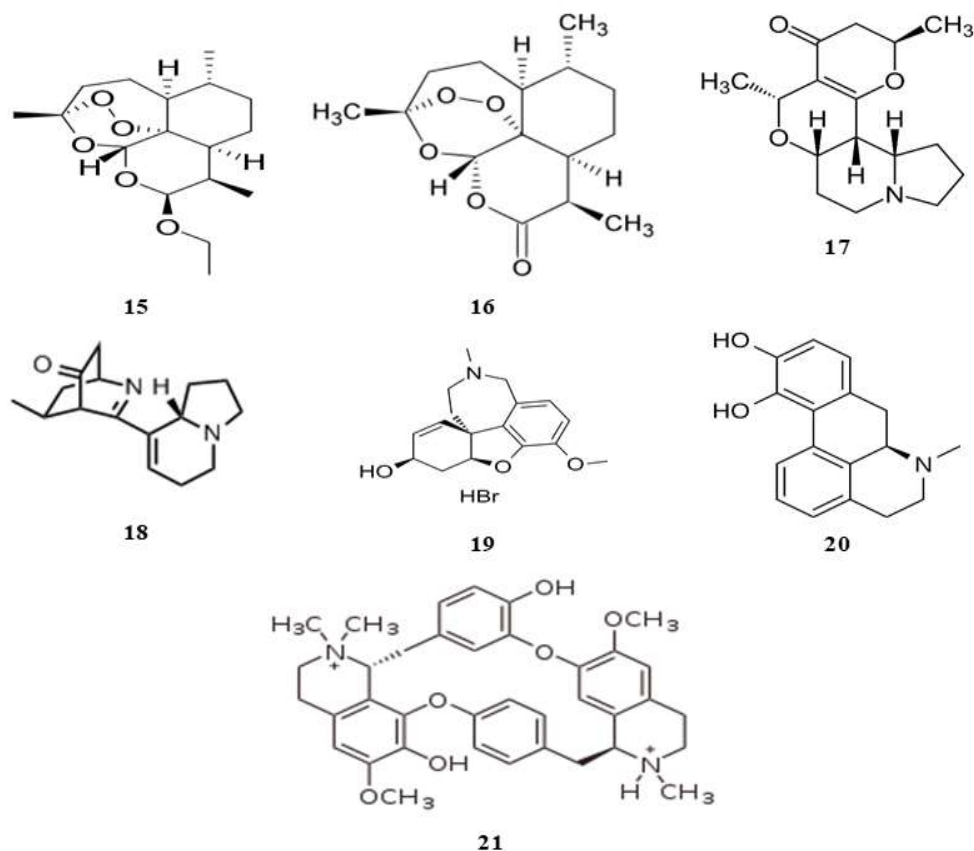
Ingenol-3-O-angelate (9) is a compound derived from the diterpenoid ingenol, which has been extracted from *E. peplus*. This compound has potential therapeutic applications in the treatment of skin cancer. Currently, Peplin Biotech is conducting clinical studies to further investigate the efficacy and safety of this compound [47, 48]. Similarly, PG490-88 (14-succinyl triptolide sodium salt) (10), the derivative of triptolide found naturally in *T. wilfordii* is used to treat autoimmune and inflammatory illnesses [49, 50]. Likewise, Combretastatin A - 4 phosphate (11) is a stilbene molecule derived from *C. caffrum* that is now undergoing Phase II clinical trials in China [51, 52].

AIDS (Acquired Immune Deficiency Syndrome) prompted the National Cancer Institute (NCI) and other research organizations to explore natural chemicals as potential sources for therapeutic options targeting this disease. A comprehensive assessment was conducted on a cumulative count exceeding 60,000 extracts in order to evaluate their efficacy against lymphoblastic cells that were infected with HIV-1. The identification of the significant category of organic compounds referred to as calanolides was predicated upon this methodology. As a result, calanolides such as calanolide A (12) and calanolide B (13) from *Calonphyllum* species, as well as prostratin (14) (Fig. 3) from *H. nutans* lead to clinical and preclinical development as an alternative therapeutic agent for HIV-1 [53-55].



