

Expert Opinion

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Successful, but often unconventional: the continued and long-term contribution of natural products to healthcare

Lutz Mueller-Kuhr

AnalytiCon Discovery GmbH, Hermannswerder Haus 17, 14473 Potsdam, Germany

Natural products are generally accepted by most industrial drug research organisations, but despite their incredible sustained track record and contribution to the pharmaceutical industries' revenue streams, they are not fully appreciated. An improved integration of natural products into state-of-the-art drug research processes is only one of the options available. What changes must be made to improve the exploitation of nature's diversity and where might natural products play a dominant role?

Keywords: cosmeceuticals, dietary supplements, natural products, nutraceuticals

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1. Introduction

Depending on the definition, drugs derived from or inspired by natural products (NPs) account for ~ US\$200 billion in sales per year, amounting to almost 40% of the global therapeutic agent market [1]. A compilation of drugs approved over the past 25 years shows a remarkable and, perhaps, unexpected steadiness of NP contribution compared with the overall decline in productivity, which analysts generally complain about (Figure 1) [2].

Compare the estimated 170,000 NPs that have been isolated and published so far with the 22 million synthetic compounds generated. The 'annual revenue' per NP is US\$1 million compared with only US\$15,000 per synthetic substance (Figure 2). Why do the chief financial officers of the companies not push more for NPs? Do some of them not know that statins, which represent an annual turnover of US\$25 billion and include the first and fifth top selling drugs in 2005, are based on a compound isolated from penicillium?

The aforementioned data and conclusions are drawn from publicly reported numbers and estimates. Still, NPs are accepted more than appreciated in the drug research arena. The data might be superficial and unfair, as there is a vagueness in the definition of 'derived from or inspired by NPs', but they illustrate the ongoing success of a kind of 'Neanderthal chemistry' [1]. Most R&D divisions in the pharmaceutical industry do not take NPs seriously; perhaps the neglect of this promising, but often uncomfortable and tricky, source is a much higher risk for a pharmaceutical company than making more use of NPs in a different way.

2. The chemspace and biospace of different organisms: how close are the needs and the potential of plants and humans on a molecular level?

Nature produces wonderful structures (Figure 3) that are either:

- unbelievably active – botulinum toxin A (with an oral lethal dose of < 1 µg for humans)

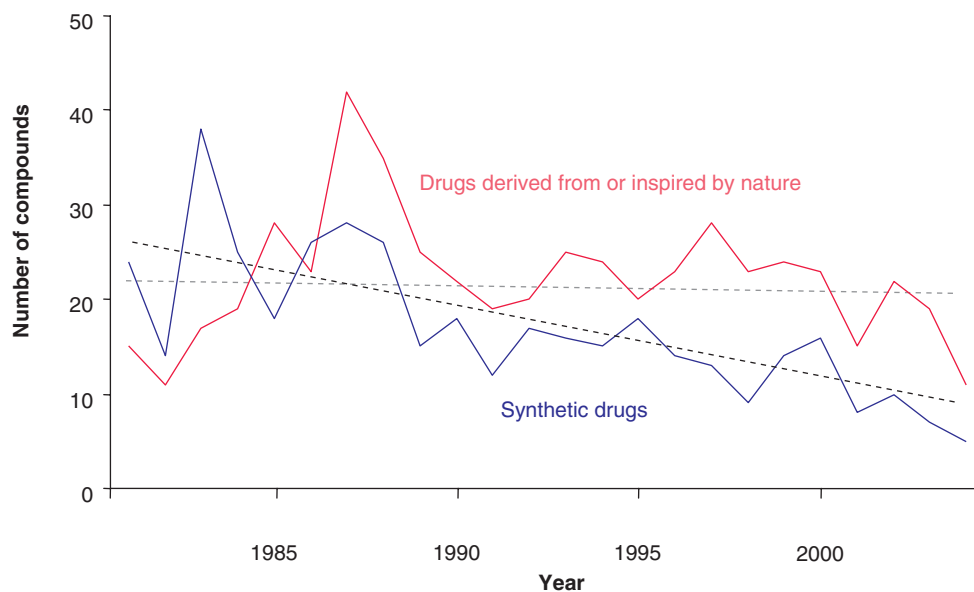


Figure 1. Approval of natural product-related drugs versus synthetic drugs from 1981 – 2004.

