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Perspective

Natural Products Extraction of the Future—Sustainable Manufacturing Solutions for Societal Needs

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Abstract: The production of plant-based extracts is significantly influenced by traditional techniques and the natural variability of feedstock. For that reason, the discussion of innovative approaches to improve the manufacturing of established products and the development of new products within the regulatory framework is essential to adapt to shifting quality standards. This perspective of members of the DECHEMA/ProcessNet working group on plant-based extracts outlines extraction business models and the regulatory framework regarding the extraction of traditional herbal medicines as complex extracts. Consequently, modern approaches to innovative process design methods like QbD (Quality by Design) and quality control in the form of PAT (Process Analytical Technology) are necessary. Further, the benefit of standardized laboratory equipment combined with physico-chemical predictive process modelling and innovative modular, flexible batch or continuous manufacturing technologies which are fully automated by advanced process control methods are described. A significant reduction of the cost of goods, i.e., by a factor of 4–10, and decreased investments of about 1–5 mil. € show the potential for new products which are in line with market requirements.

Keywords: natural products; phytomedicines; extraction; manufacturing; regulatory

1. Introduction

Patients have accepted traditional herbal medicines for a long time for treatment of mostly minor diseases. An assessment of small-molecule pharmaceuticals which were approved between 1950 and 2010 shows that approximately one third are either natural products or natural product derivatives. Counting the synthetic drugs which were "inspired by nature" increases the count to almost 50%. However, manufacturers of herbal medicinal products suffer from major problems such as increasing market pressure by, e.g., the food supplement sector, increasing regulations, and the costs of production. Due to increasingly strict regulation and approval procedures, innovation is seldom observed, and the methods used in process development are outdated [1].

The history of pharmaceuticals has been plant-based for several thousand years, and may be closely related time- and skill-wise to the origins of wine growing, i.e., over 9000 years in Georgia

and not much later in Armenia. Likewise, in Traditional Chinese Medicine (TCM) plant-based pharmaceuticals have been employed for thousands of years to treat patients. More importantly, the use of these natural pharmaceuticals has recently experienced a strong revitalization [2].

Compared to this, only the relatively recent developments, i.e., more or less over the last century, have had an impact on the synthetic chemistry on "pharmaceuticals", which grew substantially during this period. The next wave came from the new field of biopharmaceuticals during the 1980s, which, like the synthetics field, has been heavily attacked over the last couple of decades by the so-called generics/biosimilars. However, it should be kept in mind that the search for new drugs and treatments in both fields has repeatedly benefitted from stimulation by natural products, e.g., Taxol as a cancer drug, which was derived from yew needles [1,3].

Natural products are well established in many branches, like pharmaceutical drugs, nutraceuticals, nutrition additives, cosmetics, flavors, and crop protection agents, as sustainable, biodegradable, green, kosher and halal etc. products which are well accepted by consumers [1,3,4].

Manufacturers of natural extracts have to overcome challenges to keep their products within international markets and/or establish new ones, as regulatory demands and sales prices differ internationally [4–6].

The economy and market shares based on efficacy, one key-aspect which rarely comes up in the discussion of synthetics vs. herbal raw-based product molecules in healthcare application, is the fact that herbal raw-based products, be it in the form of a single compound or a complex mixture (i.e., extract), are by design, or perhaps better, by *origin* biodegradable. This is more than can be said for chemosynthetic compounds and most biosynthetic pharmaceuticals. Especially, when looking at controlled handling, and in particular disposal, of the new generation of synthetics, i.e., the so-called "high potency drugs", production can only be handled under the highest safety conditions; the people involved in production have to work under strict protection. It is obvious that the handling, and especially the disposal, of such therapeutics require significant hazard precautions, which increases costs.

With this in mind, the straightforward and safe handling and disposal of biodegradable herbal-based therapeutics might stimulate consideration of product "fate", like where does it go, where does it stay? Does it contaminate soil, water, or other environmental spheres? These questions should lead to a definition and implementation of clear rules and regulations for handling potentially dangerous products.

Plants undisputedly play an important role as a source for novel molecules and products, ranging from flavors to nutrition to cosmetics and medicines. Plant-based medicines still contribute significantly to human health. Nowadays, 11% of the 252 drugs considered as essential by the WHO (World Health Organisation) are of natural origin [7]. According to Newman and Cragg [1], up to 50% of all approved drugs within the last 30 years came directly or indirectly from natural sources. In the field of cancer treatment, 47% off all small molecule drugs are plant based [8].