**Figure 3:** Structures 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 obtained a license and approval for the use of Calanolide A in Phase II clinical trials. However, the company did not proceed with further medicinal research of the compound. In 2010, the AIDS Research Alliance in Los Angeles, California conducted the first human testing of prostratin. Artemisinin (**15**), also known as Artemisin, was derived from the plant species *A. annua* and subsequently used as a pharmaceutical agent for the treatment of malaria [56]. Arteether was introduced in 2000 as Artemotil, a derivative of artemisinin (**16**) which was isolated from *A. annua* (**Fig. 4**). *A. annua* has historically been used in traditional Chinese medicine for the treatment of fevers and chills. Other antimalarial drugs based on synthetic artemisinin analogs are in different stages of clinical trials in Europe [6, 33]. Piperaquine (synthetic bisquinoline drug), based on the 16 pharmacophores in conjunction with a synthetic trioxolane is now being explored in tandem to treat malaria [57].



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

Grandisine A (**17**) and Grandisine B (**18**) are indole alkaloids that have been extracted from the *E. grandis*. Grandisine A has a tetracyclic framework, whereas Grandisine B exhibits a structure that encompasses both isoquinuclidinone and indolizidine rings. Both of these alkaloids bind to the opioid receptor in humans and are potent analgesics [58]. Galantamine hydrobromide (**19**), an alkaloid from the Amaryllidaceae family obtained from *G. nivalis*, is extensively used in Turkey and Bulgaria for the management of neurological disorders, such as Parkinson's and Alzheimer's disease [59, 60]. Apomorphine (**20**) is a synthetic compound derived from morphine that exhibits agonistic activity towards dopamine D1 and D2 receptors, making it a valuable therapeutic agent for the management of Parkinson's disease. Tubocaurarine (**21**) is a pharmacologically active compound present in *C. tomentosum* (Menispermaceae) that is used as a muscle relaxant during surgical interventions, hence reducing the need for profound anesthesia. The presence of tubocaurarine in minimal quantities has prompted the advancement of several synthetic derivatives, which are presently preferred over their natural counterparts [33].



## V. CURRENT STATUS OF NATURAL PRODUCTS: DRUG DISCOVERY AND ANALYTICAL METHODS

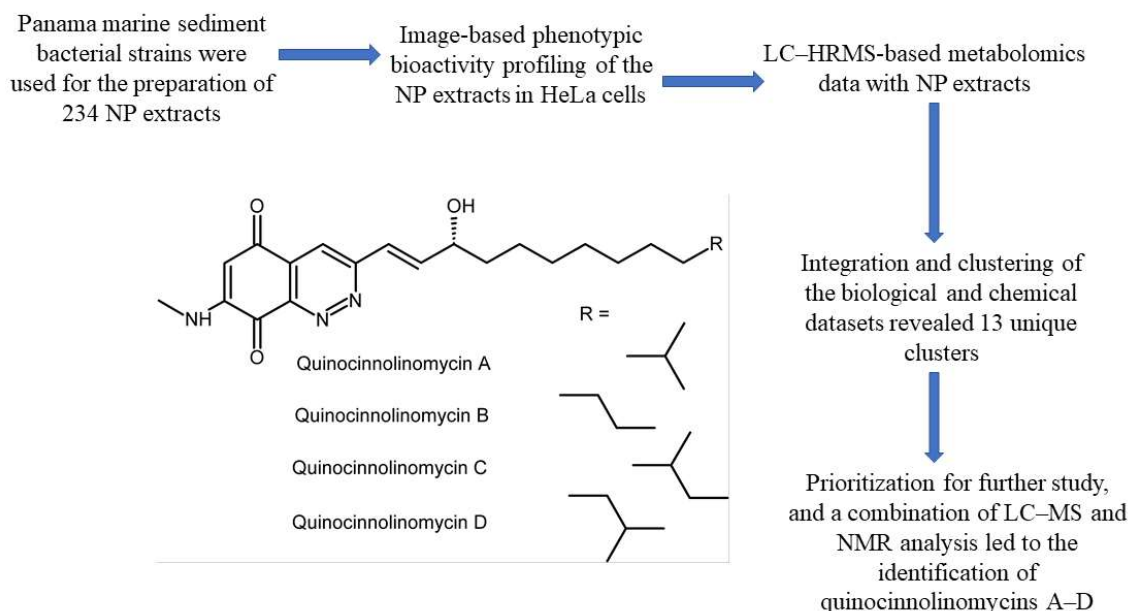
Conventional methods of drug research include the first screening of raw extracts to identify a biologically active chemical, which is then separated into fractions in order to isolate the active constituents. Many limitations are associated with bioactivity-guided isolation however, these can be solved using several techniques and technology. As an example, it is possible to partition raw extracts into distinct sub-fractions, which are better suited for automated liquid handling systems. This enables the construction of libraries that are compatible with high-throughput screening methods. In addition, it is possible to make adjustments to the fractionation protocols in order to guarantee that the resulting sub-fractions include molecules that possess drug-like properties. These approaches may be helpful to enhance the quantities/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 the field of drug development has shown to be very beneficial for researchers. It enables the identification of active compounds via the utilization of various analytical equipment and computational methods. These tools provide the generation of reliable analogs of NPs and their corresponding simulated spectra [62-64]. It is possible to use metabolomics to identify novel NP scaffolds and annotate unknown analogs and new metabolite compositions from crude extracts, all of which can aid in the separation of different NPs [65, 66]. Metabolomics may be used to identify alterations in metabolite compositions within certain physiological states of the organism responsible for their production. This approach can provide hypotheses to elucidate these changes and utilize metabolite profiles to facilitate molecular-level characterisation of phenotypes [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 (a gold standard) is often used in combination with LC in both qualitative and quantitative metabolite profiling [70]. HRMS may also be used in direct infusion mode (DIMS), a technique that permits the profiling of materials by mass spectrometry without the need for chromatography. Additionally, HRMS imaging (MSI) can be employed to determine the spatial distribution of nanoparticles (NPs) inside live plant cells [74, 75]. By using effective heuristic filtering techniques and utilizing the precise molecular mass data obtained from HRMS, it is potentially feasible to accurately determine the molecular formulas of several metabolites within a single sample, spanning a wide dynamic range exceeding five orders of magnitude [68, 76]. There are several challenges pertaining to data mining and the detection of secondary metabolites via the use of open web-based techniques [77].

