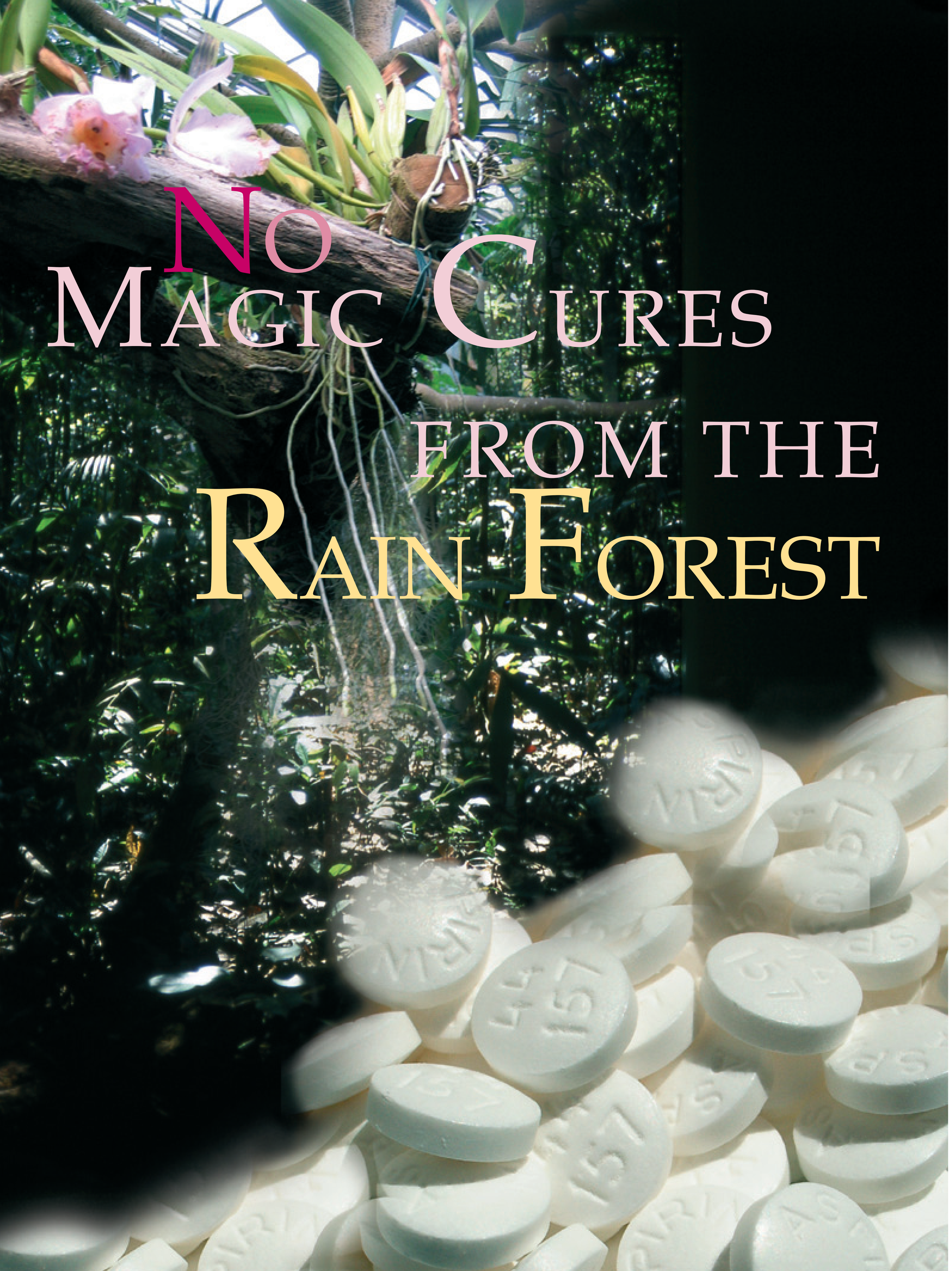
No Magic Cures from the Rain Forest



„What don't you understand? I found the cure for the fucking plague of the twentieth century and now I have lost it." exclaims Sean Connery alias Dr. Campbell in the 1992 film „Medicine man". Working in the most primitive conditions, in the middle of the jungle and in the searing heat of the tropical sun, and in a race against deforestation by bulldozers of international timber companies, the scientist had discovered the formula for a miraculous remedy for one of the most serious modern diseases, cancer – only to lose it again at the last minute.

