Fitoterapia 98 (2014) 36–44

Contents lists available at ScienceDirect

Fitoterapia

journal homepage: www.elsevier.com/locate/fitote

Review

The value of nature's natural product library for the discovery of New Chemical Entities: The discovery of ingenol mebutate

Steven M. Ogbourne [a,*], Peter G. Parsons [b]

[a] GeneCology Research Centre, Faculty of Science, Health, Engineering and Education, University of the Sunshine Coast, Maroochydore DC, QLD 4558, Australia
[b] QIMR Berghofer Medical Research Institute, Locked Bag 2000, Post Office Royal Brisbane Hospital, QLD 4029, Australia

ARTICLE INFO

Article history:
Received 12 May 2014
Accepted in revised form 3 July 2014
Available online 10 July 2014

Keywords:
Ingenol mebutate
PEP005
Euphorbia peplus
Cancer
Natural product
Drug discovery

ABSTRACT

In recent decades, 'Big Pharma' has invested billions of dollars into ingenious and innovative strategies designed to develop drugs using high throughput screening of small molecule libraries generated on the laboratory bench. Within the same time frame, screening of natural products by pharmaceutical companies has suffered an equally significant reduction. This is despite the fact that the complexity, functional diversity and druggability of nature's natural product library are considered by many to be superior to any library any team of scientists can prepare. It is therefore no coincidence that the number of New Chemical Entities reaching the market has also suffered a substantial decrease, leading to a productivity crisis within the pharmaceutical sector. In fact, the current dearth of New Chemical Entities reaching the market in recent decades might be a direct consequence of the strategic decision to move away from screening of natural products.

Nearly 700 novel drugs derived from natural product New Chemical Entities were approved between 1981 and 2010; more than 60% of all approved drugs over the same time. In this review, we use the example of ingenol mebutate, a natural product identified from *Euphorbia peplus* and later approved as a therapy for actinic keratosis, as why nature's natural product library remains the most valuable library for discovery of New Chemical Entities and of novel drug candidates.

Contents

Abbreviations: NCE, New Chemical Entity; FDA, Food and Drug Administration; PKC, protein kinase C; QIMR, Queensland Institute of Medical Research; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; IEC, intra-epithelial carcinoma; HPTLC, high performance thin layer chromatography; HPLC, high performance liquid chromatography; ADCC, antibody dependent cellular cytotoxicity; MS, mass spectrometry; NMR, nuclear magnetic resonance spectrometry.

* Corresponding author. Tel.: +61 7 54565188.
E-mail addresses: sogbourn@usc.edu.au (S.M. Ogbourne), Peter.Parsons@qimrberghofer.edu.au (P.G. Parsons).

http://dx.doi.org/10.1016/j.fitote.2014.07.002
0367-326X/

1. Introduction

During the past few decades, 'Big Pharma' has invested billions of dollars into ingenious and innovative strategies designed to develop drugs using high throughput screening of small molecule libraries generated through combinatorial and synthetic chemistry, whilst concurrently phasing out research into natural products [1–5]. Within the same time period, the number of New Chemical Entities (NCEs) reaching the market has suffered a gradual downward trend [6] to the point where the decline has been described as a "productivity crisis" [7].

These concomitant trends should come as no surprise, as it has long been recognised that natural products are the richest source of chemical diversity available [8] and without doubt represent the most successful and validated strategy of small molecule drug discovery [9]. Between 25% and 50% of approved drugs have their origins as natural products [5]. In fact, one analysis has calculated that in excess of 60% of the 1073 NCEs approved between 1981 and 2010 are natural products, derivatives of natural products, or synthetic analogues of natural products [6].

Powered by natural selection, nature has spent almost 3 billion years creating a near-perfect natural product library of small molecule ligands, targeted to specific macromolecules and their biological activities. The chemical complexity and functional diversity of nature's natural product library is vast and when combined with the fact that nature has essentially performed countless high throughput screens to remove inactive- and retain active-compounds, "natural combinatorial libraries" [6] will always be superior to any library that a team of pharmaceutical scientists can prepare [1,9]. Importantly, Feher and Schmidt [10] made the specific conclusion that natural products have better drug-like properties than a random sample of compounds prepared by combinatorial chemistry.

