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Review

Natural products: A continuing source of novel drug leads ☆

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ABSTRACT

Background: Nature has been a source of medicinal products for millennia, with many useful drugs developed from plant sources. Following discovery of the penicillins, drug discovery from microbial sources occurred and diving techniques in the 1970s opened the seas. Combinatorial chemistry (late 1980s), shifted the focus of drug discovery efforts from Nature to the laboratory bench.
Scope of Review: This review traces natural products drug discovery, outlining important drugs from natural sources that revolutionized treatment of serious diseases. It is clear Nature will continue to be a major source of new structural leads, and effective drug development depends on multidisciplinary collaborations.
Major Conclusions: The explosion of genetic information led not only to novel screens, but the genetic techniques permitted the implementation of combinatorial biosynthetic technology and genome mining. The knowledge gained has allowed unknown molecules to be identified. These novel bioactive structures can be optimized by using combinatorial chemistry generating new drug candidates for many diseases.
General Significance: The advent of genetic techniques that permitted the isolation / expression of biosynthetic cassettes from microbes may well be the new frontier for natural products lead discovery. It is now apparent that biodiversity may be much greater in those organisms. The numbers of potential species involved in the microbial world are many orders of magnitude greater than those of plants and multi-celled animals. Coupling these numbers to the number of currently unexpressed biosynthetic clusters now identified (>10 per species) the potential of microbial diversity remains essentially untapped.

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1. Introduction

Throughout the ages humans have relied on Nature to cater for their basic needs, not the least of which are medicines for the treatment of a wide spectrum of diseases. Plants, in particular, have formed the basis of sophisticated traditional medicine systems, with the earliest records, dating from around 2600 BCE, documenting the uses of approximately 1000 plant-derived substances in Mesopotamia. These include oils of *Cedrus* species (cedar) and *Cupressus sempevirens* (cypress), *Glycyrrhiza glabra* (licorice), *Commiphora* species (myrrh), and *Papaver somniferum* (poppy juice), all of which are still used today for the treatment of ailments ranging from coughs and colds to parasitic infections and inflammation. Egyptian medicine dates from about 2900 BCE, but the best known record is the "Ebers Papyrus" dating from 1500 BCE, documenting over 700 drugs, mostly of plant origin [1]. The Chinese Materia Medica has been extensively documented over the centuries [2], with the first record dating from about 1100 BCE (Wu Shi Er Bing Fang, containing 52 prescriptions), followed by works such as the Shennong Herbal (~100 BCE; 365 drugs) and the Tang Herbal (659 CE; 850 drugs). Likewise, documentation of the Indian Ayurvedic system dates from before 1000 BCE (Charaka; Sushruta and Samhitas with 341 and 516 drugs respectively) [3,4].

The Greeks and Romans contributed substantially to the rational development of the use of herbal drugs in the ancient Western world. Dioscorides, a Greek physician (100 CE), accurately recorded the collection, storage, and use of medicinal herbs during his travels with Roman armies throughout the then "known world", whilst Galen (130–200 CE.), a practitioner and teacher of pharmacy and medicine in Rome, is well known for his complex prescriptions and formulae used in compounding drugs. The Arabs, however, preserved much of the Greco-Roman expertise during the Dark and Middle Ages (5th to 12th centuries), and expanded it to include the use of their own resources, together with Chinese and Indian herbs unknown to the Greco-Roman world. A comprehensive review of the history of medicine may be found on the website of the National Library of Medicine (NLM), United States National Institutes of Health (NIH), at www.nlm.nih.gov/hmd/medieval/arabic.html.

2. The Role of Traditional Medicine and Plants in Drug Discovery

Plant-based systems continue to play an essential role in healthcare, and their use by different cultures has been extensively documented [5,6]. The World Health Organization (WHO) estimated in 1985 that

☆ Note: This chapter reflects the opinions of the authors, not necessarily those of the US Government.

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approximately 65% of the population of the world predominately relied on plant-derived traditional medicines for their primary health care, while plant products also play an important, though more indirect role in the health care systems of the remaining population who mainly reside in developed countries [7]. A survey of plant-derived pure compounds used as drugs in countries hosting WHO-Traditional Medicine Centers indicated that, of 122 compounds identified, 80% were used for the same or related ethnomedical purposes and were derived from only 94 plant species [7]. Some relevant examples are khellin, from *Ammi visnaga* (L) Lamk., which led to the development of chromolyn (in the form of sodium chromoglycate) as a bronchodilator; galegine, from *Galega officinalis* L., which was the model for the synthesis of metformin and other bisguanidine-type antidiabetic drugs [8]; and papaverine from *Papaver somniferum* which formed the basis for verapamil used in the treatment of hypertension (Fig. 1) [8]. The latter plant is better known as being the source of painkillers such as morphine and codeine [9], but probably the best example of ethnomedicine's role in guiding drug discovery and development is that of the antimalarial drugs, particularly quinine and artemisinin.

