

New uses for ancient active substances

Treating illnesses with leaves, flowers and roots: modern phytotherapy originated from the natural therapy practiced by our ancestors for thousands of years, but it has little to do with herbal teas and the like. Very few people are aware that good plant-based medicines have long been based on exact scientific practices.

Considered the best-researched plant-based medicine made by Bayer, Iberogast™ has been on the market for more than half a century now but still holds surprises in store. It is clearly an effective remedy for a large variety of gastrointestinal complaints, as proven by dozens of studies conducted over the course of the past decades. But who would have thought that, at least according to initial results from studies on animal models, the preparation with the scientific name STW5 may also offer protection against the intestinal damage caused by radiation?



Saint John's wort
Hypericum perforatum

Helps in cases of mild to moderately severe depression.

These kinds of pleasant surprises are exactly why Dr. Mohamed T. Khayyal, who led a work group that researched this effect in 2014 and 2015, enjoys his work so much. Khayyal is a professor emeritus at the Faculty of Pharmacy of Cairo University in Egypt and has been researching Iberogast™ for 20 years now. Even so, as he points out, "We still don't know all of this medication's secrets."

Long ago, the first humans likely depended on the healing power of plants.

Over time, their descendants evolved this form of natural medicine further. Today's phytopharmacologists use scientific methods to determine the mechanisms of action of plant-based medicines containing extracts from flowers, leaves, roots or essential oils. "The aim of phytotherapy is to prevent, alleviate or heal diseases and complaints using medicinal plants," explains Dr. Heba Abdel-Aziz of Bayer's Consumer Health Division, Medical & Clinical Affairs Phytomedicine.

In contrast to chemically defined medications, phytopharmaceuticals are not isolated substances but a mixture of many natural ingredients. Secondary plant substances play a role here.

Although many studies have proven the efficacy of plant extracts, researchers often do not know why the multi-component mixtures are so effective. Abdel-Aziz, who examines the mechanisms of action of phytotherapeutic drugs in cooperation with university researchers, explains it like this. "There are a large number of ingredients that contribute to the effect, some of which we haven't even identified yet." This multitude of substances amplifies the effect through synergy: two or



Common marshmallow
Althaea officinalis

Soothes dry cough and hoarseness.



Bitter candytuft
Iberis amara

Antispasmodic and anti-inflammatory; protects the mucous membranes.

more substances together have a greater overall impact than a single individual one. "Two and two does not equal four in such cases, but six or eight instead. That is synergy," says Abdel-Aziz.

Dr. Careen Fink, Medical & Clinical Affairs Phytomedicine Manager at Bayer and a pharmacist, explains the difference between phytotherapy and conventional herbal teas. "Our phytopharmaceuticals are produced according to standardized manufacturing instructions, ensuring that their quality remains constant."

The active components in flowers, leaves and roots vary, meaning that their effects vary as well. Precisely defined and established criteria in the manufacturing of phytotherapeutics reduce these variations to a minimum. Each step is monitored and documented, from extraction of the substances all the way to packaging of the drug products. "The objective is to standardize exact process workflows," says Fink, a member of the medical team responsible for scientific data on Iberogast™.

The plant-based drug products in phytotherapy differ from traditional medicinal herbs in one important way. In order to obtain approval as drug prod-



Where crops are planted, what type of soil they are planted in and how they are harvested: all phases of production for plant-based medications are strictly controlled and inspected, just like for chemical drug products.



ucts, phytopharmaceuticals are subject to strict scientific control. Their molecular mechanisms of action are examined in pharmacological or preclinical studies. Researchers then confirm their efficacy and safety in clinical studies and resulting meta-analyses.

Scientists were already searching for evidence of the efficacy of Iberogast™ back in the 1960s. The drug product is effective against gastroenterological complaints such as functional dyspepsia or irritable bowel syndrome. It consists of a mixture of nine medicinal plant extracts which exert their effect in combination with one another. This combination of active ingredients works simultaneously at several locations in the digestive tract and has proven clinically effective for

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That is synergy.

Dr. Heba Abdel-Aziz

two indications. Scientists refer to this as multi-target therapy. "Normally you could not prescribe the same drug product for illnesses with constipation and diarrhea, both of which are symptoms of irritable bowel syndrome," explains Abdel-Aziz.

