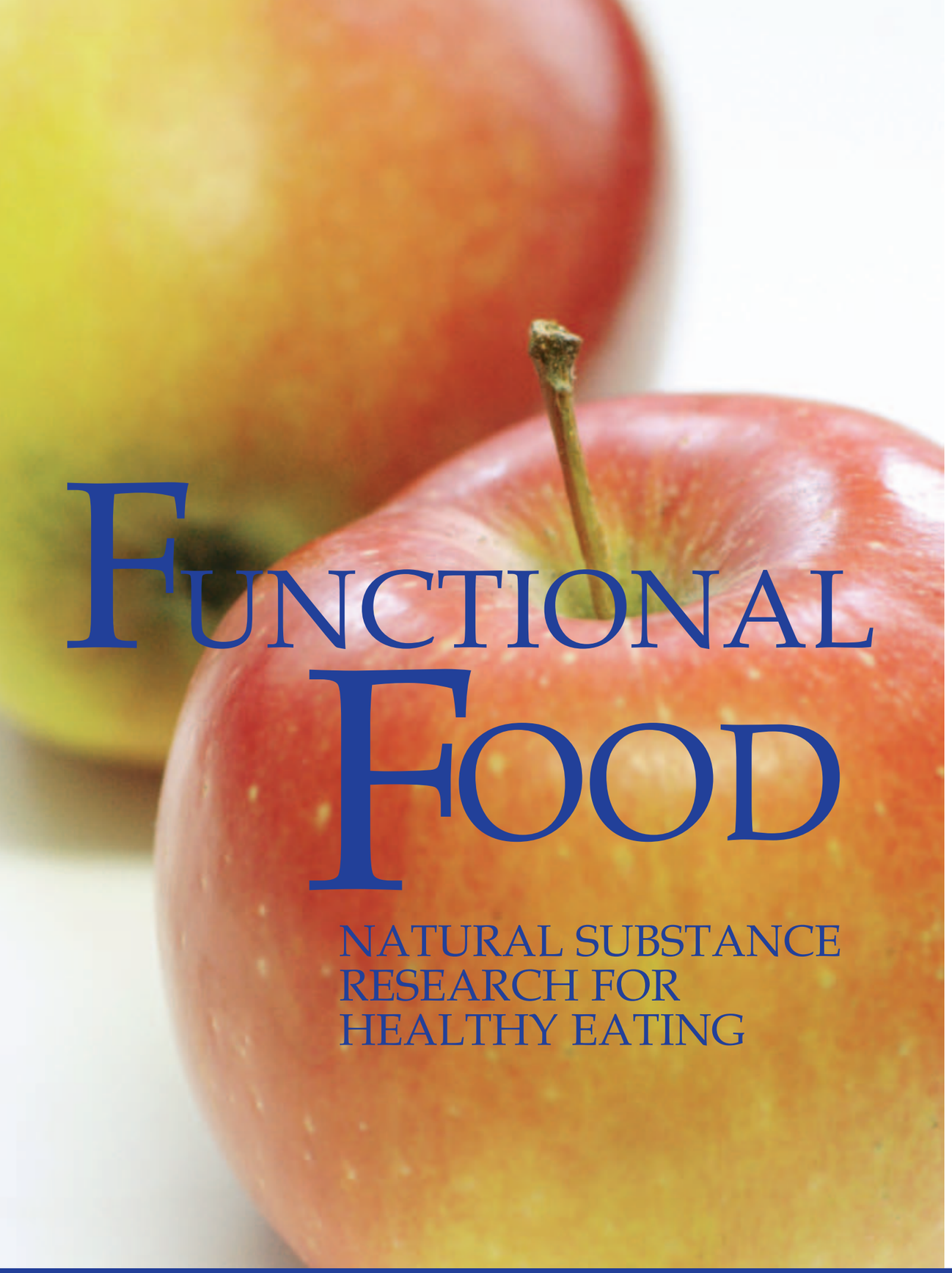


FUNCTIONAL FOOD

NATURAL SUBSTANCE RESEARCH FOR HEALTHY EATING

The media constantly remind us of what we should be taking into account at meal times to meet our daily requirements for energy, liquids, minerals and trace elements, and we learn how important a balanced supply of the essential amino acids, vitamins and fatty acids we need to survive is – all natural substances that we have been ingesting since time immemorial through cereals, fruit and vegetables, but also fish, meat and dairy products. What's more, all cultures of this world have their own recipes, handed down through the generations, for how to prepare herbs, spices and selected types of vegetables which enhance our wellbeing or provide relief in the event of infirmities and illnesses or accelerate healing processes.

