

CELTIC ADVANCED LIFE SCIENCE
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Drug Discovery from Natural Products: Vision for the 2020s

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Drug Discovery from Natural Products research overview

Natural product drug discovery and traditional medicines are important fields of research which continue to attract research interest. The process of discovering natural products requires the identification of chemical agents from natural sources that are of therapeutic value. Our natural environment is endowed with a variety of plant species from which natural products can be sourced. Other sources also found in the marine environment, including bacteria, actinobacteria, cyanobacteria, fungi, microalgae, seaweeds, mangroves, and other halophytes, which constitute more than 90% of oceanic biomass [1]. The use of plants for medicinal purposes dates back to ancient Egypt where they were frequently used for the treatment of fevers, headaches, and other maladies. The early 19th century marked the beginning of scientific pharmacy, with the isolation of alkaloids and glycosides from poppy and pomegranates [2].

As knowledge advanced, other active substances were isolated from medicinal plants, such as tannins, saponosides, etheric oils, vitamins, hormones, etc.. In the late 19th and early 20th centuries, elimination of the use of medicinal plants in therapy was a worry because of concerns raised about the mode of processing, e.g. drying, which was believed to be destructive to certain enzymes responsible for therapeutic effects. Nevertheless, it was ascertained that certain active components were long lasting. In the early 20th century, stabilisation methods for fresh medicinal plants were proposed for plants with labile medicinal components. Furthermore, much effort was invested in the study of manufacturing and cultivation conditions of medicinal plants [3]. The introduction of new stabilisation methods led to previously abandoned plant materials being restored to medical use. Presently, about 50% of all drugs in modern therapeutic agents are derived from plant materials [4]. The interest and demand in medicinal products from natural origin has attracted renewed interest from researchers around the globe. This global interest has revolutionised the drug discovery process and has resulted in the development of new methods for discovery and use.

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Why is Drug Discovery from Natural Products important?

Humans are frequently exposed to conditions that become a threat to health. Diseases such as cancer, infectious diseases of bacterial, viral, fungal and parasitic origin, and cardiovascular diseases continue to be a threat to human health. For infectious diseases, natural products can be effective as they have shown activity against some pathogenic species. As good health is important to human life, to continually sustain health one must occasionally rely on these agents with therapeutic properties. For more than four decades, natural products have served an important role in combating cancers. Taxol and Vinblastine are potent anti-cancer drugs isolated from the plants *Taxus brevifolia* and *Catharanthus roseus*, respectively [5]. Thus, extracting natural products from such sources is important in drug discovery for the treatment of other forms of cancer. As a result, the technique to isolate such compounds becomes critical. When considering ayurvedic medicines, which are prepared from crude dried herbal powders or extracts from them [6], the crude nature of these extracts, when applied in therapy, could present many health complications. The reason being that such crude extracts may contain toxins that are poisonous to organs like the kidney.

Fortunately, technologies for drug development have progressed, resulting in more advanced methods which have contributed to the discovery of novel drugs. The advent of technologies such as quantum computing, profiling, and computational biology techniques, along with the use of artificial intelligence, is enabling scientists to develop new approaches to extract therapeutic agents from terrestrial and marine sources while simultaneously studying their chemical and structural composition and biochemical and biological interactions with the body [7]. The study of chemical composition and modifications has led to the synthesis of semi-synthetic natural products.

The need to fight diseases with potent therapeutic agents highlights the importance of this field. This importance is accentuated when dealing with pathogens that are drug resistant, meaning that many current drugs are now less effective and must be replaced by new drugs with new mechanisms of action. The marine environment is known for its diversity and has yielded many chemically unique and biologically active compounds, including anticancer agents. Seaweeds are an example of marine life which are an important component of human diet, known to contain protein, iodine, vitamins, and minerals. Seaweeds also contain high amounts of polyphenols such as catechin, epicatechin, epigallocatechin gallate, and gallic acids, and are known for their chemopreventive and anti-inflammatory properties [8].

Application of Drug Discovery from Natural Products in the current climate

Natural products represent more than 50% of all therapeutic agents in clinical use in the world today, with higher plants contributing no less than 25% of this total. Additionally, about 60% of drugs approved for cancer treatment are also of natural origin [9]. Furthermore, there are semi-synthetic derivatives of natural products and synthetic compounds inspired by natural products, which are also used to treat animals and humans.

