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A REVIEW- HISTORICAL BACKGROUND OF NATURALLY PRODUCTS AND THEIR MEDICINAL APPLICATIONS

Ghulam Mohammad Jan,[1] Daljeet Singh Manhas[2]

[1]Department of Chemistry, Degree College Boys, Anantnag, Jammu &Kashmir (India).

[2]Department of Chemistry, Govt. College for Womens, Gandhi Nagar, Jammu (India).

Abstract:

This brief review aims to highlight historically significant bioactive marine and terrestrial natural products, their use in folklore and dereplication techniques to rapidly facilitate their discovery. Furthermore a discussion of how natural product chemistry has resulted in the identification of many drug candidates; the application of advanced hyphenated spectroscopic techniques to aid in their discovery, the future of natural product chemistry and finally adopting metabolomic profiling and dereplication approaches for the comprehensive study of natural product extracts will be discussed.

Keywords: *bioactive marine, metabolomics, dereplication.*

Address for Correspondence:

Ghulam Mohammad Jan,
Department of Chemistry,
Degree College Boys, Anantnag,
Jammu & Kashmir- 192211 (India).

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INTRODUCTION:

Natural products (secondary metabolites) have been the most successful source of potential drug leads [1,2,3,4,5]. However, their recent implementation in drug discovery and development efforts have somewhat demonstrated a decline in interest [6]. Nevertheless, natural products continue to provide unique structural diversity in comparison to standard combinatorial chemistry, which presents opportunities for discovering mainly novel low molecular weight lead compounds. Since less than 10% of the world's biodiversity has been evaluated for potential biological activity, many more useful natural lead compounds await discovery with the challenge being how to access this natural chemical diversity [7].

The Chinese Materia Medica (1100 B.C.) (Wu Shi Er Bing Fang, contains 52 prescriptions), Shennong Herbal (~100 B.C., 365 drugs) and the Tang Herbal (659 A.D., 850 drugs) are documented records of the uses of natural products [4]. The Greek physician, Dioscorides, (100 A.D.), recorded the collection, storage and the uses of medicinal herbs, whilst the Greek philosopher and natural scientist, Theophrastus (~300 B.C.) dealt with medicinal herbs. During the Dark and Middle Ages the monasteries in England, Ireland, France and Germany preserved this Western knowledge whilst the Arabs preserved the Greco-Roman knowledge and expanded the uses of their own resources, together with Chinese and Indian herbs unfamiliar to the Greco-Roman world [8]. It was the Arabs who were the first to privately own pharmacies (8th century) with Avicenna, a Persian pharmacist, physician, philosopher and poet, contributing much to the sciences of pharmacy and medicine through works such as the *Canon Medicinae* [9].

Some medicinal plant Derivatives

The plant, *Alhagi maurorum* Medik (Camels thorn) secretes a sweet, gummy material from the stems and leaves during hot days [10]. This gummy sap is called "*manna*" and consists mostly of melezitose, sucrose and invert sugar and it has been documented and claimed by the Ayurvedic people that the plant aids in the treatment of anorexia, constipation, dermatosis, epistaxis, fever, leprosy, and obesity [11]. It was also used by the Israelis who boiled the roots and drank the extract as it stopped bloody diarrhea. The Konkani people smoked the plant for the treatment of asthma, whilst the Romans used the plant for nasal polyps [12]. The plant *Ligusticum scoticum* Linnaeus found in Northern Europe and Eastern North America was eaten raw first thing in the morning and was believed to protect a person from daily infection; the root was a cure for flatulence [13-15], an aphrodisiac [16] and was used as a sedative in the Faeroe Islands [17-18]. *Atropa belladonna* Linnaeus (deadly nightshade) is found in central and Southern Europe, Western Asia, North Africa, North America and New Zealand. Its notoriously poisonous nature (three berries are sufficient to kill a child) firmly excluded it from the folk medicine compilation and seemed to have been accepted as dangerous to handle or to experiment with [19].