With the ever more advanced possibilities of modern bioanalytical methods we are increasingly able to decipher the complex links between diet, health and wellbeing. We realise that beyond the well known natural substances such as caffeine in coffee, theanine in tea or capsaicin in chilli peppers, which take effect quickly and noticeably, there is a multitude of so-called secondary food constituents which as natural active substances have a long-term impact on our metabolism and therefore our wellbeing and health. From here, it is just a small step to engineering the composition of new foods to have functional properties – these ***functional foods*** have already been available on our supermarket shelves for a long time now and are designed to enhance our quality of life. At the moment, however, sound data is scarce and advertised statements and product propositions do not always live up to scientific criteria. Nonetheless – the door has been opened and the desire for food with an added benefit awakened, with the promise not just of health-promoting qualities but also the ability to respond specifically to the needs of individual groups of customers, such as athletes, pregnant women, elderly or stressed people or also consumers with increased risks of contracting certain illnesses. As a result, the food industry faces new challenges and possibilities to create visionary new markets. Natural product chemistry and the sciences around it will be a key enabler for this endeavour.

The range of foods on offer is constantly increasing. But what about the quality?

100 years of the food industry

It is the third time within the last 100 years that food industry has had to re-invent itself. At the start of the 20th century, the main challenge was to provide the population with calories, of constant and reliable quality and shelf life. After the Second World War, consumers began to call for "convenience" products. Customers wanted a broader range of products and to follow the trend towards international cuisine. Second, with changing lifestyles which prior to this had included set rituals such as eating meals together as a family, they also wanted to spend less and less time on the preparation of meals and for food to be available conveniently and "around the clock". This helped "snacking-and-grazing" make the breakthrough. At the same time, food prices sank in relation to people's incomes and in Germany in particular the market is still dominated by competition for the lowest prices today. Whilst this means more food is available for each individual, quality has been dragged into a downward spiral.

Consumers find themselves confronted with an excess of relative low-cost food products with a high energy density. Basically, there is a calorie everywhere and anytime "at arm's length". Resisting the food craving can often be hard. So it's hardly surprising that with the

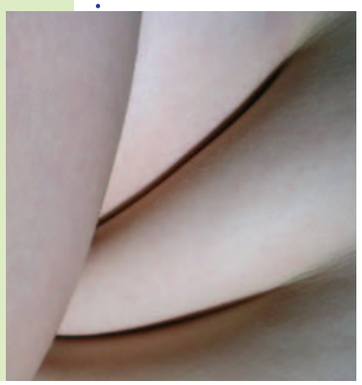
Functional Food
Food or parts thereof which as well as providing nutrition are said to provide additional benefits which improve wellbeing and keep us healthy.

WHO
(World Health Organization)
Founded on 17 April 1948, 192 Member States, a United Nations institution, HQ Geneva (Switzerland). The aim of the WHO is to attain an optimal state of health for all people including physical, emotional and social wellbeing.

increasing lack of exercise in large sections of the population many people's energy intake is no longer balanced and dietary diseases such as obesity, diabetes and atherosclerosis are on the rise worldwide. According to the *WHO* there are now over 300 million obese people who thus risk cardiovascular diseases. For the economy of the USA alone this means annual costs totalling around USD 117 billion.

The range of cheap foods with a high energy density is hard to escape nowadays.

These figures demonstrate quite clearly that due to the current consumer behaviour in the industrialized and emerging countries the food industry faces a special responsibility that goes far beyond mere food supply. With the global challenge of 1 billion people overweight – and the same amount undernourished – it has to preserve the health of consumers in the long-run. This includes a balanced diet with tasty products and a return to daily rituals as well as inhibiting the excessive intake of calories. Functional foods can play an important role in all of this. Four health areas deserve special attention: combating excess weight, improving people's cardiovascular condition, promoting intestinal health and improving people's mental and physical performance. Although one may assume these to be problems of the affluent societies that lead a "western" lifestyle, emerging countries such as China and India are facing similar problems. When ever people are leading a sedentary and less active lifestyle that comes with increasing economic wealth obesity, diabetes and vascular diseases are developing in parallel.



Obesity is becoming an increasingly big problem in the industrialized nations.