In May 2018, BMBF (Bundesministerium für Forschung und Bildung) Germany started a joint international initiative which recognizes that new active substances are urgently needed against infectious diseases; natural sources show enormous potential [9–19]. Over the last decades, the improper application of antibiotics has caused more and more bacteria strains to develop resistance. This has fatal consequences. Every year, about 25,000 patients die due to infections by resistant microbes in Europe alone, as estimated by the WHO [20]. The development of new antibiotics even against resistant microbes is laborious and offers the pharmaceutical industry low commercial incentives. Therefore, over the past 30 years, almost no innovative antibiotic drug has been approved for the market. In the research and development pipelines, hardly any new developments can be seen. Consequently, an impulse must be set for the industry to change this situation regarding research in this field of urgent societal needs. BMBF has committed 500 mil. Euro to support these activities over the next ten years.

The scope of this paper is to provide the reader with an overview of the topic of plant-based product extraction and purification, and to analyze future trends. Therefore, the individual markets

are depicted with their individual economic key figures alongside trends in, and resulting demands for, future research.

A detailed overview was published in the position paper of the working group "Phytoextracts—Products and Processes" [4]; thus, only a brief overview is provided in Table 1.

Table 1. Overview of trends, perspectives, market situation, and research demand based on [1] when not stated otherwise.

Category	Agrochemicals	Cosmetics	Aroma, Flavours and Nutrition	Pharma
Market volume	1 Billion USD	200 Billion USD	10 Billion USD	107 Billion USD (forecast 2017) [21]
Market growth	Double digit annual growth rate	Double digit annual growth rate	Double digit annual growth rate Market for nutrition additives decreases Market for aromas grows	Double digit annual growth rate Decline in prescription market Growth in over-the-counter market
Challenges	Market dominated by SMEs as well as global players Small volume/low cost products bulk High cost/low volume niche products	Significant amount of products with natural claims but up to 75% synthetic ingredients; No uniform and binding standards for natural, fair-trade, organic labels	Low cost products (in the order of 1–10 €/kg) Many products with small volumes (100–1000 kg/a)	Most products are OTC Only few blockbusters Restrictive regulatory hamstringed R&D
Medium-term research demands	Efficient total process design for SMEs; Integrate process intensification Methods for SMEs and scale-up of infrastructure to fully integrated manufacturers; Energy efficient and low waste processes for decentralised utilization of natural resources [21,22] *	Efficient ways of finding new natural ingredients [23,24]; * Ensuring sustainability of supply	Apply and adopt more often $scCO_2$, bio-based solvents *, PHWE Biomass valorization, e.g., carrot, broccoli, artichoke etc. do have 30–80% herbal raw material waste	Speed up of development of herbal raw cell fermentation by omics [25] * Process Analytical Technology for inline-analysis of extraction processes; Parametric defined release at manufacturing of herbal raw extracts; * Homogeneity at production of extracts in large-scale Lyophilisation instead of vacuum-belt drying; Fresh herbal raws instead of dried raw material; HGACP instead of GMP on field incl. extraction media and pomace to be deposited on field again
Long-term research demands	Development of new products	Shift from wild collection to greenhouse or field cultivation in Europe; Energy efficient and low waste processes for decentralised utilization of natural resources [21,22]	Energy efficient and low waste processes for decentralised utilization of natural resources [21,22]	Determination of distribution behaviour of herbal raw ingredients in "single pot model" with herbal raw cell membranes and a gastrointestinal membrane for fast prediction of bioavailable components; Efficacy studies for new herbal raws and products which enable IP protection to cover the costs via patents on the new processes

* alternative cultivation techniques, bio-based solvents, and product development are excluded from this discussion in order to maintain the focus on issues regarding production.

2. Products and Business Models

The status quo and trends in phytomedicines are proposed for discussion from an engineering point of view, taking market and regulatory aspects into account.

Figure 1 describes a typical value chain from cultivation/wild collection over extraction towards tableting/marketing in a typical scale of amount/effort and costs/margins. Finally, about 200 t/year of a natural drug/phyto medicine can be provided to the market.