Data from [2].

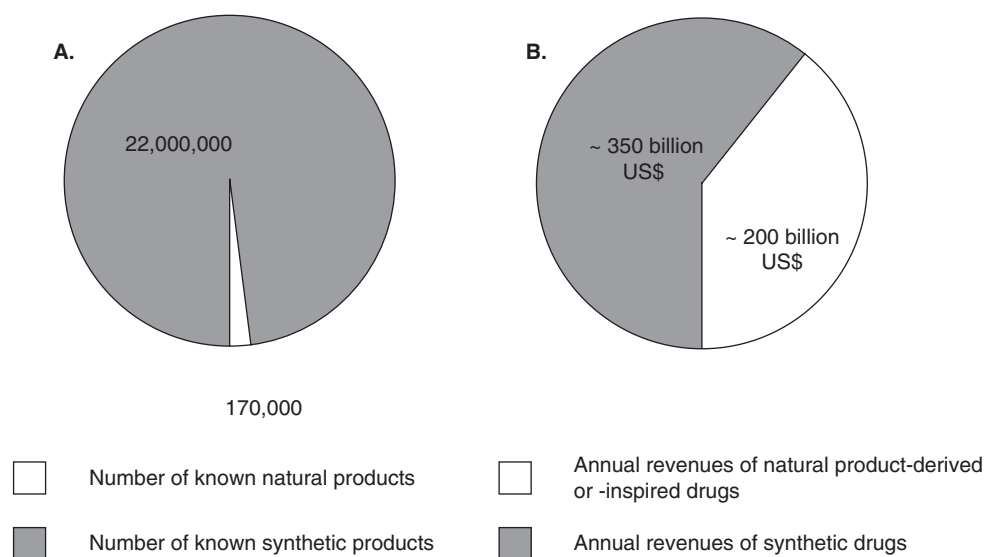


Figure 2. Natural products versus synthetic compounds. A. input versus B. output.

- just nice – endiandric acid C
- both the above – tetrodotoxin
- surprising – ladderane
- incredibly simple – toxin responsible for the Dogger Bank itch
- quite complex – vescalene, a potent topoisomerase II inhibitor produced during wine ageing from oak-barrel-derived castalagin
- incredibly complex – maitotoxin

and, often enough, powerful starting points for a career as a blockbuster drug.

Not every NP has been designed by nature to eventually become a compound that will cure a human disease. Nevertheless, increased attention has been turned to thoroughly analyze structural relationships between proteins of quite different biospheres. The common protein-fold topology of plant biosynthetic enzymes and several human protein kinases and as a logical consequence, the fact that the biosynthesized NPs