Healthy foods – the bar is set high

Foods with a functionality that preserves and promotes better health could easily induce the spontaneous illusion of the supermarket as your future pharmacy. This picture is entirely wrong, moreover will the strategies of the pharmaceutical industry not lead to better foods. However, it is true that both the pharmaceutical industry and the food industry hope to improve people's health with their products but there is a serious difference in perspective: drugs are for sick people who want to return to health by taking medication. Functional foods on the other hand are meant to be bought by consumers in their prime who are healthy and free of symptoms of illness. Again, the WHO leads the way here with their visionary definition from 1948 of health as more than just "not being ill": "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." With this in mind it becomes clear that a curative approach for functional foods misses the potential of this product group by far. And the second not less important fact is that the consumer will decide what to buy. The decision is made each and every time when standing in front of the supermarket shelf. The choice undoubtedly will fall on products that will taste good and will fit into the individual lifestyle and dietary context of that particular human being.

When it comes to marketing functional foods, lawmakers have set strict limits for good reasons. Adverts relating to illness are not permitted in order to protect the consumer from misleading statements. Health-related statements or "claims" have to be worded positively and need proper scientific foundations. Even more than regulatory bodies, the consumer self takes decisions not only on the basis of one single health parameter. It is within the "magic triangle" of health, convenience and taste, where decisions are made. Experience shows that the average consumer does not want to have to compromise on any one of these three requirements in favour of another. This, in order to meet the consumer expectation and even go beyond this to lead the market, the manufacturers have to change their perspective into a holistic one.

What consumers expect from a food manufacturer instead is a "modern" and internationally "inspired" cuisine without having to spend hours on food preparation; because it's important to them to have time for their family and social life and, on top of it all, be active and in good shape.

In contrast to the objectives and strategies of the pharmaceutical industry for developing new drugs, so far little is known in public of the concepts the global food corporations work to and what priorities they have set for cornering the regulated functional food market. Market analyses, the brand images of the products later launched and the financial investment required in the technical and scientific development of it play a crucial role. However, companies relying solely on market analysis often produce just the next generation of the same, and seldom a radical breakthrough with a new market potential. Second, the brand image needs to set the stage for the new product; it has to reflect its potential that – being a health proposition – will not become obvious and immediately perceivable to the consumer. And third, the financial implications in health related research seem sometimes prohibitive for a fast moving consumer good with in relation to pharmaceutical products a fraction of the margins.

Especially the research side is cost intensive with a long lead time: not only is it necessary to characterise the active components and their mechanisms of action pharmacologically and biochemically, the long term behaviours when consumed over a period of many years in a variety of doses also have to be investigated because the innocuousness expected of a foodstuff has to be proven beyond all doubt. With these high investments for naturally short-lived consumer goods, protection of the intellectual property and security in the regulatory world is becoming a prerequisite of every business plan. It is very understandable that a company is not willing to invest into studies that underpin general health claims for products that are easily copied or to generate the science from scratch only to help its competition to piggyback on the fruits of their work and investments.

How then will a new "lead" be generated? Epidemiological methods have been especially used in the past to obtain information on factors which promote disease such as environmental pollutants. They can however also be used, as a first step, in the search for active substances which promote health. The original proof of a biological effect can however still only be provided by intervention studies with a sufficient number of participants, a control with placebos and a sophisticated study design – a very time-consuming and costly process with an uncertain outcome. Depending on the results obtained during the study there may even arise ethical problems either from toxicity, but also in extreme cases from the finding that a substance is showing a marked effect in preventing a serious illness, if compared to the placebo group. In such cases, for example, if the intervention drastically reduces the risk of myocardial infarction in a long term study, the study would need to be discontinued, de-blinded and the placebo group to be subjected to the same intervention.

Added substances in foodstuffs can be used to deliberately produce specific positive effects, for example, by lowering cholesterol levels in the blood thanks to plant sterols.

It is also the length of such end-point intervention trial process that has led the community to seek alternatives for the generation of leads. Now so-called biomarkers have led us to discover natural reporters within the body which according to current medical knowledge are directly linked to a particular illness or a health risk. By observing these parameters it is possible to detect effects of functional foods more quickly in intervention studies. A biomarker that is well-known amongst non-scientists as well and that is used on a wide-scale in advertising is cholesterol. In many intervention studies is has

Lead compounds
The structure, for example, of a natural substance serves as a "molecular template" for producing new substances with similar effects by making targeted changes to the structure. The aim is to improve the properties of a substance, which can then be used as a drug, for example.

Secondary metabolism
Synthetic processes whose end products, the secondary metabolites, do not have a direct role in the economics of the living cell. Whilst the primary metabolism is more or less conserved in all living organisms, the secondary metabolism is often limited to lower lifeforms and is then strain-specific.

