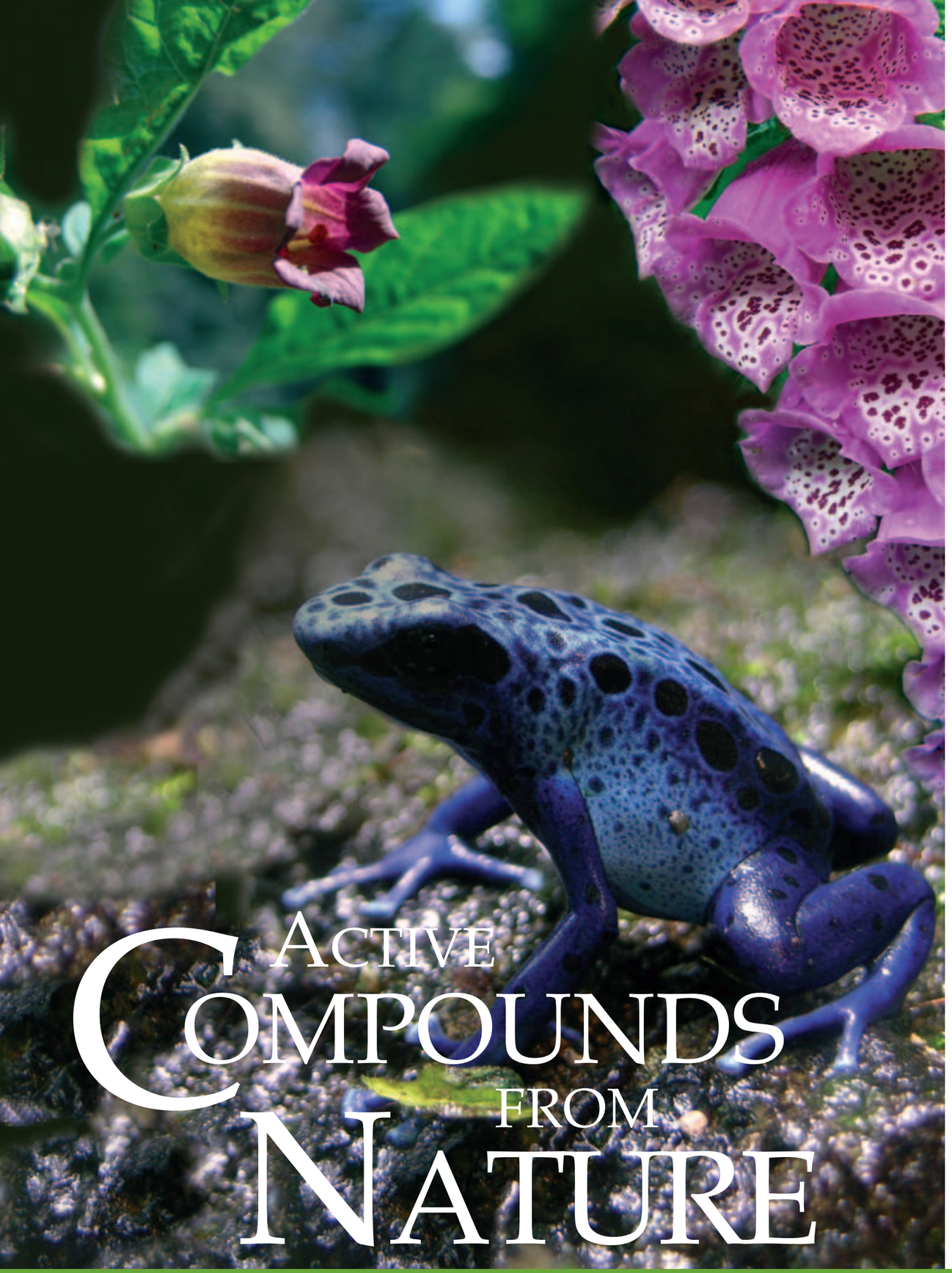


Active Compounds from Nature

Since thousands of years mankind uses active compounds from the pool of natural products for its own benefit. In the time of prehistoric days people have learned not only to distinguish between edible and toxic plants, but also to exploit toxins for their own advantage. Evidence exists, that already in the Stone Age deadly nightshade was extracted for the preparation of poison arrows. Even today the hunt with poison arrows is widely distributed and for example Indians in the Amazon know that not only plant extracts but also animals are rich sources of efficient toxins. They exploit highly potent frog toxins to paralyze their prey animals within seconds after contact with the toxin.

