Biomedicine & Pharmacotherapy 101 (2018) 929–937

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Review

New therapeutics from Nature: The odd case of the bacterial cytotoxic necrotizing factor 1

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ARTICLE INFO

Keywords:
Drug discovery
Bacterial products
Synaptic plasticity
Memory
Neurological disorders
Energy metabolism

ABSTRACT

Natural products may represent a rich source of new drugs. The enthusiasm toward this topic has recently been fueled by the 2015 Nobel Prize in Physiology or Medicine, awarded for the discovery of avermectin and artemisinin, natural products from *Bacteria* and *Plantae*, respectively, which have targeted one of the major global health issues, the parasitic diseases. Specifically, bacteria either living in the environment or colonizing our body may produce compounds of unexpected biomedical value with the potentiality to be employed as therapeutic drugs. In this review, the fascinating history of CNF1, a protein toxin produced by pathogenic strains of *Escherichia coli,* is divulged. Even if produced by bacteria responsible for a variety of diseases, CNF1 can behave as a promising benefactor to mankind. By modulating the Rho GTPases, this bacterial product plays a key role in organizing the actin cytoskeleton, enhancing synaptic plasticity and brain energy level, rescuing cognitive deficits, reducing glioma growth in experimental animals. These abilities strongly suggest the need to proceed with the studies on this odd drug in order to pave the way toward clinical trials.

1. Introduction

Historically, almost all medicinal preparations have been obtained from natural products (NPs) and then used as potential remedies against a plethora of diseases. Saying NPs, we refer to products from animals, plants, soil, water and microbial world whatever environment they belong to (Fig. 1). More recently, many of these NPs, in particular, secondary metabolites and compounds derived from NPs, have entered in clinical trials to become current drug candidates and have been the starting points for most of the anticancer and antimicrobial agents [3,4].

Actually, it is suggestive that the period from the 1950s to 1960s was called the 'Golden Age' of antibiotic discovery, also after the award of two Nobel Prizes [5]. In 1945, Fleming, Chain, and Florey were awarded for the discovery of penicillin, and in 1952 Waksman for the discovery of streptomycin, both derived from microbial products. This highlighted, once again, the importance of Nature as a source for the discovery of new drugs. A specific analysis of new drugs approved by the United States Food and Drug Administration (FDA) between 1981 and 2010 reported that 34% of those drugs based on small molecules were NPs or derived from NPs [3,6]. Despite this, starting from the late 20th century, many pharmaceutical companies have significantly reduced their researchers about drug discovery from NPs, too tough and challenging to face [5,7,8], and the interest in using NPs was principally confined to universities and research institutes [9–11].

De facto, the role of natural sources in providing exciting discoveries leading to new medicines has been finally recognized again: the 2015 Nobel Prize in Physiology or Medicine was divided, one half jointly to Campbell and Ōmura, for their findings concerning avermectin, a therapeutic agent against parasitic diseases caused by roundworm, and the other half to Tu, for her studies about the artemisinin, an innovative drug against malaria. The high impact of such international recognition is meaningful for several reasons [12–14]. Researchers in NPs have recognized a new pride for their efforts. Avermectin and artemisinin have targeted the parasitic diseases, one of the major plagues of mankind, that represent a huge barrier towards improving global health. Also, noteworthy is the fact that both these drugs have their origin in NPs, considering that the avermectin belongs to the kingdom of *Bacteria* and the artemisinin to the kingdom of *Plantae*. Therefore, thanks to Campbell, Ōmura, and Tu, therapies for those poorest patients affected by parasitic diseases have been completely revised and renovated. The global impact of these findings in moving forward eradication of infectious diseases [15] and the resulting benefits to mankind is of paramount importance [16,17]. It is also notable that avermectin is

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https://doi.org/10.1016/j.biopha.2018.02.140
Received 8 November 2017; Received in revised form 19 February 2018; Accepted 26 February 2018

Fig. 1. Discovery of new drugs from Nature. In this drawing, several ways to pick up from the natural world are depicted, showing researchers: (a) dealing with reptiles and scorpions from which beneficial venoms are gained; (b) gathering up sea water, that every year offers hundreds of new compounds from the metabolites of its organisms [1]; (c) collecting from plants, that are virtual source of most medicinal preparations; (d) searching for new microorganisms in the soil. Finally, the microbiologist in the middle (e) is wondering what kind of bacteria could live inside us, playing essential roles in health and disease [2]. Artwork by Maurizio Moretti.

today confirmed to be an enigmatic multifaceted drug that acts as antibacterial, antiviral and anti-cancer agent, even if its mechanism of action as antiparasitic drugs has still to be clearly defined [18,19]. At present time, recent studies are focusing on the promises that avermectin still bears, in particular as a complementary vector control tool against malaria [20–23] and as a remedy against a new range of diseases, including asthma, epilepsy and other neurological diseases, HIV infection, dengue, encephalitis, cancer [24].