Target
The target location of an active substance (for instance, enzyme, receptor, DNA).

now been possible to prove the positive effects resulting from the addition of plant sterol and stanol esters in various products on the cholesterol levels in the blood. It is now generally accepted that consuming a margarine containing plant sterol esters for a three-week period can reduce the LDL cholesterol value by 10-15%. This example, however, also illustrates how far the journey is from a scientific observation in animal or in vitro experiments to recognized effect of a food constituent. Usually the process is even more delicate due to the fact that for consumer goods, tests on animals usually aren't considered acceptable and the reliability of in vitro tests must be high enough for the human studies to follow directly without any risks.

This also allows us to understand why the traditional search for new ***lead compounds*** conducted in pharmaceutical research in natural substance screenings, for example, is not an option for food corporations involved in research.

First, to develop the food additive, a suitable assay system must be available which models the often more complex in vivo situation. Second, in contrast to drug development, the natural substance being investigated must be active as such. Any modulation of activity, bioavailability or specificity by medicinal chemistry methodology is not permissible for foodstuffs.

Since we are dealing with extracts, a premature decision in favour of an isolated single constituent can also prove wrong as effects that can be demonstrated in the pure substance often can no longer be traced in food. And finally, it is important not to lose sight of the real purpose of food development – the final product has to taste good. Many health-promoting plant constituents, which often taste bitter, cannot be incorporated into functional foods for this very reason.

Many plant constituents have a bitter taste and consequently often cannot be incorporated into food as the product has to taste good to the consumer.

Chemistry and biochemistry are indispensable

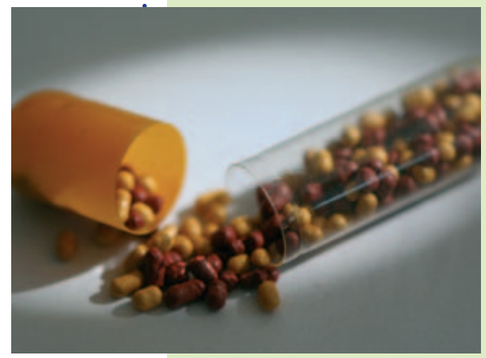
Although there is not a great deal of leeway for developing new healthy foods, the use of modern methods from chemistry and biochemistry does promise a range of possibilities. For example, there are now countless biomarkers which have proven to be reliable parameters in human intervention studies. Today we can build on the experience of many decades of natural substance screening with plant extracts and we have gained in-depth knowledge on the secondary metabolic products of most important useful plants. We also have comprehensive data on indigenous herbs used over the centuries as "household remedies" or medical herbs used in the prevention and treatment of disease. Furthermore, there are plant extracts listed world-wide with a long tradition of use as remedies; investigating the constituents and effects of these extracts remains an important area of world-wide research in the field of pharmaceutical biology at universities and natural substance research institutes. Further potential, which cannot yet be fully estimated, could be harnessed from using the knowledge in traditional medicines throughout the globe. Whilst this area is being systematically and intensely explored using modern procedures from bioanalysis and instrumental analysis, it is still very much in its infancy. Here we need to strive for a clear and concise methodology in compositional analysis and recording of clinical data that also meets highest international scientific standards.

With the databases available to us today on the chemical structure and biological functions of plant constituents – and these are being constantly added to and developed - we have an important tool at our disposal which can be a long-term support in selecting the candidates to develop as active substances in functional foods. Chemoinformatics provides us with methods for conducting molecular similarity tests. These analyse, in particular, whether structurally known natural substances are chemically related to drugs available through comprehensive international studies on properties and tolerances. Two methodically different approaches are pursued here: the first starts with a large set of active substances which all bind to a particular molecular ***target*** – usually an enzyme or a receptor protein. The chemical structures are then matched on the computer, allowing a model of a minimal consensus structure to be generated, whereby it is still possible to weight the individual contribution of each and every structure. The other method is based on a binding protein whose spatial structure is well known and for which a consensus structure can then be found. Both procedures provide good search grids for checking natural substance databases, such as the Dictionary of Natural Products and then analysing ***hits***.

The next step is to then find evidence supporting the hypotheses developed on the basis of theoretical deliberations. Provided that the plant extracts shortlisted are innocuous, piloting studies – at least in theory – can give a first glimpse on whether biomarkers are changeable in vivo. This route is only possible in the rarest of cases, however, as in general small test groups will not give a significant result. And large-scale studies in this development phase would be far too costly, however, alternative strategies are called upon.