Malaria remains one of the greatest health challenges confronting humankind, and the search for better drugs, both in terms of efficacy and cost, is a global health imperative. The isolation of the antimalarial drug, quinine (Fig. 2), from the bark of *Cinchona* species (e. g., *C. officinalis*), was reported in 1820 by the French pharmacists, Caventou and Pelletier [9]. The bark had long been used by indigenous groups in the Amazon region for the treatment of fevers, and was first introduced into Europe in the early 1600 s for the treatment of malaria. Quinine formed the basis for the synthesis of the commonly used antimalarial drugs, chloroquine and mefloquine which largely replaced quinine in the mid 20th century, but with the emergence of resistance to both these drugs in many tropical regions, another plant long used in the treatment of fevers in Traditional Chinese Medicine (TCM), *Artemisia annua* (Quinhaosu), gained prominence [10].

This discovery in 1971 by Chinese scientists using data from ancient texts in Traditional Chinese Medicine provided an exciting new natural product lead compound, now known as artemisinin, which was subsequently reported from US-sourced *Artemisia annua* by investigators at the Walter Reed Army Institute of Research (WRAIR) in 1984 in an article in the Journal of Natural Products [11]. A fuller description of the importance of this drug class was given by the lead author in the WRAIR report in 1985 in an article in the journal Science [12]. In 2011, recognition of the importance of the initial finding was demonstrated by award of the Lasker prize to Dr. Y. Tu for her leadership in what was then known as Project 523 [13].

Artemisinin analogues are now used for the treatment of malaria in many countries [14]. There is still debate as to its actual mechanism of action (MOA) which may involve complexation with hemin by coordination of the unusual endoperoxide bridge with iron, which in turn interrupts the detoxification process used by the parasite and generates free radical species which can attack proteins in the parasite [15]. Or as suggested the same year, it might involve mitochondrial attack [16]. Many analogues of artemisinin have been prepared in attempts to improve its activity and utility [14], and two of the more promising of these are the totally synthetic analogue OZ277 (Fig. 2) [17], and the dimeric analogue (Fig. 2). Single doses of the latter compound were shown to cure malaria-infected mice, while corresponding treatments with artemisinin were much less effective [18]. It is also relevant that artemisinin and related compounds also have significant anti-tumor activity *in vitro* but again, MOAs are not known.

Other significant drugs developed from traditional medicinal plants include: the antihypertensive agent, reserpine, isolated from *Rauwolfia serpentina* used in Ayurvedic medicine for the treatment

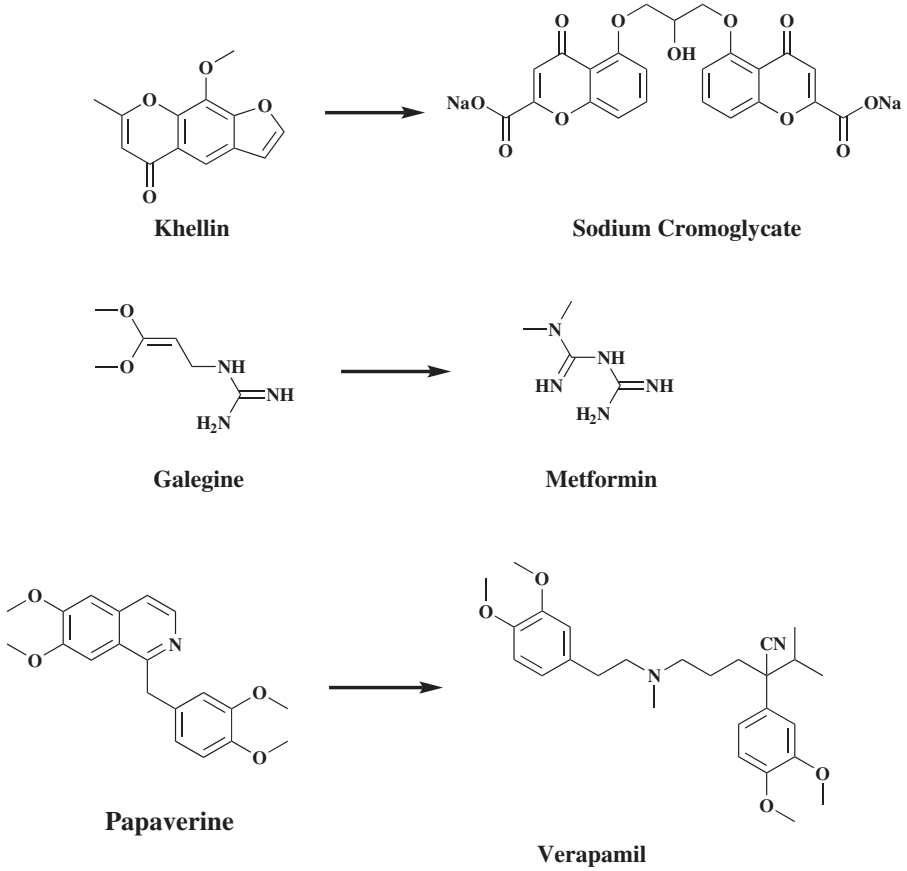

Fig. 1. Drugs based on traditional medicine leads. (khellin, sodium chromoglycate, galegine, metformin, papaverine, verapamil).