Determining the molecular weight and the formula of secondary metabolites, as well as consulting the literature or structural NP databases with taxonomic data that significantly facilitates the identification process, are all steps in the process of dereplication. Private databases such as the Dictionary of Natural Products (DNP) provide comprehensive collections of NP structures, along by corresponding references to their respective biological origins. Nevertheless, the absence of a complete experimental tandem mass spectrometry database including all reported NPs to date, as well as the absence of standardized collision energy parameters for fragmentation in LC-MS/MS, poses challenges in conducting a thorough search for experimental spectra across different platforms [62]. The molecular networking platform developed in the Dorrestein laboratory represents a significant and important addition to the existing toolbox in this domain [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 modeling 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]. The GNPS molecular networking technique has several flaws, including non-specificity because certain classes of NPs exhibit superior performance than other extracts and ambiguity in structural assignment among potential anticipated candidates. To increase the credibility of annotation platforms, efforts are being made to address these challenges, for as by overlaying molecular networks derived from extensive natural product extract libraries with taxonomic information [82-85]. In general, molecular networking strengthens the process of eliminating duplicates and determining how NP analogs are connected, which aids scientists in prioritizing the isolation of undiscovered molecules. We shouldn't ignore the importance of elucidating the structures of relevant NPs.

Another useful tool for metabolite identification is METLIN. The high-resolution MS/MS database on this platform can be utilized to identify unidentified chemicals [86]. Identification of Compound Structures (CSI) The databases' fragment ion spectra may be searched using FingerID and Input-Output Kernel Regression (IOKR), as well as spectra that aren't in the databases can be predicted [87]. It has also been revealed that a new computer program can anticipate the structural identification of metabolites that result from any given drug, which should make finding NPs simpler [88]. The metabolomics data may be used to facilitate the identification of bioactive NPs inside extracts by comparing it with the biological activities shown by these extracts [89]. Many types of chemometric methods 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. The concurrent evaluation of bioactivity and identification of substances at a small scale (analytical level) and complicated chemical combinations may be accomplished by connecting several analytical modules [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 mapping

platform to forecast the component identities. Design and implement a mapping platform to forecast the component identities and processes of action. The researchers successfully discovered the quinocinnolinomycins as a novel group of natural products that induce endoplasmic reticulum stress [94, 95] (**Fig. 5**).