The current most effective antimalarial drug is derived from the sweet wormwood plant (*Artemisia annua*). This plant was used for the treatment of fevers in Chinese medicine as long ago as 340 CE; however, its active ingredient was only identified by Chinese scientists in 1971 [10]. It is currently available in a variety of formulations including dihydroartemisinin, artemether, and artesunate, all of which are used globally as effective antimalarial drugs.

3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA reductase) is a rate limiting enzyme in the cholesterol biosynthetic pathway [11]. Inhibiting this enzyme is an attractive target for reducing plasma cholesterol concentrations. In the search for a compound that could inhibit this enzyme, compactin was found to be very effective. Compactin was discovered from fermentation broth of the fungus *Penicillium citrinum*. The discovery of this natural compound led to the discovery of other anti-cholesterol agents such as simvastatin, lovastatin, pravastatin, and atorvastatin. Also, penicillin which is used for the treatment of various forms of bacterial infections, was obtained from a fungus of the same genus, *Penicillium notatum*.

Aspirin is known for its analgesic activity and was obtained from plants of the *Salix* (willow) and *Populus* (poplar, aspen, cottonwood) genera [12]. Plants belonging to the families Asteraceae and Fabaceae are known for their activity against herpes simplex virus (HSV) [13].

These are just a few examples from the long list of natural products that have impacted medicine and are used in therapy today.

Potential impacts of Drug Discovery from Natural Products in both academia & industry moving forward?

Unquestionably, our natural environment is a rich source of natural products from which we can isolate therapeutic agents. Searching the natural environment has led to an unprecedented growth in the numbers of natural products with diverse potential therapeutic properties discovered, thus impacting the growth of scientific knowledge. The knowledge base around plants, microorganisms and marine organisms with therapeutic agents has also increased significantly. This knowledge also extends to the biochemical and biological properties of these natural products. As knowledge in this field, and interest in discovering novel natural products continues to grow, technological tools to harness their potential are also advancing, impacting the manufacturing and pharmaceutical industries and economic activities. Through machine learning, we now understand that molecules can be extracted from whole extracts. This has been demonstrated in a study where a new chimeric macrolide, symplocolide A, was extracted from cyanobacterial extract mixture [14]. Thus, with the aid of computational tools, novel natural products can be discovered. To translate scientific knowledge into real world products, there must be collaboration between academia and the pharmaceutical industry. While these impacts are positive and progressive, some challenges remain. The lack of funding to support academic research may weaken this collaboration and affect the knowledge transfer process. Undoubtedly, humankind has benefited from natural products as a result of academic research and collaboration with the pharmaceutical industry. In the next decade, it is probable that pharmaceutical products sourced from nature will dominate over synthetic medicines. However, it is important to maintain collaboration between academia and industry to remove barriers that might stop this becoming a reality. Key factors such as standardising procedures for the extraction of natural products and documenting clinical trials must be addressed.

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Summary of thoughts and how is your institution working towards utilising this to drive innovation:

Through CALIN, Cardiff University's School of Pharmacy and Pharmaceutical Sciences, with support from the University's Pharmabees project, are working with Celtic Wellbeing, a company based in North Wales which is part of the Conwy based PharmaGroup, to develop a lipbalm based on natural products derived from honey and Welsh medicinal plants. Our ancestors had known for centuries that honey possesses medicinal properties which can be used to treat infections. Honey contains naturally derived compounds which stimulate the immune system, reduce blood pressure and act as potent antioxidants. Using antimicrobial Welsh honey and plant extracts identified from our research, we are developing a prototype lipbalm formulation which will be translated into a real-world product. Once the cosmetic has been launched, we will seek funding to support the development of a therapeutic version of the formulation with the ability to treat cold sores caused by the Herpes Simplex Virus.

This is by no means the only work of this kind being undertaken at Cardiff University. Research is ongoing into the isolation and characterisation of discrete biologically active molecules from large scale plant sources. One research group has been focussing on the design and synthesis of novel anti-cancer agents using lead compounds isolated from natural sources such as Welsh marine organisms. This research has identified anti-cancer and anti-bacterial activity from extracts of Welsh sponges. Another research group is exploiting the anti-microbial and anti-inflammatory properties of natural products with a focus on pomegranate (*Punica granatum*). A research group in the School of Biosciences is working with a Welsh company called Mikota, who have previously been involved in a CALIN project, to investigate haemocyanin extracted from the slipper limpet (*Crepidula fornicata*), an invasive species found around the Welsh coast. Haemocyanin - as well as being useful for retarding tumour growth in its own right - is also a protein adjuvant. That means it will bind itself to other medicines and make them easier for the body to detect.



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