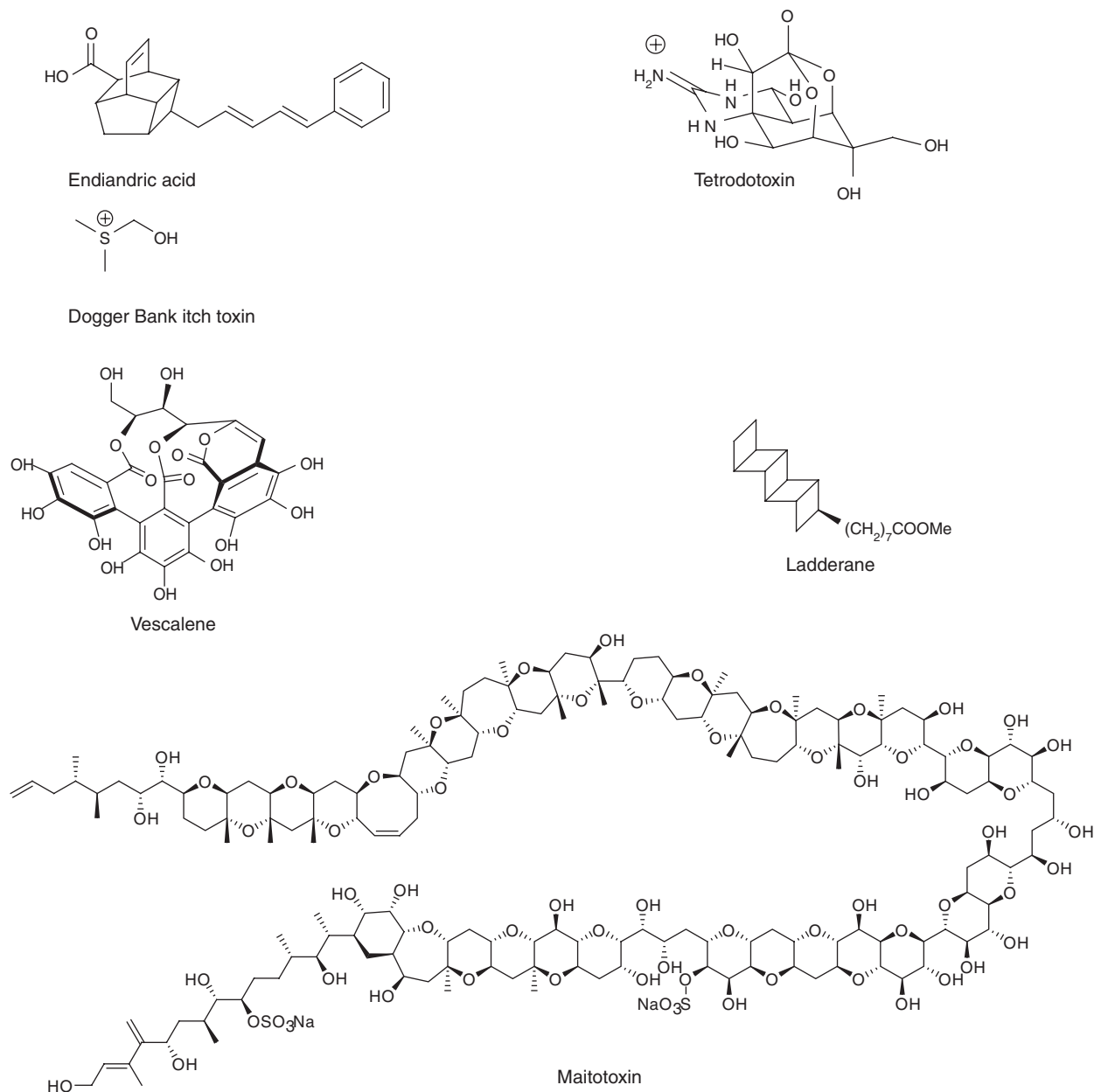


Figure 3. Illustration of nature's diversity.

inhibit exactly these targets [3], underlines how close the biospaces of apparently distantly related species are. Several further examples could be listed, among them the ability of human cells to produce a compound that was known for a long time only as an opium poppy metabolite: morphine [4].

The overlap between the chemspace that nature offers and the 'imprints of biospace' or chemspace expected by humans and animals has been considerably underestimated. The question seems to be less whether we should, but how we can optimize the standing of NPs in industry to give these

extraordinary resources a chance to support our efforts to find new therapeutic agents.

3. Key requirements to reintegrate natural products in pharmaceutical drug research

The search for and the development of a drug is one of the most complex challenges faced by mankind. Enormous progress has been made in our understanding of the human genome, new targets and their linkages in pathways and

networks. In spite of that, the process of understanding how the human body works, whether healthy, sick or anywhere in between, is still in its early stages. In 'orthodox medicine' molecular phenomena is focussed on almost exclusively, without being able to judge whether other presently excluded aspects might have a significant impact.

