# Phytopharmaceuticals – fighting disease with natural substances

**Phytopharmaceuticals are herbal medicines whose efficacy is down to one or several plant substances or active ingredients. They have been used for treating diseases since time immemorial. This traditional knowledge is still the basis for many medicinal products made from plants or parts thereof. Herbal medicines have been produced in Baden-Württemberg for many generations.**

Plants produce an incredible variety of natural compounds. It is therefore not surprising that humans make use of this huge diversity. Historical sources show that the use of medicinal plants goes way back to the Bronze Age. Europe has a culture of using medicinal plants that starts with Hildegard von Bingen, continues with Friedrich Sertürner who was the first to isolate morphine in pure form and ends with the modern-day production of herbal medicines.

## Plant extracts as the basis for ointments, tablets and teas

Relationship between the different terms used in phytopharmaceutical production (modified from Hänsel and Sticher[1])

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The secret of phytopharmaceuticals, i.e. herbal medicines lies in plants. Plants or parts thereof are used for the production of herbal medicines. In pharmacology, crude drugs are, amongst other things, defined as the naturally occurring, unrefined material of plant, animal or microbial origin used for medicine. Herbal crude drugs (also called herbal material, starting material) are therefore plants or parts (e.g. flowers, seeds, fruit and stems) thereof in an unprocessed state, in either fresh or dried condition, whole or reduced in size by grinding or chopping. They usually contain a large number of chemical compounds with or without medical effect. They are the basis for finished herbal products, i.e. phytopharmaceuticals. Herbal crude drugs are processed into herbal extracts (i.e. herbal preparations) by drying, extracting, etc., thus leading to an enrichment of the bioactive compounds. Phytopharmaceuticals, i.e. herbal medicines, therefore consist of several compounds with a therapeutic effect. Herbal medicines are sold in dry form as granules, tablets, capsules and lozenges. Medicinal oils such as arnica flower oil can be used to make ointments.[1]

## Phytotherapy is not the same as homoeopathy

The German Medicines Act (AMG) defines what herbal medicines are (see definition). The AMG regards plant compounds that can be isolated in pure form from plants such as atropine and morphine as chemically defined compounds, and therefore classifies them as classical medicines. Phytopharmaceuticals, on the other hand, always contain entire plants, parts or materials thereof. Phytopharmaceuticals are used for treating diseases based on scientific knowledge (phytotherapy). Although the AMG classifies phytopharmaceuticals, homoeopathic and anthroposophic drugs as special therapy options, phytopharmaceuticals differ from homoeopathic and anthroposophic drugs in terms of production, approval and the therapeutic approach for which they are used.

AMG § 4 Other definitions (29): Herbal medicinal products are medicinal products which exclusively contain, as active substances, either one or more herbal compounds, one or more herbal preparations, or one or more such herbal compounds in combination with one or more such herbal preparations." (http://www.gesetze-im-internet.de/englisch_amg/englisch_amg.html#p0074)

The German Federal Institute for Drugs and Medical Devices (BfArM) grants marketing authorisation for medicinal products, including herbal medicinal products. Drug manufacturers must provide documentation on the efficacy, safety and quality of the product they want to register with the BfArM. Traditional herbal medicines that have been in use for 15 years within the EU and 30 years outside the EU are subject to a simpler approval procedure than traditional chemical

drugs on the basis of monograph collections, and no additional clinical trials are required.

## Phytopharmaceuticals are made from secondary plant metabolites



The flavonoid quercetin is synthesised through the polyketide pathway and large quantities of quercetin are found in lovage (Levisticum officinale).
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But what determines whether plants are suitable as food and for use as remedies for humans and animals? All plants function with a so-called primary metabolism that produces and degrades amino acids, fats, carbohydrates and nucleotides. These synthesis pathways are therefore present in all plants and also quite similar between different plant families. The so-called secondary metabolism is connected to the primary one as it uses building blocks from the primary metabolism to produce a large number of specialised compounds. These are classified into a very small number of groups according to their biosynthetic origins and chemical structures.