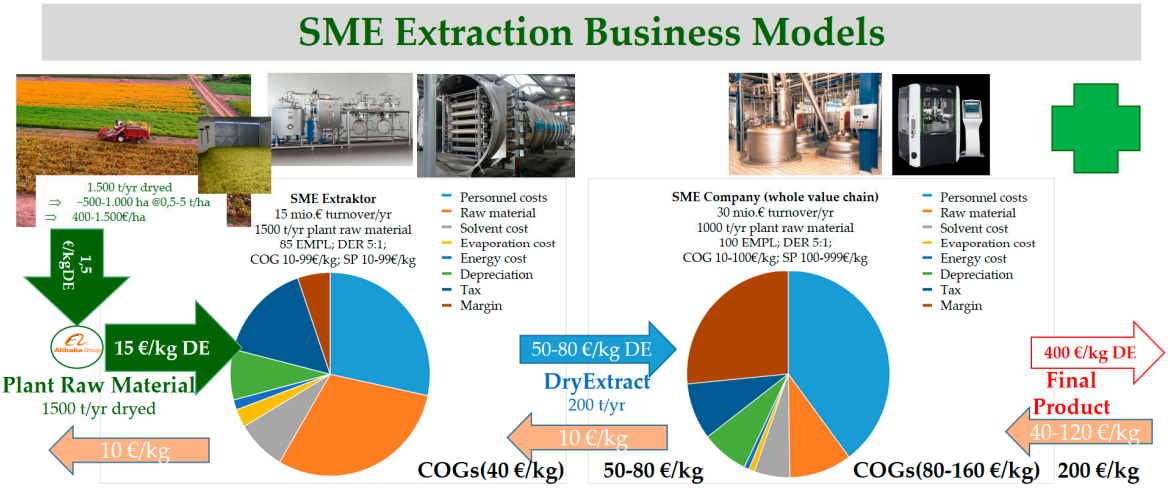


Figure 1. Business models along the value chain: cultivation, extraction, formulation and sales. DE, dry extract; SME, small and medium enterprises; EMPL, employee; DER, drug extract ratio; COG, cost of goods; SP, selling price.

Therefore, about 1500 t/year dried herbal raw material has to be harvested from about 500–1000 ha, assuming a typical harvest of 0.5–5 t/ha of herbal raw species. This results in a yield price of about 400–1500 €/ha typically. The benefit for the farmer is thereby about 1.5 €/kg dry extract for intermediate trade, to be sold further with about 15 €/kg dry extract. Herbal raw trade and cultivation has about 10 €/kg dry extract current revenue from the extraction industry.

The extraction company operates with about 40 €/kg dry extract COGs at the cost distribution as depicted, which is dominated by herbal raw material purchasing costs including solvent and staff. The extraction industry sells to the final formulation and tableting/packaging partners with about 10 €/kg dry extract margin, to which value is added by gaining about 200 t/year dry extract out of about 1500 t/year raw dry herbal raw material. The dry extract has, in the meantime, a value/cost of about 50–80 €/kg dry extract before it is tableted and packed as a phytomedicine, with typical market values of about 400 €/kg dry extract on the consumer market.

Typical extraction companies are SMEs with about 15 mil. € turnover per year, about 85 employees, an average drug extract ratio (DER) of 5:1 at about 1500 t/year dry raw herbal raw material in the order of 10 €/kg dry extract COGs, and a sales price in the same order of magnitude. Typical scales of added value are around 10 €/kg dry extract.

Typical SME phytomedicine companies have a turnover of around 30 mil. € per year, with around 100 employees and 1000 t/year herbal raw material throughput. Average DER of 5:1 results in COGs around 10 €/kg dry extract which have an end sales price in the order of 100 €/kg in relation to the dry extract. The cost distribution of such phytomedicine companies may be seen in the second pie chart; it is dominated by personal, herbal raw material, and energy/solvent. The scale of added value is around 40–120 €/kg, i.e., much higher than the two preceding steps, namely, cultivation and extraction. It is, in any branch, quite usual that the highest value generation occurs close to the end consumer.

3. Regulatory of Herbal Products

In Europe, herbal medicinal products are strictly regulated. Every herbal raw or herbal raw part used for the production of herbal products is described by monographs and is based on assessment reports which are published by the European Medicines Agency's Committee on Herbal Medicinal Products (HMPC) [26,27]. These texts contain information on efficacy, medical indication, toxicological safety, and extract definition. Additional regulations concerning the quality of herbal preparations are established by the European pharmacopeia [28].