Morphine, isolated from opium in 1817 [11], was probably the first demonstration that the activity of a medicinal plant could be attributed to a single chemical constituent, but numerous examples of successful natural product derived drugs exist today. From 1981 to 2010, nearly 700 natural product or natural product derived NCEs were approved [6]. Paclitaxel (reviewed in [12]; reviewed in [13]), camptothecin (reviewed in [12]) and artemisinin (reviewed in [14]) are probably the most well-known examples.

The discovery, isolation and development of natural products as pharmaceutical drugs are exceptionally challenging, requiring a multi-disciplinary approach to unlock their potential. Consequently, there are numerous sound reasons why Big Pharma withdrew resources (with the potential exception of Novartis) from isolating and screening natural products while redirecting them toward the creation of vast chemical libraries and development of high throughput assays. Examples of these challenges include difficulty of isolating active constituents, inherent variability of source material, incompatibility of crude extracts with high throughput screening techniques, high numbers of false positives and false negatives, co-elution of compounds that interfere with bio-assays, availability of source material for drug manufacture and uncertainty of ownership of biomaterials posed by the 1992 Rio Convention on Biological Diversity (reviewed in [15,1,3,4,9,5]). Redirection of resources away from natural product screening is not necessarily the only reason for the recent reduction in approval of NCEs; with several reviews citing disruption to programs due to mergers and acquisitions, increasing costs of drug development, the conservative approach by the US Food and Drug Administration (FDA) to drug approvals, a reduction in research into infectious disease (a traditional area of strength for natural products), the advance of the genomics era driving focus to target-based rather than phenotypic-based screens and the emergence of biologics offering additional explanations (reviewed in [16,17,9,18,5]).

Nature's natural product library is already highly enriched for drug candidates. However, by targeting organisms used in traditional medicine or folklore, or by following ecological cues, the likelihood of obtaining drug leads can be increased further. Analysis of bioactivity databases such as the National Cancer Institute's list of 'active plants' revealed that plants with recorded traditional use in medicine were 2–5 times more likely to generate 'active extracts' compared to plants without an ethnopharmacological record [19]. Similarly, a literature survey conducted by Fabricant & Farnsworth [15] identified that of 122 natural product small molecules used as drugs, 80% had ethnomedical origin.

The cases of exendin-4 and ingenol mebutate provide perfect examples of how using ecological cues or folklore use can lead to successful natural product drugs. The Gila monster (*Heloderma suspectun*) from the deserts of north-western Mexico and south-western United States is one of only two venomous lizard species in the world. It is a sedentary animal, spending months at a time in its burrow or in rocky shelters, before feasting on lizards, eggs, rodents and rabbits totalling as much as one-third its own body mass [20]. It was subsequently discovered that the physiological basis behind the ability of the Gila monster to endure extended periods of fasting was due to a 4.2 kDa salivary hormone named exendin-4 [21], which possessed gluco-regulatory activity similar to those of the mammalian glucagon-like peptide-1. The identified activities included the ability to amplify insulin secretion [22,23], slow gastric emptying [24], protect against β-cell apoptosis [25–33], promote β -cell proliferation [34–38] and inhibit inappropriately elevated glucagon secretion [39,40], activities which represent an attractive anti-diabetic drug-candidate (reviewed in [41,42]). Ultimately, a synthetic form of exendin-4, Exenatide was developed as Byetta and was approved by the FDA in 2005 for the control of type II diabetes for patients who respond poorly to oral diabetic agents [43]. *Euphorbia peplus* has a long history of folklore use for a variety of conditions, including topical self-treatment of skin cancers with *E. peplus* sap [44]. In a survey of home remedies for skin cancer, topical administration of *E. peplus* sap was unanimously considered by