The medicinal benefit the medicinal benefit of plants is known for a long time even if our understanding of active compounds themselves developed only recently. Detailed records dating back till the 5th millennium BC document the usage of plants as source for pharmaceuticals. Some of these early reported active plant extracts are still popular in today's treatments of diseases! Especially ancient written records from China give detailed descriptions of the preparation and usage of plant- and animal derived cures.

An impressive example of the sound and clear documentation of active principles from plants is the "Papyrus Ebers" from 1.550 BC. This extensive Egyptian scroll was discovered 1873 in Luxor by Georg Ebers. It describes plant extracts as cure for diseases and gives detailed directions for their preparation and dosage. As an example, a detailed record of the action of heart active glycosides from digitalis can be found in this papyrus. Natural products are still indispensable in modern medicine. But not only the ancient Chinese and Egypt cultures knew of the force of natural products, also in Europe the knowledge of how to deal with plant toxins and medicinal herbs was widely distributed. But there, till the 18th century, the healing power of plant extracts was often associated with witcheries suitable to expel daemons of the disease.

Natural products were not always used as a cure. In 399 BC Sokrates, who was found guilty of corrupting the mind of the youth of Athens was sentenced to death by drinking a mixture containing poison hemlock. But the ancient Greek also knew of the beneficial aspects of plant derived medicines. We know that they used willow bark for the alleviation of pain and in the case of high fewer. They also recommended pregnant women in labor pain to chew on this bark.

Interestingly, Aspirin®, the most successful drug of all times is derived from the active ingredient of willow bark even if mankind had to wait till 1899 for its success as chemically pure substance to start.

Even today it is most remarkable to read how exact the benediction monks knew to dose the opium poppy ***Papaver somniferum***, which was used to relieve pain or for narcosis. Due to the inheriting variability of the contents of active compounds in plants it is always a challenge to base a therapy on extracts. Modern medicine often relies on the quantification of the ingredients using elaborated analytical techniques or on the pure active compounds themselves. It took several hundreds of years from the first usage and abuse of opium poppy until the

Alkaloids
A group of nitrogen containing natural products that is mainly found in plants. Alkaloids have often remarkable activities.

ASPIRIN – A STORY LEADING FROM NATURAL MEDICINE TO ANALYTICAL AND SYNTHETIC NATURAL PRODUCT CHEMISTRY

The bark of willow trees (***Salicis cortex***) was used over centuries as pain killer from natural medicine. In the 19th century a development started that illustrates how the empiric discipline of natural medicine developed to a science that systematically addresses properties of natural products. At this time scientists started to isolate the active ingredients from the bark and determined their structures as derivatives of salicylic acid. They also started to modify the natural products chemically thereby generating new compounds with altered properties. The first synthesis of salicylic acid was carried out by Hermann Kolbe, a German Professor for Chemistry. From this breakthrough it took only few years until the first industrial production started. The effectiveness of salicylic acid to fight fever was accepted but there were significant side effects that hampered the broad success of this drug. A lot of effort was thus undertaken to modify the structure of salicylic acid chemically which was not successful for a long time. The breakthrough was the made in October 1897 by the young scientist Felix Hoffmann in the laboratories of Bayer. He improved the synthesis of acetylsalicylic acid, a product which was already known in the literature. Since Bayer already lost interest in this compound class Hofmann had firstly to undertake self experiments in order to motivate further progress. These successful trials motivated Bayer to intensify the research on this compound which was already released in 1899 as Aspirin. Since then Aspirin developed to the most successful drug, and still today an immense amount of ca. 50.000 tons of Aspirin are sold worldwide. But despite more than one century of research the mode of action of this miraculous drug is not fully understood.