The development of new products containing herbal raws, which have not been described yet by HMPC, is rare. Expenses for (pre-) clinical studies are significant, and make product development economically infeasible. Besides, the market application process is time-consuming and fraught with risk, which deters potential investors.

The international approach is not standardized. The US-American Food and Drug Administraion has very strict requirements for the registration of phytomedicines, as described in their legislation "Botanicals" [29]. Generally, it does not recognize herbal products as traditional drugs, but as dietary supplements. According to the FDA, these "supplements are not intended to treat, diagnose, prevent, or cure diseases" [30].

The Chinese Food and Drug Administration (CFDA) licenses herbal products based on 9 different categories [31]:

- Registration Category 1: An active ingredient obtained from herbal raw, animal or mineral materials and its preparations that have not been marketed in China.
- Registration Category 2: A newly-discovered Chinese crude drug and its preparations.
- Registration Category 3: A new substitute for Chinese crude drug.
- Registration Category 4: A new part for medicinal use from currently-used Chinese crude drugs and their preparations.
- Registration Category 5: Active fraction(s) extracted from herbal raw, animal or mineral materials and its preparations that have not been marketed in China.
- Registration Category 6: A combination preparation of TCM or natural medicinal product, which has not been marketed in China.
- Registration Category 7: A preparation with changed administration route of a marketed TCM or natural medicinal product.
- Registration Category 8: A preparation with changed dosage form of a marketed TCM or natural medicinal product.
- Registration Category 9: Generic TCMs or natural medicinal products

This categorization rewards research aimed towards gaining a deeper understanding of the active ingredients and modes of efficacy actions [2,32–40], and not only allows but directly demands the implementation of innovative production techniques as well as actual process development and manufacturing data evaluation methods like QbD- (Quality by Design), combined with PAT- (Process Analytical Technology) approaches for regulatory approval [41,42]. Those technologies are, in the meantime, transferred from biologics to botanicals, successfully applied, and made ready for industrialization at the Sustainable Manufacturing Center for the Chemical-Pharmaceutical Industry at the institute in Clausthal [6,43–47].

With its MIC (Made in China) 2025 strategy [48], China has defined key-technologies which are of crucial national interest. TCM and natural products are of course included. Therefore, the decision has already been made, and substantial resources are already available to gain these aims. Expectations from former comparable actions are that international manufacturers will be reduced to niche markets or need to speed-up their technology and product innovation, which in most cases have been neglected for several decades.

Besides pharmaceuticals, some additional noteworthy aspects of herb-based products are pointed out for other branches:

Herbal based nutritional supplements

- Factor 10–100 larger scale of production compared to pharma,
- regulated environment, but more freedom regarding extraction process,
- semi-purified products

Herb-based herbicides and crop protection

- Factor 100–1000 larger scale of production compared to pharma,
- regulated environment regarding quality, but more freedom regarding extraction process,
- semi-purified products

Cultivation of herbal raw material and resources

- **Pharma**: Regulations specify the origin of herbal raw material; most resources have to be collected from natural habitats, which can problematic because of higher natural variability, environmental impact, risks in supply chain management etc.
- **Nutritional supplements, herbicides, and crop protection:** Cultivated herbal raw material is preferred due to advantages regarding quality, logistics, and secured supply chains.

Quality assurance is based on intensive and expensive laboratory work with a very low degree of automation and data utilization, especially in herbal pharmaceutical production. Innovation regarding inline measurements, data collection and evaluation, and real-time analysis of herbal raw material has the potential to drastically increase the amount of data and ensure stable quality, while maintaining or even reducing current labor costs.

4. Manufacturing Operation of Extracts

Finally, operation of the manufacturing scale has to be discussed for any developed approach. To keep batch variability of natural feedstocks within regulatory demanded requirements is the key challenge.

A fundamental challenge in extracting herbal raws and producing phyto-pharmaceuticals is the natural variety of the feedstock. Therefore, nine different batches differing in harvest year and place were investigated. The overall amount of hyperoside, year, and the country of harvest are summarized in Table 2. Charge I is the reference batch.

Table 2. Overview of Hawthorn lot variety [49].

Lot	Year	Origin	Overall Amount	Deviation Referred to Lot I
A	2017	Southeast Europe	0.87%	146%
B	2016	Macedonia	0.35%	−1%
C	2017	Bulgaria	0.58%	64%
D	2017	Rumania	0.41%	16%
E	2014	Bulgaria	0.60%	71%
F	2017	Albania	0.42%	20%
G	2017	Southeast Europe	0.57%	62%
H	2017	Serbia	0.51%	43%
I	2017	Germany	0.35%	-

The overall amount with respect to the reference batch I varies from −1% to +146%. The percolation runs are depicted below in Figure 2.