Accepting the fact that modern drug research can only be built on today's scientific level of understanding, resulting simplifications and rules need to be followed. These enable scientists to find their way through the jungle of non-selectivities and side effects, instabilities, bioavailabilities, metabolisations and so forth. These barriers and limitations are appreciated, as they allow us to take our minds off the precipice beyond and to only focus on our narrow and curvy road to find the hit, the lead, the candidate and the drug. It seems to be the only way to organize and control an extremely complex process involving dozens of disciplines.

NPs do not fit ideally into the present framework of rules, thresholds and operation charts of each and every therapeutic area or pharmaceutical company. Many successful drugs derived from NPs before the era of high-throughput technologies would not even have made it into today's average compound repository due to the usual organizational and economical restrictions. Lipinski's rules or a drug-likeness prediction are not referred to – these are typically not even the main barriers for an NP. The question is how to follow up a hit, how to come up with a validated lead or even a candidate within the workflow and timelines in which a specific project is embedded.

More important than compound characteristics are the following three key requirements a company needs to address for the best possible exploitation of NP potential.

3.1 The genuine willingness (acceptance is not enough) and commitment of senior management as part of their long-term strategy

The readiness to return to an internal or external NP center of excellence that manages discovery and preclinical projects for several therapeutic areas – not just antibiotics and cancer – in a company that stepped out 10 or 20 years ago is a decision that needs a much stronger senior management commitment than to venture into the next promising new topic in nanotechnology or some other more fashionable areas.

Several additional facts beyond the aforementioned might make this decision easier for them.

A lot of progress has been made within the last 10 – 15 years to make NP drug research more accessible and attractive. Highly sophisticated analytical instrumentation and software is used in the dereplication process to improve and accelerate the bioassay guided approach. A growing number of available pure NP collections and libraries synthesized in a parallel fashion based on NP-templates of proven relevance following the biology-oriented synthesis (BIOS) approach [5] increased the compatibility of NPs for a state-of-the-art drug research process.

Furthermore, senior decision makers have to consider that the complexity of a specific NP that might be a hurdle in the beginning enhances the chances for the development of second- and third-generation products, as the structures leave more room for postmarket optimization and differentiation. The statins are good examples and the number of paclitaxel derivatives and conjugates in clinical trials is still enormous. As a consequence, if an NP makes it into the clinical trial stage once, the number of competitors increases above the average. At present, at least four top companies are in different stages of clinical trials with epothilones and their synthetic derivatives. The motivation to develop competing candidates for an NP that has already reached the late preclinical or early clinical stage is obviously quite high. However, it is much harder to get the same passion for research or early preclinical NP projects.

3.2 Modification of the process

The most significant difficulty for scientists following NPs in an industrial discovery environment and even a preclinical project is the fact that decisions are almost never pending at the right time. The process starts with the compound acquisition. No biological activity can be proved at such an early stage, so why pay more for a NP? If a set of compounds makes it into a screening campaign and delivers attractive biological results, it is generally much harder to deliver a few grams of a NP compared with a five-step synthetic compound. It will be challenging to bring this up in a medchem meeting in which the compound has to compete with a synthetic drug of the same activity. A general lecture regarding the enormous track record of NPs will probably not be sufficient.

Two recommendations can be made: first, a confident advocate in the drug research division with a certain freedom to operate beyond the general rules is needed to fight for an NP. Second, although it is not intended to allow the NP to step outside of the decision-making process, a more competitive NP-focussed resolution process must be created with different timelines and clear, but different, milestones starting from hit confirmation. Instead, alternative decision trees that allow competition with synthetic candidates to be on a macro level, rather than each decision looked at in detail, must be allowed. Of course, there must be a clear and economical answer to the question: how to come up with 100 g of a compound for extensive preclinical studies? Of course a compound has to be produced later on at a reasonable cost and needs to be bioavailable and so forth. However, it should not be the sticking point whether the next 100 mg costs US\$100 (synthetic compound) versus US\$3000 or takes 2 instead of 8 weeks to produce.