Detail of the Papyrus Ebers, an Aegyptian scroll from 1550 BC. It is exhibited in the university library in Leipzig Germany.

Fríedrich Wöhler (1800-1882) was one of the most influential German Chemists of his time. He is the founder of the discipline of natural product synthesis.

Bacteria
Microscopically small mostly unicellular organism that do not possess a true nucleus

Immune suppressive agents
Substances that can suppress the action of our immune system

The compound digitoxin can be isolated from Foxglove. It can be used for medicinal purposes to lower the heart rate.

active ingredient morphin was available as a pure substance. It was the German pharmacists Friedrich Seetürner who made Morphin (named after Morpheus the Greek good of sleep) available in 1806. It took another 20 years until the production of Morphin for the general use as drug was established by another German pharmacist Heinrich Emanuel Merck. He was the first to deliver Morphin with certified purity thereby pioneering new standards for drugs. This also marks the foundation for an internationally successful pharmaceutical enterprise. A similar lengthy history of development is known from Chitin, which is used until today in the treatment of Malaria. The bark of the Peruvian Cinchona-trees was first utilized in Europe in the 17th century to treat the fever but it took more than 200 years until Chitin, the active ingredient could be isolated and marketed.

Today we believe that the evolution of the molecular structures of active natural products can be seen as an answer to the numerous challenges an organism is confronted with in its natural environment. It took a long time until we could recognize the molecular diversity of natural products. With the ongoing development of analytical chemical methods at the beginning of the 19th century it was possible to determine the content and purity of natural products in extracts and also structural features came more and more accessible. After isolation and purification of active metabolites, the elucidation of their structure represented a major challenge, one that has not suffered any loss of timeliness. Still today natural product chemists find themselves confronted with the fascinating challenge to unraveling new structures generated by nature's creativity. Even with modern methods and elaborate instrumentation some structures still represent major problems. The complexity of the structures explains why the elucidation of natural products in the late 19th and early 20th century required decades of hard work and was not always devoid of errors. As an example one could refer again to Morphin, a complex alkaloid of which the structure was finally elucidated 120 years after its first preparation by Seetürner (see also "Sorbicillacton A", p. 36).

In the 19th century chemists undertook first efforts to build and modify active compounds found in nature in their laboratories. The starting signal for this new discipline in synthetic chemistry was given by Friedrich Wöhler in 1828. He synthesized urea from inorganic starting materials, a synthesis that was a landmark in the history of Science. It disproved and undermined the Vital Force Theory which was believed for centuries. Till Wöhler's work it was commonly accepted that all compounds found in nature comprise a vital force that cannot be created by men. By showing that organic compounds could be synthesized from inorganic materials Wöhler motivated numerous organic chemists to take on the challenge of synthesizing even complex natural products. This development led to the rapid success of organic synthetic methods and helped Europe's chemical industry to become a key player in the industrialization. Early industrial syntheses focused on cheap and non bleaching substitutes for natural pigments. But soon new applications were required to deal with waste- and side products of the pigment industry and to maximize profit of this young branch of the economy. It was nearly self-evident to search for novel pharmaceutically active compounds that could be generated synthetically. First efforts focused on the production of pain killers. Ludwig Knorr, a scholar of Emil Fischer, was the first to synthesize the synthetic drug Antipyrin in 1883. And only one year later this compound from the "Farbwerke Hoechst" was the first synthetic product on the market; despite the fact that its structure was still unknown. Knorr as would-be professor was mainly interested in academic merits and it was hard to convince him that a patent application should be filed before publication of his results (things have not changed a bit today). Since Knorr, who became Professor in Jena, was later generously funded by Hoechst he would not have regretted it in a second guess.

In 1888 Bayer, the most important competitor of Hoechst was able to release Phenacetin. This product was the first drug on the market where the discovery, the pharmacological verification of its activity, and production process was entirely done in one enterprise. This did not only set a standard for further developments in pharmaceutical industry but also was a hallmark and subsequently Bayer devoted itself to the development of numerous successful drugs.