To summarize Figure 2, extraction variability due to feed lot variability, such a lot variability, represents the magnitude of statistical variability in that example, i.e., operation points in manufacturing do not influence the natural lot variability with regard to DER and component ingredient content. In contrast, the given approved manufacturing operation point does not influence relevant product quality attributes like DER or component content. Therefore, a regulatory line is discussed in the following section.

Figure 3 depicts a flowchart describing the process from extraction to solvent/auxiliary evaporation/recycling, granulation, and formulation/tableting. Influencing parameters are listed for each unit operation. Easily derived from that overview, critical product quality attributes are only gained at the last tableting step. The effects of the preceding process steps do not influence the criteria for tableting ability, stability, and overall content.

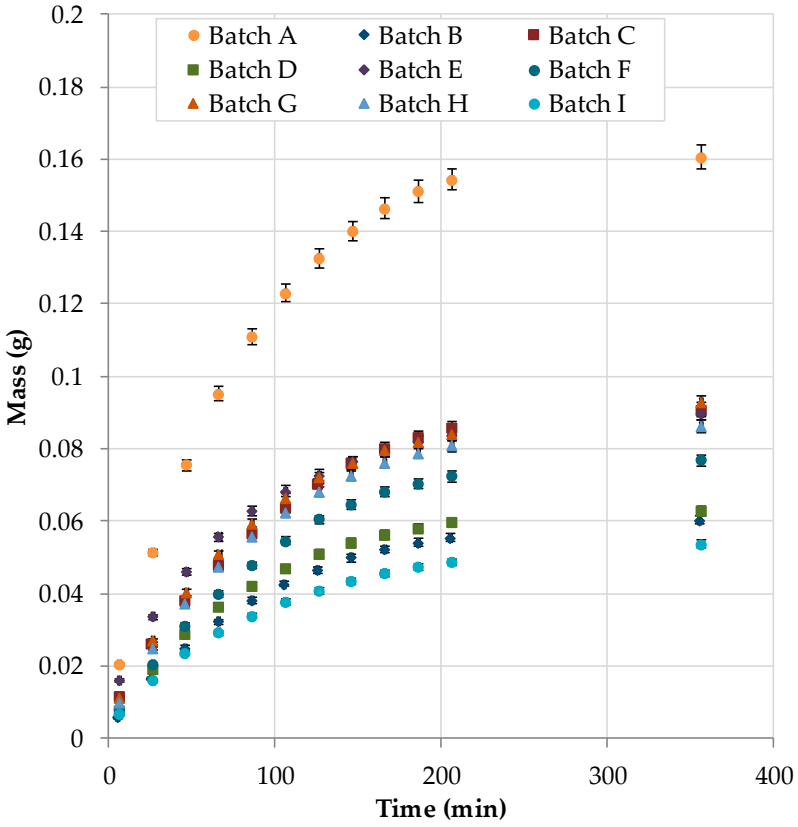


Figure 2. Percolation of the various hawthorn lots [49].

A factor of 2 in feed material content with factor 2 in DER range results in factor 4 in product content; see Figure 4. This may over or under cut the therapeutic ranges, i.e., need to define a therapeutic index, which is, as a standard of modern efficacy-based medicines, quite narrow.

At the typical DER-ranges (4–7.5:1) described in a Pharmacopeia or package insert, and typical content deviations of 0.1–0.5% due to nature, harvest region/time/season/weather, storage/transportation/pre-treatment etc., the range of deviation from active component content is significantly high. Moreover, during temperature-elevated operations like PHWE or SFE or strong active solvents types, components tend to decompose with increasing residence time.

A deviation of factor 4 in content is simply reached by factor 2 in herbal raw material and factor 2 in DER range definition. Due to the fact that this deviation in content of drug charges is statistically obvious, i.e., that efficacy related to at least any therapeutic index, there are significant patient groups which did not get any drugs with enough content for any efficacy. Proof of the efficacy of potential drugs by clinical trials is due to the fact that competition with existing therapies causes too many adverse effects occur, because there is too much content of other/different components inside.