The tropical rain forest, the largely unexplored oceans and other exotic environments are continually cited as potential sources of miraculous remedies for diseases that can be treated at best unsatisfactorily or not at all. In view of the enormous variety of life in these environments, the hopes are justified; the more varied the environments are, the more complex are the chemical signal systems with which the organisms communicate with each other or defend themselves from competitors or enemies. Because the signals must be not only transmitted but also received, these signal molecules show interesting pharmacological effects based on their abilities to bind to biological structures. It is nevertheless utopian to believe that these compounds, which are often complicated and present in extremely small quantities, can be routinely identified in a portable rainforest laboratory. However, precisely these problems make natural product chemistry so fascinating!

Why are plants, of all things, regarded as a source of important, pharmacologically relevant substances? Plants contain an extremely wide variety of unusual chemical structures; for the higher plants alone, more than 120 000 new natural products have been isolated and their chemical structures established. Our current understanding is that this variety is the result of evolutionary processes that have continued for millions of years. Plants have developed so-called **secondary metabolites**, e.g. to attract pollinating insects, but also to protect themselves; in contrast to animals, plants are literally rooted to the spot in their habitats and are thus reliant upon efficient defence and communication systems that are based, as for other **sessile** organisms, on chemical compounds – the secondary metabolites. The secondary metabolites have been optimised by evolution so that they – to stay with the example of defence mechanisms – induce a reaction in the animal to be repelled. In the simplest case, this consists of the recognition of a bitter taste; a much more devastating reaction may consist of effects on the nervous system or the circulation. Such effects are often the basis of many poisons whose consumption may be fatal. The **biological activity**, i.e. the induction of clearly defined reactions in an animal, also applies to humans. This is the reason that so many plant substances or derivatives thereof are successfully employed in medicine, when appropriately diluted.

Dried flowers in the laboratory.

When using plant natural products, it is important to distinguish between plant extracts and chemically pure compounds. The extraction of plant material leads to mixtures of the most varied substances. Chemically pure compounds, on the other hand, must be isolated from the extracts and prepared as single substances before they can be used in defined qiuantities as medicines. If their chemical structure is known and not too complex, chemical synthesis may provide an alternative to the extraction from plant material. Pure substances have the great advantage over extracts in that they can be dosed exactly. This is particularly important for compounds with a small **therapeutic index**. In these cases, the concentration that is necessary for successful therapy lies close to those higher concentrations that induce unwanted side-effects (see p. 16, many-component mix-

Secondary metabolites
Products of secondary metabolism; the organism can exist without these products as far as its fundamental metabolism is concerned, but due to their ecological importance they are essential for its long-term survival (e.g. flower colours, defence substances).

Sessile
Organisms are sessile if they cannot move from their habitat but are firmly rooted. This category includes all multi-cellular plants and corals.

Biological activity
A substance is regarded as biologically active if it interferes with the biological processes of an organism and thereby has a scientifically provable effect.

Therapeutic index
A measure of the safety of a medicament; it expresses the range between a therapeutically sensible and a toxic dose. The larger the index, the safer the use of the medicament.

Poisonous fly agaric.

Ethnomedicine
A branch of medical research concerned with the medical knowledge and practices of various cultures. Its goal is the preservation of this cultural inheritance and the planned utilisation of generations of experience.