"However, Iberogast provides reliable relief, restoring the balance in the muscles of the digestive tract. We have initial indications that it impacts intestinal microbes as well."

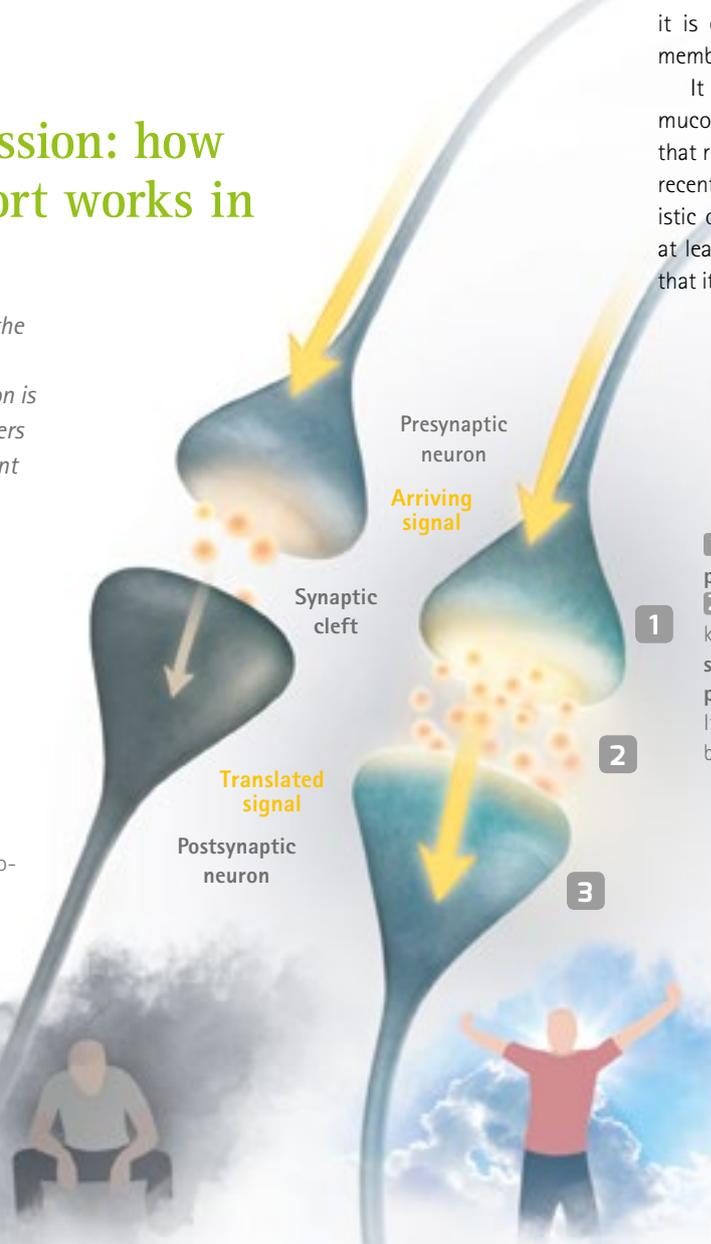
Another well-known plant-based drug product from Bayer is the cough medicine Phytostil™, which is based on marshmallow root. Phytostil™ lays a soothing protective film on the cilia of the throat. "Coughing is a very helpful reflex, especially if you have mis-swallowed something. It keeps the airways clear," explains Dr. med. Jürgen Müller, of Medical & Clinical Affairs Phytomedicine in Bayer's Consumer Health Division, who is responsible for Phytostil™ worldwide. "In comparison, dry cough stems from irritation of the receptors without mucous development. It is a vicious circle. Because it is continually irritated, the mucous membrane is unable to recover."

It is above all the substances called mucopolysaccharides in Phytostil™ that relieve the urge to cough. Scientists recently discovered additional characteristic of the cough syrup. "Experiments, at least on a cellular level, have shown that it also has a biological effect, reduc-

Escaping depression: how Saint John's wort works in the brain

Saint John's wort takes effect at the chemical switching points in the brain, the synapses. When a person is depressed, the chemical messengers are lacking at these synapses. Saint John's wort helps to increase the number of signal molecules.

When a person is depressed, neurotransmitters such as serotonin, noradrenaline and dopamine are lacking. Because of the low level of messenger substances in the synaptic cleft, the postsynaptic neuron is less active.