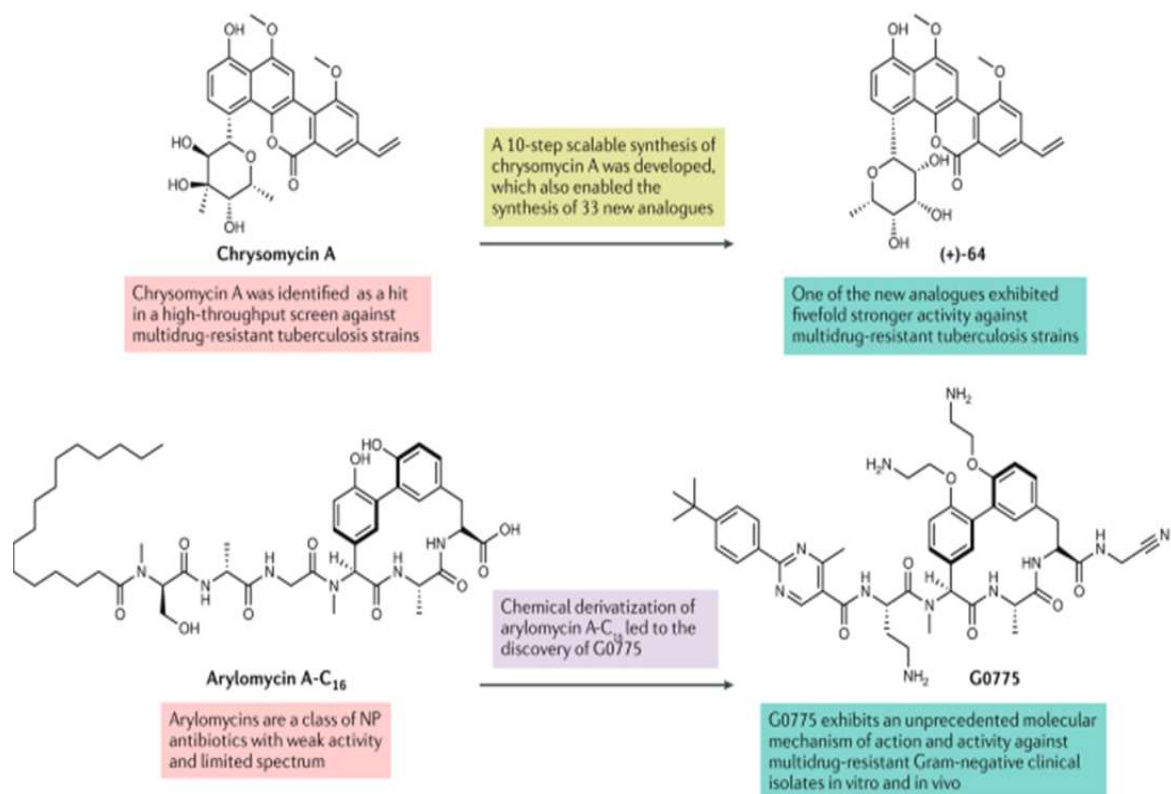
**Figure 5:** Modern Natural Product-Based Medication Discovery Using Improved Analytical Methods (LC-HRMS Profiling of NPs)

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 led to the discovery of new bioactive polyketides after evaluating bone marrow biopsy single-cell responses [96]. Because NP quantities are often limited (below 10  $\mu\text{g}$ ), higher-field NMR apparatus and probe technologies are needed [97-100]. Microcrystal electron diffraction (MicroED) is a cryo-electron microscopy-based method for the 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 [103, 104].