Chemical lead
The structure of a natural product serves as a molecular template for deliberate structural modifications in order to provide new materials with similar properties. The goal is the improvement of the properties of substances that are to be used as medicines.

tures as pharmaca). Many plant materials in their pure form have become highly important medicines (see box).

EXAMPLES OF THE SUCCESSFUL USE OF PLANT-DERIVED SUBSTANCES IN THERAPY

- Glycosides such as digoxin and digitoxin (treatment of heart disease)
- Morphine (painkiller)
- Codeine (sedative)
- Paclitaxel (Taxol®; against cancer)
- Camptothecin (against cancer)
- Artemisinine (against malaria)

The quote from Sean Connery's film is certainly not realistic, as films are subject to different rules from the often tedious search for new drugs and the mechanisms of cures. How, then, should one imagine such a discovery of a "wonder cure from the rainforest" and its development to a broadly usable medicine? Any generalisation cannot even remotely do justice to the extensive spectrum of planned and accidental routes that are now known, but some fundamental steps can be established (see Scheme, p. 22).

The probability that the investigation of a random sample of plant materials, from the rainforest or other botanical sources, will lead to really interesting drugs is relatively small. It is therefore necessary to scrutinise a large number of samples, which in turn necessitates the use of elaborate technology. Because of efficiently automated methods in the laboratories of the pharmacological industry, an effectively unlimited number of samples can be investigated, but the process is still time-consuming. In the past, it was a common strategy to orientate onself, within the framework of **ethnomedicine**, to the traditions of native peoples and to utilise their experience in the use of plants against particular diseases. This knowledge of the healing properties of plants has been passed down over generations and serves as a basis for the purposeful tracing of interesting and novel drugs.

Once one has found such a promising natural product, the next problem arises: the balance between desired effects and undesirable side-effects may be so unfavourable that the material itself cannot be used as a medicine. There is however a possible solution; one uses the compound as a so-called **chemical lead**. Chemists then modify the structure to produce various derivatives of the non-optimised natural product in the hope of obtaining a compound that optimises the positive aspects while minimising the side-effects.

A further restriction of the clinical development of a natural plant product may be its availability in sufficient quantities; either the extraction yields are too low or there is not enough material for extraction. This is the case for rare or threatened species that cannot be cultivated, grow very slowly or need extreme habitats. If it is impossible to find the same substance in a cultivatable plant, chemical synthesis ***de novo*** was usually the first alternative to be considered. Nowadays, a combination of chemical and enzymatic syntheses promises more rapid success. In the more distant future, the methods of **metabolic engineering** may provide tailor-made drugs of plant origin by growing genetically modified plants or by using cultures of micro-organisms.

Primeval forest of the Pantanal, a tropical wetland in South America.

Expedition to the primeval forest on the banks of the Amazon.

EXAMPLES OF THE ELABORATE AND NON-STRAIGHTFORWARD DEVELOPMENT OF NATURAL PLANT PRODUCTS TO MEDICINES.

CAMPTOTHECIN (DERIVATIVE OF THE INDOLE ALKALOIDS)

In **1958**, extracts of the native Chinese tree ***Camptotheca acuminata*** (already used in Chinese traditional medicine TCM) were shown to possess anti-tumour activity.
Its structure was established in **1969**.
Clinical studies in the early **1970s** were disappointing; the attempted development to a usable medicine was halted.
Only in **1985** was the unique mechanism of camptothecin explained (inhibition of *topoisomerase I*); this discovery made possible the specific use of camptothecin as an anti-cancer agent.
Today, highly active derivatives of camptothecin, prepared via partial synthesis, are used against a variety of tumours.