Medicinal Natural Products from Other Sources Used in Folklore

The fungus *Piptoporus betulinus*, which grows on birches was steamed to produce charcoal, valued as an antiseptic and disinfectant [20]. Strips of *P. betulinus* were cut and used for staunching bleeding and were also found to make very comfortable corn pads [21]. Another example is the fungus *Agaricus campestris* Linnaeux ex Fries (field mushroom) found in the northern and southern temperate zones and the Caribbean. *A. campestris*, had reportedly been stewed in milk to soothe cancer of the throat [22].

As early as the 17th–18th century, lichens had been used as dyes and were far more valued than oriental spices. To date there are no lichen derived drugs approved on the market but their applications in folklore has been well documented [23]. Lichens have been used as the raw materials for perfumes and cosmetics, medicine from the time of the early Chinese and Egyptian civilizations [24]. Well known examples include *Usnea dillenius* ex Adanson which was traditionally used for curing diseases of the scalp and is still sold in pharmacies as an ingredient in anti-dandruff shampoos and in Ireland to treat sore eyes [25]. The lichen *U. subfloridana* Stirton was mixed with tobacco and butter, boiled and then cooled and applied as a lotion [26]. *Parmelia omphalodes* (Linnaeus) Acharius, which is abundant in the British Isles, was used in brown dyes. In the highlands it was traditionally sprinkled on stockings at the start of a journey to prevent inflammation of the feet [27-28] and in Ireland it was used as a cure for bad sores under the chin as well as for burns and cuts [29].

By comparison, the marine environment has very few reported applications in traditional medicine. The red algae *Chondrus crispus* and *Mastocarpus stellatus* were sources of a beverage, which was popular as a folk cure for colds, sore throats, chest infections including tuberculosis. The alga was also boiled in milk or water and used for kidney trouble and burns [30-31]. Furthermore, three spoonfuls of

the juice of the red alga *Porphyra umbilicalis* (Linnaeus) Kützing, taken every morning followed by fasting for three weeks was found to be effective against cancers, in particular breast cancer. *P. umbilicalis* has also been described in the Aran Islands for easing indigestion. and was also boiled and given to cows to relieve their springtime constipation [32-33].

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Natural Products from Fungi

Macro and micro fungi have been part of human life for thousands of years. They were used as food (mushrooms), in preparation of alcoholic beverages (yeasts), medication in traditional medicine and for cultural purposes. Currently with the advances in microbiology, their uses have extended to enzymes, biological control, antibiotics and other pharmacologically active products.

Undoubtedly one of the most famous natural product discoveries derived from a fungus (microorganism) is that of penicillin (**7**) from the fungus, *Penicillium notatum* discovered by Fleming in 1929. A countercurrent extractive separation technique which produced **7** in high yields was required for the *in vivo* experimentation that ultimately saved countless lives and won Chain and Florey (together with Fleming) the 1945 Nobel prize in Physiology and Medicine (Figure 1) . This discovery led to the re-isolation and clinical studies by Chain, Florey and co-workers in the early 1940s and commercialization of synthetic penicillins, which ultimately revolutionized drug discovery research [36]