A possible solution is the mechanistic route. For instance, there may already exist a link between a health benefit and a molecular target responsible for a particular biochemical effect and for which in vitro test systems already exist. Or additional cellular models have to be developed through genetic-engineering methods, in which the target proteins – enzymes, receptors or entire signal cascades – are present in such a way that enables quantifiable statements on structure-effect relationships of pure substances and natural extracts. As only relatively small effects are sought and not maximum ones like in pharmaceutical research – as toxic side-effects have to be ruled out to the greatest extent possible – the necessary models are often painstaking, not particularly robust and hardly suited to a high throughput screening. The most important consideration is not to authorize any false-positive results from the studies for the next phase of development.

If the sought-after biological effects are found in the extracts, these samples are considered "positive hits", and they are then further investigated and sorted into active and non-active factions using chromatographic techniques. Pure substances are isolated and their structures analysed. The aim is to be able to trace the identified biological effect to a single active principle, so to the interaction of a single chemical structure with a single molecular target. On top of this, the active principle should then also be quantitatively recordable by taking in vitro readings. This usually stays in the realm of wishful thinking however. In practice it is often already huge progress if the active principle can be delimited. In addition to verifying the effect, the biological availability of an active substance or mixture thereof has to be investigated, i.e. it must be ensured that the active substance does actually reach its molecular target in vivo, without being rendered inactive by metabolic processes such as biotransformations beforehand. Sophisticated models have been developed for this as well which, for example, trace the journey of an active substance in its later product matrix – a cereal bar, yoghurt or a fruit drink, for example – through the digestive tract. This involves in particular imitating the influences that arise through stomach acids and proteases. Statements on the resorption of active ingredients in the intestine can be made by studies of the intestinal epithelial cells which track the passage of the individual components one suspects constitute the effect, broken down in time. Possible biotransformations can be proven beyond doubt by mass spectrometric analyses, so that both, chemical identities and the respective concentrations can be linked to each other. This is also decisive in situations, where a natural substance is activated by metabolic processes - for example in the liver.



Will the traditional supplements in pill form soon be a thing of the past?

The long journey to the shelf

Once biological activity, chemical structure and toxicity have been determined in comprehensive chemical and biochemical tests, confirmatory clinical and nutritional studies required can take place. They end finally in an open discussion between the various interest groups such as consumer associations, media, health organizations and national and international regulatory bodies. Here one of the issues is also how the finished product can be marketed to reach the consumer.

The question of which health-specific statements are allowed on the packaging and the list of ingredients in commercials and

Hit
Substances or extracts which identified in high throughput screenings and whose biological activity has not yet been proven or supported by further studies.

Clinical study
Examination of the therapeutic efficacy of a drug on humans. Clinical studies are subject to strict legal regulations.

adverts, on the internet or in brochures is of particular importance. For this purpose – like in the case of plant sterol esters – clinical studies, ideally by independent institutes and institutions, must confirm the in vivo effect of the new product to be statistically relevant for a randomised, healthy population with a standard "normal" background diet. Furthermore, it is also necessary that physicians, biochemists and physiologists come to a consensus based on the data available as to the mechanisms of action. This isn't always easy and often there are heated discussions on the scientific facts until a final decision is made. And yet, in spite of all the difficulties, food corporations are generally very interested in finding a consensus for their functional food. To do so, scientific experts are included in a review process which also deals with details whose results are fed back into the scientific community so that the quality of the scientific evidence is documented. Discussions are also conducted with physicians, dieticians and their institutions to find the best possible way to communicate the often complex and difficult scientific contexts to the customer. The discussions also deal with how far the statements on the health-promoting qualities of the product should go and how statements can be worded as simply and understandably as possible.

Functional food supports a healthy diet

Functional food will certainly not become the "magic bullets" of the food world in the future. Functional foods are not supposed to combat disease and end will definitely not end up on the table as a substitute for drugs. In that sense, the term "nutraceuticals" is largely misleading. They should instead be seen as supporting a balanced, healthy and varied diet, but one which has to be accompanied by a healthy lifestyle. The combined efforts of nutritional physiologists, physicians, chemists and biologists should make it possible to bring onto the market high-quality, industrially produced foods resulting from scientifically recognized development programmes. As a result these products can be claimed healthy, work to counteract health risks caused by modern lifestyles, reduce risk factors and help the consumer to adopt a more aware and active lifestyle.

Will today's supermarkets be tomorrow's pharmacies? – An illusion and totally misleading

Werner Klaffke

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Links on the Web

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Chapman &Hall/CRC, Dictionary of Natural Products
www.chemnetbase.com/scripts/dnpweb.exe?search+SNnCNhly0ME

Functional food itself is not enough. As well as a healthy diet, a healthy lifestyle is important.