Colchicine is a toxic alkaloid and the major one found in autumn crocuses (Colchicum autumnale).
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Alkaloids and amines are formed from amino acids. Other secondary metabolites include polyketides, steroids and phenylpropanoids. Around 80,000 unique chemical structures have been isolated from secondary higher plant metabolites.[1] Different plant families produce different secondary metabolites, which also vary considerably in their chemical structure, resulting in a huge number of closely related structures. Plants produce different secondary metabolites in different developmental phases. Secondary metabolites are important for communicating and interacting with other organisms and with the environment. Tomatoes are an excellent example for illustrating the effect of certain secondary metabolites as defense barriers. The glycoalkaloids tomatine and dehydrotomatine protect green tomatoes from being eaten by herbivores, and from infection by fungi and lichens. They are gradually degraded as the tomatoes mature. Ripe tomatoes contain little or no tomatine and dehydrotomatine and are safe to eat. Some secondary plant metabolites are formed only when the plant is infested by microbial pathogens. These so-called phytoalexins have an antimicrobial effect.[1,2]

## Active plant substances for treating congestive heart failure

The example of tomatoes shows that active plant ingredients are not necessarily individual active ingredients, but a mixture of several. Only a few herbal ingredients are used for therapeutic applications without further processing. Digitoxin is one such compound. It is isolated in pure form from purple foxglove (Digitalis purpurea) and is effective as a cardiac glycoside for treating congestive heart failure. However, in the majority of cases natural compounds are used as models for chemically synthesised pharmaceutical substances: salicylic acid, which is produced by the plant Filipendula ulmaria (commonly known as meadowsweet), and a salicylic acid derivative, acetylsalicylic acid, which is produced by willows, have a long tradition of reducing pain and fever, but have been produced using chemical methods for over a century.[3]

## St. John's wort is a well-known herbal medicine



St. John's wort extract is a popular herbal medicine for treating depression.

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St. John's wort is an excellent example for illustrating the variety of structures and effects of secondary plant metabolites. The herbal medicine (Hyperici herba) is extracted from dried Hypericum perforatum flowers and aerial parts. Amongst other things, the preparation contains naphthodianthrone hypericin (antiviral effect), the phloroglucinol derivative hyperforin (antibacterial effect) as well as other flavonoids (hyperoside) and xanthones. The presence of all these substances in the finished medicinal product, which is produced from hydroalcoholic extracts (ethanol 50-60%, methanol 80%), is determined during the production process using thin-layer chromatography. While the antiviral and antibacterial effects of the herbal substance are derived from hyperforin and hypericines, the actual mechanism of action in the plant's proven antidepressant effect is not yet known. In this case, the total extract exerts the medical effect, and is thus the active ingredient of the medicine.[1]

## Phytopharmaceuticals from Baden-Württemberg



Sought-after active ingredients are enriched and unwanted constituents are removed or depleted in a highly technical, multi-stage extraction process. The solvents used during the process are subsequently removed.
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Twenty-four percent of all pharmaceutical companies in Baden-Württemberg listed in BIOPRO Baden-Württemberg GmbH's company database fall under the category "phytopharmaceuticals manufacturers".[4] Despite the

2004 healthcare reform, which rendered most herbal medicines no longer eligible for reimbursement, the demand for herbal medicines remains strong. According to the German Medicines Manufacturers' Association (BAH), non-prescription medicines for special therapies accounted for 2.09 billion euros in 2015, or 32 percent of the total turnover of pharmacies from all non-prescription medicines. Two thirds of the revenues came from herbal medicines.[5] Data collected by the German Pharmaceutical Industry Association (BPI) makes Germany the leader in phytopharmaceuticals production in the EU.[6]

Dr. Willmar Schwabe GmbH & Co. KG from Karlsruhe is one of the companies in Baden-Württemberg with a long tradition of producing herbal medicines. The company uses complex extraction methods to produce herbal extracts with high concentrations of sought-after ingredients. Producing special extracts like these involves removing unwanted ingredients and enriching ingredients that increase the efficacy of the herbal medicine. It goes without saying that the production process is highly technical. In order to guarantee the efficacy, quality and safety of their products, Dr. Willmar Schwabe GmbH & Co. KG invest around 30 million euros per year in controlled randomised double blind studies as part of their drug discovery process. Amongst other things, the company has effectively demonstrated the efficacy of its patented special Ginkgo biloba leaf extract EGb761® in several studies. The extract contains standardised amounts of flavonglycosides, terpene lactones and no more than 5 ppm of ginkgolic acids. It has the ability to improve brain function, concentration disorders, tinnitus and dizziness.[7,8]

## Plants still harbour many secrets

These examples show that even though the use of medicinal plants has a long tradition in Europe, intensive research is continuing in this area to optimise existing drugs and identify new indications for known medicinal plants. Researchers from the Institute of Naturopathic Medicine and Clinical Pharmacology at the University of Ulm, in cooperation with colleagues from France and Tunisia, have shown in the mouse model that arglabin, which has promising antitumour activity, also has the ability to reduce the progression of type 2 diabetes mellitus. Arglabin is extracted from plants of the Artemisia genus, including mugwort.[9,10] Ongoing research therefore contributes to the discovery of new areas where known secondary plant metabolites can be used.


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Dr. Ariane Pott


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