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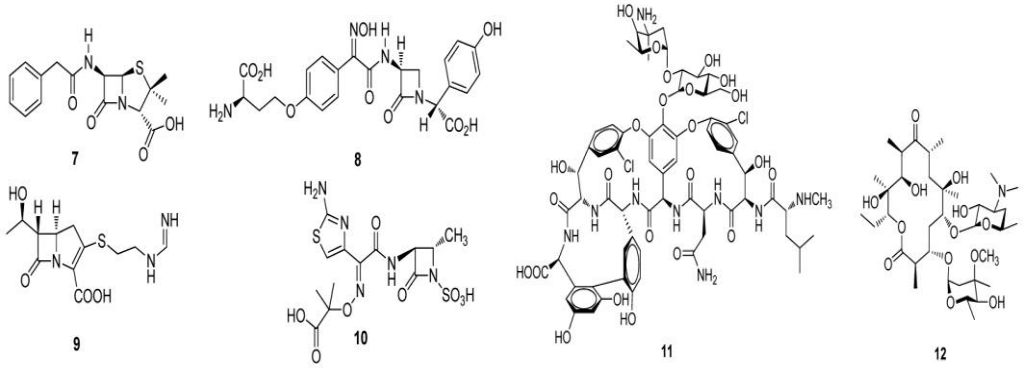
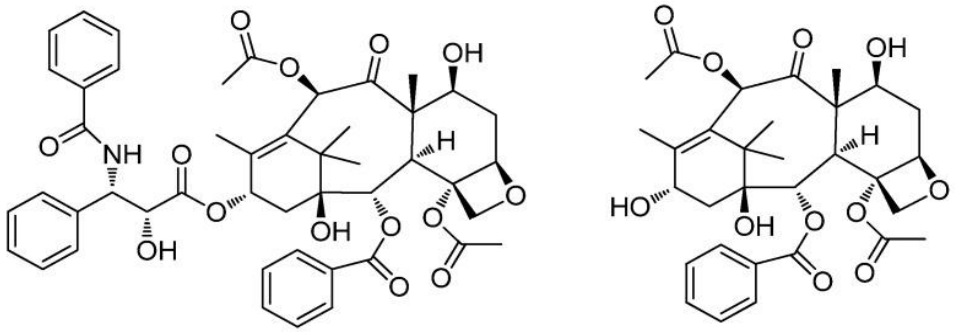


Natural Products from Plants

Plants have been well documented for their medicinal uses for thousands of years. They have evolved and adapted over millions of years to withstand bacteria, insects, fungi and weather to produce unique, structurally diverse secondary metabolites. Their ethnopharmacological properties have been used as a primary source of medicines for early drug discovery [37]. According to the World Health Organization (WHO), 80% of people still rely on plant-based traditional medicines for primary health care and 80% of 122 plant derived drugs were related to their original ethnopharmacological purpose. The knowledge associated with traditional medicine (complementary or alternative herbal products) has promoted further investigations of medicinal plants as potential medicines and has led to the isolation of many natural products that have become well known pharmaceuticals.

The most widely used breast cancer drug is paclitaxel (Taxol) (**19**), isolated from the bark of *Taxus brevifolia* (Pacific Yew). In 1962 the United States Department of Agriculture (USDA) first collected the bark as part of their exploratory plant screening program at the National Cancer Institute (NCI) [38]. The bark from about three mature 100 year old trees is required to provide 1 gram of **19** given that a course of treatment may need 2 grams of the drug. Current demand for **19** is in the region of 100–200 kg per annum (*i.e.*, 50,000 treatments/year) and is now produced synthetically. The first of several FDA approvals for various uses for Taxol® was announced in 1992. Taxol (**19**) is present in limited quantities from natural sources, its synthesis (though challenging and expensive) has been achieved, Baccatin III (**20**) present in much higher quantities and readily available from the needles of *T. brevifolia* and associated derivatives is an example of a structural analogue that can be efficiently transformed into **19** [40-43]



CONCLUSION:

Multi-parallel analysis using metabolomics technologies will also enhance and increase throughput of chemical characterization processes of many different species from natural resources. Secondly, as mentioned above, natural product chemists have collected a lifetime of compound libraries of active and also inactive pure compounds which can now be analyzed to construct mass spectral and NMR spectral libraries and therefore improve biological interpretations of metabolomics data. The advancements in analytical instrumentation and sophisticated hyphenation of separation techniques with high sensitive detectors have allowed for greater detection of small molecule compounds measurable in biological systems (*i.e.*, primary and secondary metabolites) and undoubtedly will now be used to advance the discovery of natural product chemistry to identify potential novel drugs candidates which will assist in sustaining health and the fight against disease and illness.

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