- 1 A flow of current arrives at a presynaptic neuron – the sender.
- 2 It releases signal molecules, known as neurotransmitters, into the synaptic cleft.
- 3 These reach the postsynaptic neuron – the receptor. It then converts the chemical signal back into an electrical signal.

Highly concentrated Saint John's wort extract increases the number of neurotransmitters in the synaptic cleft, restoring a condition more similar to a healthy brain.



Interdisciplinary expertise: doctors, pharmacists and biologists at Bayer are conducting research into phytomedicinal active substances (from left: Dr. Jürgen Müller, Dr. Careen Fink, Dr. Heba Abdel-Aziz, Dr. Christiane Kolb).

Interview



Mohamed Khayyal

“The results are very promising”

research spoke with pharmacologist Dr. Mohamed T. Khayyal about his work in the field of phytotherapy. Khayyal is a professor emeritus at the Faculty of Pharmacy at Cairo University in Egypt. He has conducted many pharmacological studies, including on Iberogast™.

What should people know about phytotherapy?

Many people choose active substances from plants because they are concerned about harmful side effects caused by chemical products. However, herbal-based medicines often offer more important advantages than that. They could sometimes have a broader spectrum of activity when multiple herbal combinations are used and often have milder side effects than conventional therapies. However, there can be no effect without any side effects. Herbal total extracts are often better tolerated than isolated active components, since they usually contain other constituents that modify and compensate for undesirable effects of the active ones.

In your opinion, what is so special about Iberogast?

I have been researching Iberogast for 20 years. The results are promising and we are always discovering new therapeutic horizons. The best therapeutic effect is achieved as a result of the “synergy” between the nine components, and this contributes towards the multi-target concept of activity of Iberogast. In research, we try to explore new therapeutic strategies. That is what motivates us as scientists. What is more important, continuous learning helps to keep one young – even if it is a placebo effect!

What should people be aware of?

Not all manufacturers produce their products according to such strict standards as Bayer. Accordingly, the amount of active substances contained in plant-based products can sometimes vary from one batch to another. It is a problem that some manufacturers are satisfied with minimal results and do not provide sufficient proof of therapeutic benefit. This undermines the credibility of phytotherapy.

ing inflammation and strengthening the immune system.” These characteristics set Phytohustil™ apart from chemical cough medicines that suppress the urge to cough in the brain, adds Müller.

However, phytotherapeutics can also take effect in the brain – such as the Bayer medications Laif™900 and Laif™900 Balance, which are derived from Saint John’s wort (*Hypericum perforatum*). Laif™900 helps combat mild to moderately severe depressive episodes and must be prescribed by a doctor. The prescription-free product Laif™900 Balance, by contrast, is approved only for milder forms of the disease. “The cause of depression is unclear,” says Dr. Christiane Kolb, a Medical & Clinical Affairs Phytomedicine Manager and an expert on the drug product derived from Saint John’s wort. “We know, however, that the metabolism in the brain is impaired and that chemical messengers are missing. As a result, impulses are no longer adequately transmitted.” Saint John’s wort extract enables more of the neurotransmitters to reach the synaptic cleft. Substances in Saint John’s wort such as hypericin, hyperforin and flavonoids contribute to this effect. “The extract in Laif 900 has proven therapeutically effective in clinical studies,” says Kolb. “We have observed effects

known to us from synthetic medications – but with significantly fewer side effects. That is a big advantage.”

Nevertheless, some doctors doubt that plant-based medications are as effective as synthetic ones. Bayer specialist Müller cannot understand this skepticism among his colleagues. “Plant-based and chemical medications are scientific equals in terms of efficacy. Plants are in fact at the very root of medicine.”

For thousands of years now, nearly all the peoples of the world have recognized and used the healing power of plants. Many plant-based medications were empirically developed and their therapeutic benefit clinically proven later. “Earlier, humans made individual observations regarding the efficacy of plant substances. Nowadays we are able to scientifically prove the effectiveness of medicinal plants,” explains Kolb. One of the most fascinating aspects of phytotherapy for her is that plants are able to form a large number of substances that humans can use. “These plant substances are not designed for humans, but we have discovered which ones help us,” says Kolb. “And although we have been familiar with these plants for a long time, we are always discovering new possibilities for their use.” ■