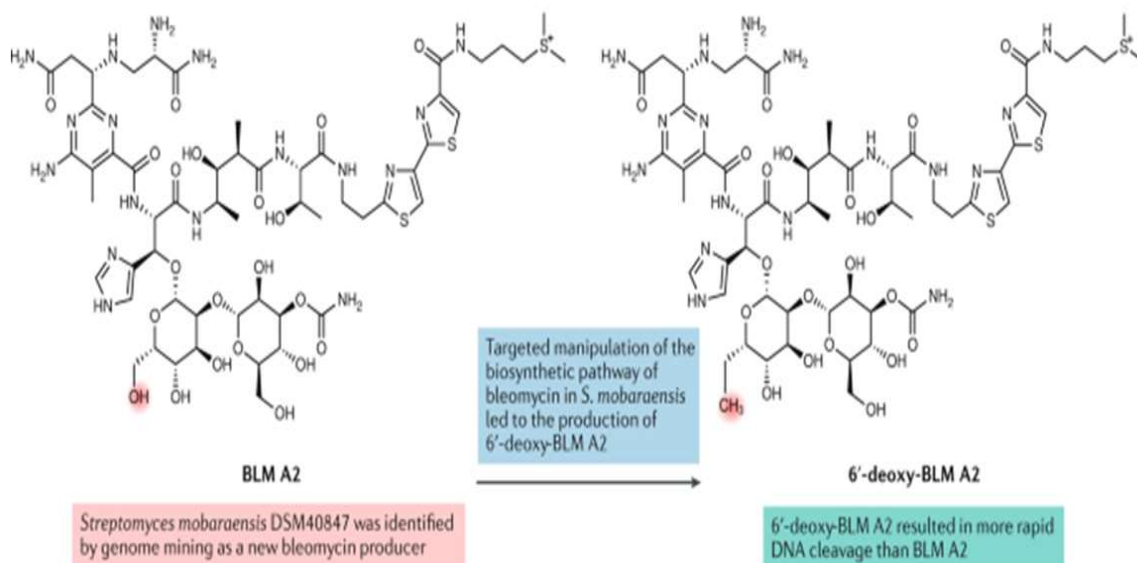
## VI. FUTURE OF NPS IN DRUG DEVELOPMENT

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]. Strategies to leverage the human microbiome for new NPs with antibacterial characteristics were discussed in previous sections (Fig. 5) [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. Given the current interest in methods that might raise immune checkpoint inhibitor response rates by making "cold" tumors "hot," this is a novel possibility in the field [119]. For instance, stress and dying cancer cells may produce damage-associated molecular patterns (DAMPs), which may increase their immunogenicity and open up new avenues for therapeutic development or repurposing [120-123]. The interest in botanical therapies utilizing complex mixtures of NPs has persisted due to the potential for synergistic therapeutic effects resulting from the combination of components in plant extracts [124, 125]. 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].



**Figure 6:** NP-Derived Antibiotics with Semisynthetic and Synthetic Derivatives



**Figure 7:** The Biosynthetic Engineering Approach for the Generation of Bleomycin

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]. The investigation of individual microbial species originating from microbiota for targeted medicinal purposes is a potential avenue of future study. The aforementioned progress in culture methodologies, genome exploration, and analytical approaches will play a crucial role in this endeavor. 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). Finally, it should be noted that NP-based drug development offers a distinct opportunity for academic-industry collaboration. However, a significant challenge arises from the fact that scientific and technological expertise is often distributed across several academic institutions and companies. 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. Several organizations, including the Austrian Drug Screening Institute, the Michael Popp Research Institute for New Phyto-Entities, Bionorica Research, and Biocrates Life Sciences AG have collaborated to establish Phytovalley Tirol, which is based in Innsbruck, Austria, and aims to accelerate NP-based drug discovery. The recently established International Natural Product Sciences Taskforce (INPST) provides a venue for the fusion of knowledge, tools, and resources from the collaborating academic and industrial groups. Natural products (NPs) remain a highly promising resource for the discovery of scaffolds exhibiting a diverse array of bioactivities and remarkable structural variability. These scaffolds may be directly used or serve as a foundation for the synthesis of novel pharmacological agents. High attrition rates

continue to limit medication development, but NPs also face difficulties with supply sustainability, accessibility, and other factors.

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 NPs have been identified, constituting approximately 40% of the whole pool of potential new therapeutic molecules. In contrast, the remaining 60% comprises several million synthesized molecules [135]. The productivity disparity may be elucidated by the observation that a limited quantity of molecules play a significant role in diverse life processes, and that nature has effectively selected molecules that impact certain metabolic activities in organisms [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. In cases when the mechanism of action of a chemical is not well understood, the production and investigation of carefully crafted derivatives of the primary molecule may be used to optimize the interaction between the medicine and its molecular target, resulting in the desired biological effect. Lead modification is a viable approach for altering the physical characteristics of a molecule, hence enabling its formation in certain desired forms, such as an oral dosage form.

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