In conclusion, during the last two centuries, new active molecules have been discovered from NPs and some of them are the basis for drugs still used today (Fig. 2). So, with the recent advances essential to understand NPs' world, we are hopefully entering a new 'Golden age' of NPs drug discovery [12].

2. A great help from an unlikely source: the bacterial world

2.1. Bacteria from the surrounding environments

Bacteria can be both a complication and a treasure. Since the dawn of time, bacterial infections have represented the first cause of death for humanity and pneumonia, tuberculosis, diarrhea, and diphtheria have played the role of dangerous killing agents for adults and children during the 19th century [35]. In the last years, however, bacteria have also represented a source of new drugs, thus contributing to improve the quality of people's life.

In this context, bacteria that reside in the interesting and complicated soil environment [36] represent a cornucopia of microorganisms living together, some of them potentially harmful or deadly to humankind, other potentially benefactors and other that have already changed the history of mankind. Besides antibiotics, microorganisms produce a number of biologically active substances such as – for example – plant growth factors, vitamins, alkaloids. One of the keys to finding new drugs derived from microorganisms is to have the belief that they can produce any desired substance [37].

Clostridium botulinum, a microorganism commonly found in soil and dust, can be defined 'Janus faced': one is the cause of life-threatening disease and the other one is used in clinical practice. Its story started in 1817 when its potential for the therapeutic use was recognized [38]. *C. botulinum* produces heat-resistant spores that, in absence of oxygen, germinate, grow and then excrete dangerous neurotoxins (BoNTs), one of the most lethal substances known. BoNTs can cause foodborne botulism and block nerve functions, causing respiratory and muscular paralysis, and have been also considered for many years as a potential bioterrorism weapon. Modern botulinum toxin treatment was pioneered in an effort to find a nonsurgical treatment for strabismus. In 1997 first experiments were performed with botulinum toxin type A to weaken skeletal muscle in monkeys [39] and in 1989 the FDA approved the use of BOTOX® for use in strabismus, blepharospasm, hemifacial spasm and other disorders in adult patients. Since then, different preparations have been used to treat disorders previously without cure [40], in particular, conditions associated with muscular disorders [41–43], headache [44] and trigeminal neuralgia [45], urinary tract disorders [46–48] and other diseases and conditions. BoNTs have also found a niche in the' therapy' for facial wrinkles [49,50].

Turning back in the past, another fundamental milestone in the delivery of new drugs from the natural world was the discovery of streptomycin, the first remedy active against tuberculosis, for which Waksman, a soil microbiologist, was awarded the Nobel Prize in 1952. Inspired by the exploitation of Fleming's discovery of the penicillin, he conducted his researches on the *Streptomyces*, the largest genus of actinobacteria, as members of the soil microbial community. His work was pivotal in the development of the post-penicillin antibiotics, considering that a few years later, in 1954, the FDA approved tetracycline for clinical use.

From soil bacteria, rapamycin, also known as sirolimus, comes as well produced by a strain of *Streptomyces hygroscopicus*. Rapamycin was isolated in 1972 [51], during a discovery program for novel antimicrobial agents from natural sources, from a soil sample collected in Rapa Nui, the indigenous name of Easter Island, which sits in the Pacific Ocean 2000 miles from anywhere. Approved by the FDA in 1999, rapamycin has exhibited various biological and pharmacological potent activities, reducing the amount of protein synthesis and promoting autophagy. Rapamycin has been also studied for its antitumor, neuroprotective and anti-aging activity [52].

2.2. Bacteria living inside us

Donia and Fischbach [53] ask an interesting question: 'the many known examples of microbe-host mutualisms in which the microbe synthesizes a metabolite important for the ecology of the pair raise an