3.3 Is a pharmaceutical company the right place for natural product drug research?

The history of the research and development of important NP-based marketed drugs was never straightforward, nor did it follow the general rules of today's industrial processes and project management principles. With NPs, the exception is

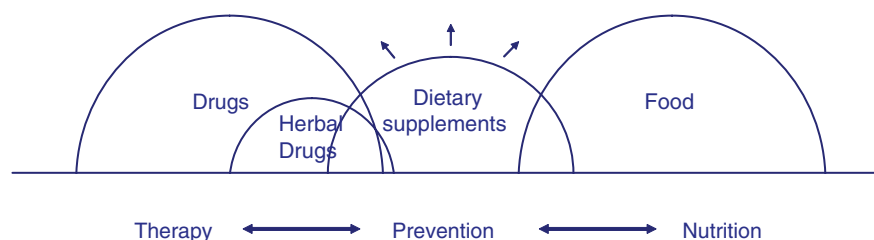


Figure 4. Filling the gap: the growing influence of dietary supplements on healthcare.

more often the rule. Often, an NP-derived drug has been identified in a different therapeutic area first, often as an antibiotic compound. Frequently, the initial discoveries and inventions were made in university laboratories or other non-industrial research institutions.

- Paclitaxel was identified and developed further in a more academic environment in the 1960s as a cytotoxic compound by NCI chemists Wani and Wall. Later, Susan Horwitz from the Albert Einstein College in New York contributed the discovery of the corresponding mode of action in the late 70s.
- The statin story also started at the Albert Einstein College, when Akira Endo came up with the idea to establish a fungi screening program to identify a compound that blocks HMG-CoA-reductase and finally found Sankyo as a supporting partner.
- There are examples of quasi-academic approaches to drug research in an industrial environment. The discovery of desmoteplase, a potent clot-busting substance, originally extracted from the saliva of vampire bats and presently in a Phase III study for stroke treatment, is an example. Biological observation by Schleuning followed by an 'academic-like persistence' within Schering, Germany, led to the development of a candidate that is now being developed by the biotech company Paion.
- A deeper insight into biological events generally seems a promising way to discover new strategies and compounds for the treatment of diseases, preferably in antibiotic and cancer research. Very often, efflux pumps, responsible for the elimination of extrinsic substances, put the potency of specific enzyme inhibitors and other agents into perspective. Finding inhibitors of these natural defense mechanisms will open new doors to reintroduce traditional antibiotics or anticancer drugs. Plants that are in a constant fight with bacteria and other microorganisms have developed interesting mechanisms to defeat these bacterial efflux pumps. Piperine [6] turned out to be a phytochemical potentiator of ciprofloxacin against *Staphylococcus* and is just one of a growing number of examples.

It would be an exaggeration to say that NP-based drugs necessarily need to have their roots in academia. However, it is beneficial to allow a certain open atmosphere to investigate a molecule, to take the time to try unusual approaches, to follow interesting or unexpected biological observations reported in literature (often more as a phenomenon than as a completed discovery on a molecular level), to learn more about a compound – even if it failed to meet initial expectations – and lastly to link all this information together.

To fully exploit the potential of NPs, the strategy of 'hit hunting by screening campaigns' should be supplemented by these kinds of alternative approaches as part of an industrial drug research strategy. The pharmaceutical industry would be well advised to once again increase cooperation with university groups and life science companies that are often able to take more risks, or even to establish non-conformist in-house groups to follow promising results with a higher degree of stubbornness, which is surely needed for NPs.

4. Where natural products will play a preferred role: nutraceuticals and cosmeceuticals

NPs are in constant competition in the pharmaceutical field. However, there are areas where NPs have an even better perspective and a higher standing per se. An emerging sector in which this is clearly the case is the rapidly growing arena of dietary supplements and nutraceutical ingredients to improve 'beauty and health' by disease or symptom prevention.