PACLITAXEL (TAXOL®; A TAXANE ALKALOID)

In **1962**, bark samples of the Pacific yew (***Taxus brevifolia***) were collected, by chance, with other plant samples and screened for *biological activity*. The extract showed an effect on leukaemia cell lines.
In **1966**, the pure substance was isolated in extremely low yield (0.5 g from 12 kg of dried bark, corresponding to 0.004%).
Its structure was established in **1971**.
The unique mechanism of paclitaxel (stabilisation of the *microtubules*, inhibition of *mitosis*) was discovered in **1979**.
In **1985**, the compound was „partially synthesised" starting from related plant-derived compounds, in turn obtained from regenerating needles or related yew species.
The medicine was first licenced in **1992**.
Today, paclitaxel and its derivatives are used in the therapy of various carcinomas, including ovarian and breast cancer and bronchial and prostate carcinomas.

Metabolic engineering
The deliberate recombination of the genetic material of metabolic and regulatory proteins of an organism, with the goal of optimising the production of a particular material in that organism or of producing new substances with improved properties.

Clinical study
A test of the therapeutic ability of a drug on man. Clinical studies are subject to strict legal regulation.

Microtubules
Extremely thin tubes (diameter 25 nm) whose walls are composed of 13 protofilaments. These are in turn composed of adjacent tubulin units. During cell division, the microtubules form the spindle apparatus, which is responsible for the correct distribution of the chromosomes to the daughter cells.

Mitosis
Division of cell and nucleus, leading to genetically identical daughter cells.

Topoisomerase I
An enzyme that alters the topology of DNA molecules; it untwists the multiply-wound DNA superhelix.

BIODIVERSITY TREATY OF RIO DE JANEIRO

This agreement, signed in Rio de Janeiro on June 5, 1992, was ratified by Germany on August 30, 1993. Starting from the assumed sovereignty of a country over its own genetic resources, the agreement establishes the following goals: the preservation of biological diversity and its sustainable utilisation, the balanced and just distribution of any advantages thus accruing. This involves an appropriate financial reward, the corresponding technology transfer and the consideration of the rights to the resources.

Biodiversity treaty of Rio de Janeiro
see green box.

In vitro test systems
(*in vitro*, Latin literally „in glass“, hence „in the test-tube“). Investigative methods providing information on the effects of substances (e.g. natural products) on the metabolic processes or viability of cells grown in culture (i.e. outside the human or animal organism).

Target
Intended destination of an active substance (e.g. an enzyme, a receptor, DNA).

Thus, the isolation and identification of new drugs from plants and their subsequent development to medicines require close co-operation between biologists, chemists, pharmacists, pharmacologists and clinicians on the one hand and between academic and industrial research on the other hand. Such co-operations have already led to promising starting-points for novel research. The applied utilisation of genetic resources from the species-rich lands of the Third World is covered by the ***Biodiverstiy Treaty of Rio de Janeiro***. In this context especially, academic research needs competent partners who can provide a legally valid background for research and product development.

The dream of miracle cures from the rainforest does not have to remain a dream; however, for the foreseeable future, a simple portable rainforest laboratory will not suffice.

Dietrich Ober

The first step is the identification of plants or parts thereof that could contain interesting biologically active substances. To this end, extracts from the plant material are tested for biological activity. The extent to which new compounds can be identified depends on the test system and the *target* with which the active substance is intended to interact. A substantial number of extacts are collected to form an extract library and stored, so that they can be tested, when required, for biologically active components in various in vitro test systems.

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Next, the biologically active compounds are isolated and their structures determined.

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Thirdly, the compounds are tested with respect to their biological activity, selectivity, absorption, distribution within the organism, metabolism and excretion, and acute and chronic toxicity. Natural plant products often serve as chemical lead structures that are chemically modified and optimised to provide candidates for further development and eventual marketing.

Additional Literature

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Lorence A, Nessler CL: Camptothecin, over four decades of surprising findings (2004), Phytochemistry 65, 2735-2749

Links on the Web

Bundesverband der Arzneimittelhersteller e. V. mit Informationen u. a.
zu Pflanzlichen Arzneimitteln
www.bah-bonn.de

What other treasures remain hidden here? Nightfall in the tropical rainforest.