Often the biggest success stories have a starting point that is marked by an accidental observation leading to further research efforts. These can then connect nature's chemistry with the technical production beneficial products. It was such a discovery by the British bacteriologists Alexander Fleming in 1928 that led to the development of antibiotics, one of the most important classes of drugs known in modern medicine. Flemming recognized that a colony of the mold fungus *Penicillium notatum* inhibited the growth of bacteria that cause live threatening infectious diseases. Instead of throwing away the molded bacteria cultures he started a consequent search for the active principle which led to the discovery of the first antibiotics penicillin. Penicillin allowed for the first time the treatment of heavy, often deadly berterial infections. In the 1940ies a high demand of antibiotic drugs by the wounded of the world war led to accelerated research effort towards new active compounds for clinical use. Demand for new drugs, their economic success, and the availability of novel concepts for the identification of active principles led subsequently to a revolution of the industrial pharmaceutical research. Today drugs like penicillin are produced in 100 m^3 bioreactors (fermenters) with optimized ***Penicillium*** strains giving yields of up to 80 g of the drug per liter of culture broth. Penicillin is the first natural product from microorganisms that was developed to a drug. Its discovery and success caused an intense search for novel antibacterial natural products from microorganism. This search is still going on today, mainly motivated by increasing resistance of pathogenic bacteria to the known drugs. But despite all problems associated with resistance the ***β-lactam*** antibiotics that all bear the central structure element of penicillins, are today among the drugs with the largest business volume (see "Infection – The Underestimated Danger", p. 24).

Microbial natural products have also gained importance as ***antimykotika*** to fend off fungal infections and as central ***antiproliferative*** agents in cancertherapy. A hypothesis developed that microorganisms living in complex communities e.g. in the soil produce such active compounds to inhibit growth of competitors. As a result it was overlooked for some time that microorganisms can also be a rich source for other active principles. Several compounds with new modes of action that might soon be developed to drugs have been found from ***actinomycetes*** and fungi that are masters in the synthesis of highly potent structural complex natural products.

Today we know of more than 120.000 natural products from plants. Despite the fact that this structural diversity exceeds that of products from microorganisms most natural

BIRTH OF A NEW SCIENTIFIC DISCIPLINE: NATURAL PRODUCTS SYNTHESIS

Wöhler wrote 1828 in a letter to Berzelius: „I can no longer, so to speak, hold my chemical water and must tell you that I can make urea without needing a kidney, whether of man or dog; the ammonium salt of cyanic acid is urea… Perhaps you can remember the experiments that I performed in those happy days when I was still working with you, when I found that whenever one tried to combine cyanic acid with ammonia a white crystalline solid appeared that behaved like neither cyanic acid nor ammonia… This artificial formation of Urea, can it be considered as an example for the formation of an organic compound from non organic matter?"

NATURAL PRODUCTS FROM FUNGI THAT SUPPRESS THE ACTIVITY OUR IMMUNE SYSTEM

Cyclosporin A was developed by the Swiss pharmaceutical company Sandoz as an antimycotic drug from a culture of a fungus. Further tests showed that the compound is also a potent immunosuppressive agent. Only seven years after this description – a rather short time considering the development of modern drugs – this compound was released as "Sandimmun®". It was the first commercial drug that could be used in organ transplantation enabling surgeons to suppress the immune reaction leading to tissue rejection without reducing the ability of the body to fend of microorganisms.This progess has its price: patients remain dependent on Sandimmun® for the rest of their lives.

Actinomycetes
Filamentous bacteria that form a mycelium which is similar to fungi. They represent a substantial proportion of the microorganisms in the soil and are a prolific source for novel natural products.

Antibiotics
Compounds that are capable to kill bacteria or to inhibit their further proliferation.

β-Lactam Antibiotics
Antibiotics with a characteristic structural element that can inhibit cell wall formation in certain bacteria.