The diagnosis and treatment of diseases has been the focus of the pharmaceutical industry in the past and still is at present. Prevention is an area between the pharmaceutical and food industry (Figure 4). To prevent, instead of treat, a disease is more the exception than the rule for a number of reasons. The search for a useful and evidence-based prophylactic agent is a tough job; a clinical trial seems to be impossible in several areas, such as cancer prevention. The development and marketing of a

prophylactic agent seems to be too far from the core business of any pharmaceutical company. Furthermore, hardly any prophylactic product will be available on prescription. These major reasons, as well as others, have kept the pharmaceutical industry outside this business opportunity until now, with only a few exceptions.

As pharmaceutical companies have hesitated to take advantage of this business opportunity, the food industry and its ingredient suppliers have entered into this market and presently sell a lot of supplements beyond the well-known vitamins and minerals. Although the quality of these products and the scientific evidence supporting them was, and often still is, unacceptably low, things have changed in the last few years. Authorities in the US, as well as in Europe, have established standards, whereas Japan has scientifically dominated the area for quite a while already. Companies have recruited people from the pharmaceutical industry to let them research at a high level, thus exploiting their pharmaceutical expertise.

Although the differentiation between a therapeutic and a prophylactic compound is often difficult and the claims of nutraceuticals are sometimes close to a drug, several differences are observed. Compounds that never really made it in a pharmaceutical environment, such as flavonoids and isoflavonoids, appear as of one of the preferred classes in the dietary supplement arena. For example, the (fermented) soy ingredient genistein is probably one of the most promiscuous binders, a substance no pharmaceutical compound acquisition manager likes to take in his repository. However, it is precisely this non-selective compound that is one of the most wanted compounds in prophylaxis. A product for the prevention of osteoporosis is already on the market and the compound is under investigation to serve as a cancer preventive in several clinical trials. More 'fallen NP-angels' of pharmaceutical discovery will soon reach the market in lower doses as ingredients of functional food products.

Prophylaxis will gain increasing attention and NPs will play the central role in that economically and socially important space between pharmaceutical and food

products. NP-based prevention guarantees the highest available customer acceptance as they prefer compounds or extracts derived from what they always believed to be healthy: fruits and vegetables.

5. Expert opinion

An increased consideration and implementation of NPs in various ways will separate the winners from the also-rans. Generally speaking, there are two possibilities that both make sense, depending on the culture and history of a pharmaceutical company. One is to adapt NP-based research efforts to the existing process. Pure NP collections as well as semisynthetic compound libraries are the obviously easiest ways to incorporate nature's pool and to feed screening campaigns that need to produce immediate results. The second is accepting on the one hand the enormous potential NPs could contribute into an increasingly challenging world of drug research and development, and on the other hand the abnormality of ways in which many successful NP-based drugs have been discovered and developed. So it might be worthwhile to give NPs room for a more non-conformist concept to deliver. This might take place in a reorganized NP department of a pharmaceutical company, in specialized life science companies with expertise, rules and possibilities differing from those in the pharmaceutical industry or within long-term cooperation between the pharmaceutical company and a carefully selected small company or academic institution. These kinds of environments will often be better places to follow the needs of a successful NP-based drug research programme with significantly higher persistence and occasionally unorthodox methods.

Lastly, NPs are strongly advised to take over the lead in areas in which they have even more advantages. One of these is the area of prevention presently far too neglected by the pharmaceutical industry. In the arena of health and beauty products, the consumer is much more inclined to not only accept, but very much prefer, NP-based products.

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Affiliation

Lutz Mueller-Kuhr PhD

AnalytiCon Discovery GmbH, Hermannswerder

Haus 17, 14473 Potsdam, Germany

Tel: +49 0331 2300300; Fax: +49 0331 2300333;

E-mail: lmk@ac-discovery.com