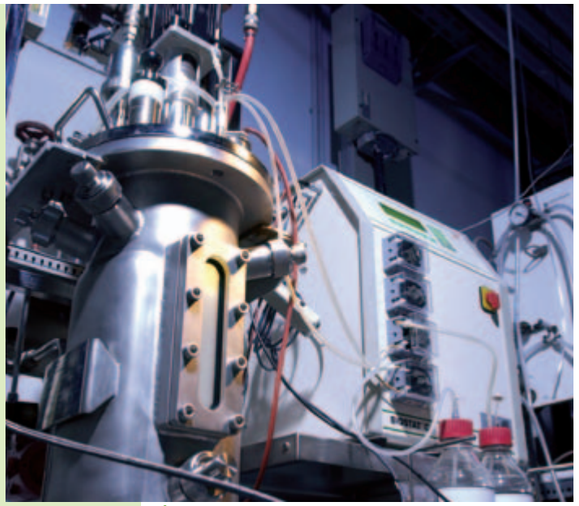
Microorganisms
Microscopically small organisms with independent metabolism.

Fungi
Fungi are so called Eukaryotes that have cells with nuclei and a cytoskeleton. Their proliferation occurs sexually through spores or asexually through the formation of so called myceles.

Secondary metabolites
Products from living cells that are not essential for the basic metabolic processes of an organism. Secondary metabolites often play essential roles in the ecological interactions of organisms with their environment.

Opium poppy contains more than 40 different alkaloids besides the well known morphine and codeine. Some of these compounds are used for medicinal purposes.

Fermenter

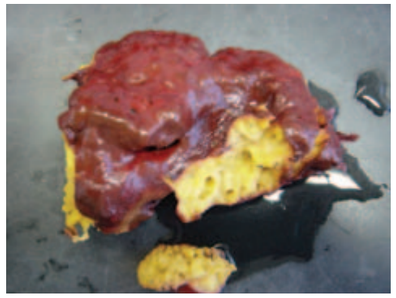


product based drugs developed in the mid 20th century were derived from microorganism-cultures. Plant extracts still had their place in modern medicine (see "Plant Extracts As Medicines?!", p. 14) but for a long time novel developments from plants were rare. This picture changed in 1987 when ***Artemisinin*** was introduced as a novel malaria treatment. This development was followed by the introduction of ***Taxol*** and ***Taxotere***, two drugs that are now indispensable in cancer therapy. These novel drugs were found in mugwort and the bark of the yew tree, respectively.

End of the 20th century novel natural products from marine resources became more and more a focus of natural products chemists. Marine organisms produce an impressively diverse amount of new structures and some of them are highly potent candidates for the development of novel pharmaceuticals. Thus it could be shown that ***sponges*** and other invertebrates from the sea produce structurally novel pharmaceutical products, but the access to high amounts of chemicals for pharmaceutical testing or drug development is often restricted due to the rareness of the producing organisms. Nevertheless, some marine natural products have already found their way into clinical products (see "Marine Life Science", p. 44).

The discovery of novel compounds is strongly supported by the development of modern methods in structure elucidation. While 120 years were required to unravel the Morphine structure, today only less than a milligram of a compound and a couple of months of work are sufficient to learn about the connection of the atoms making up new structures. In addition, natural product chemists have developed sophisticated methods for the synthesis of structural analogues of the natural products with improved pharmacological properties. In combination with elaborate facilities for biological testing the best candidates among thousands or millions of molecules for a further ***clinical development*** can be identified in little time. Novel developments also include drugs where only a part of the structure is a natural product that is further modified by synthetic methods in the lab of chemists. Such an example is Camptothecin, where chemical modification led to better solubility thereby increasing the biological activity (see "No Magic Cures From The Rainforest", p. 18).

Natural products are not only recognized for their pharmaceutical activity. Non prescription products, such as food additives or plant extracts with beneficial effects on human health are also an important market. More and more research effort is invested into the elucidation of beneficial properties of compounds or compound mixtures from plants, animals or even in food additives derived from microorganisms. The idea of functional food, namely groceries with beneficial properties, becomes more and more popular. With products like bread substituted with omega 3 fatty acids or margarine which is rich in phytosteroles the consumer shall be motivated to buy products reducing the risk of cardiovascular diseases. Also milk or cereals enriched with vitamin D can be found in the shelves of our supermarkets (see "Functional Food – Natural Substance Research For Healthy Eating", p. 90).



Sponges are rich sources for natural products with interesting activities.

ACARBOSE – A SUGER TO TREAT DIABETES

Another disease of civilization with dramatically rising incidences is diabetes mellitus. The natural product acarbose, which was isolated from cultures of an Actinomycete can be used to treat patients. Acarbose is a compound consisting of four sugar moieties that inhibits the digestion of carbohydrates in the gut and thereby reduces the glucose level in the blood.

But not only pharma and food benefit from novel developments of natural products research. Innovative solutions for plant protection can also be discovered during the search for novel activities of natural products. One success story is based Strobilurin A, a compound isolated from a higher fungus. This compound acted as a leitmotif for the synthesis of a novel generation of fungicides used in agriculture (see "Fungi – A Kingdom Of Their Own", p. 58). In contrast to older products Strobilurin A derived compounds are highly ecologically compatible and show no toxicity against mammals.

It is evident that natural product chemists have delivered numerous useful and innovative products, some of which form the basis of modern medicine and technology. But also general scientific progress has been driven by this discipline. This is, for example, illustrated by numerous Nobel prizes awarded to researchers of this discipline. One of the laureates is the US scientist Robert Burns Woodward, who received this award for this synthesis of Vitamin B12. It took his group of more than 100 scientists 15 years to synthesize this exceptionally complex molecule which can be considered as a hallmark of synthetic chemistry. During such work novel synthetic methods are developed that can be exploited in other scientific disciplines and might lead to new industrial applications.

All this progress now opens up new opportunities for researchers from chemistry and biology to investigate the function of natural products in their ecological context. While most of the research was motivated by the search for products that can be of use for mankind we still know comparably little about the actual function of natural products in nature. In the mid 20th century first progress was reported from the field of pheromone chemistry. It was Adolf Butenandt, another Nobel laureate, who succeeded to elucidate the structure of the compound released by female silkworms to attract their males for mating. With these studies he showed that living beings are capable to speak a language that is not based on sounds but on chemical compounds. The future in this discipline, that was termed chemical ecology, lies in the interdisciplinary work of chemists and biologists to unravel more than single chemical "words" and to learn the language of nature (see "Of Sirens And Venus Flytraps", p. 52).

Georg Pohnert and Susanne Grabley

FIGHT CHOLESTERIN WITH FUNGI

A series of structurally related natural products have been isolated from fungi. These compounds can inhibit the biosynthesis of cholesterin and can thus contribute to the lowering of the cholesterol level in the blood. The compounds, which are termed "statins" are marketed successfully. Not only the compounds from the fungi themselves but also synthetic compounds which are designed after the prototypic natural products are today marketed to lower blood lipid level and decrease the risk of coronary heart diseases.

Many filamentous fungi produce important drugs like, e.g. penicillin.

Artemisinin (also known as Qinghaosu)
A plant secondary metabolite that belongs to the so called sesquiterpenes. It is found in the leaves and flowers of *Artemisia annua* and can be used for the treatment of malaria tropica.

Camptothecin
Compound derived from the bark of the Chinese tree *Camptotheca acuminata* that exhibits cancer inhibiting properties.

Functional food
Groceries that serve not only as nutrition but also as shuttle for active products that are supposed to promote well being or health.

Clinical development
The process where an active compound that has proven to be effective in animal trials is developed as drug. During clinical development strongly monitored groups of patients are treated with the active compound and both its effect and its side effect is documented.

Omega-3-fatty acids
Fatty acids that have double bonds at certain positions. Humans cannot synthesize these essential fatty acids and have therefore to take them up with their nutrition.

Phytosterole
Steroids from plants

Sponges
Early developmental form of multicellular organisms. Sponges live exclusively in the water and are distributed worldwide in the marine environments. Only very few sponges can be found in freshwater.

Taxol and Taxotere
Compounds from the yew tree that can be used to inhibit the growth of tumors.