Figure 5 exemplifies the influence of manufacturing parameter during extraction and formulation, tableting on critical product quality attributes.

The effects of manufacturing parameters for critical product quality attributes ends at formulation and tableting. Extraction operation does not effect those quality attributes if products are defined as *extracts*. Only if standardized or quantified extracts are approved does extraction operation has an impact on CQAs, and it is of interest to be controlled in order to gain CQAs robustly at typically changing natural feedstocks.

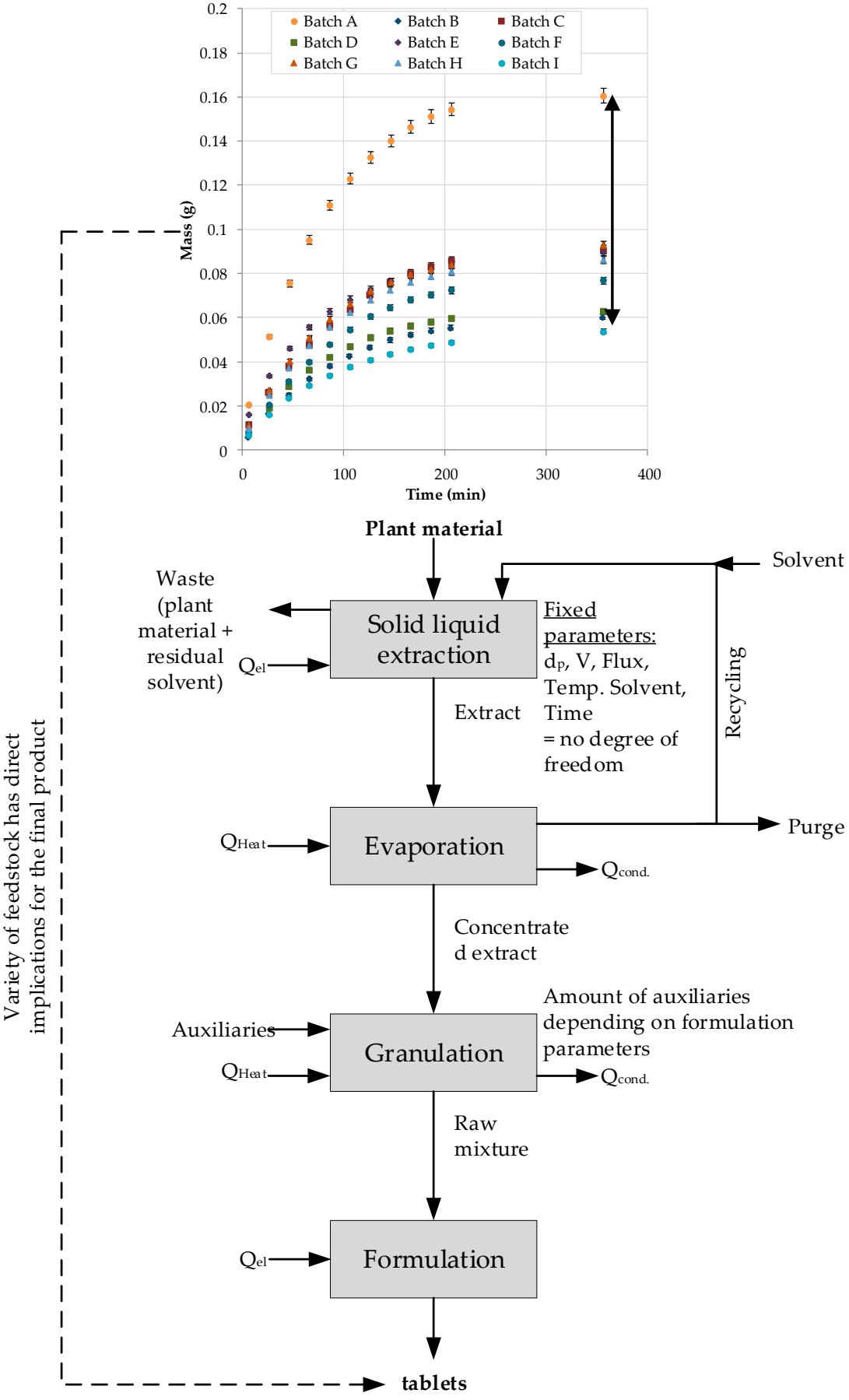


Figure 3. Basic scheme of phytoextraction processes [50].

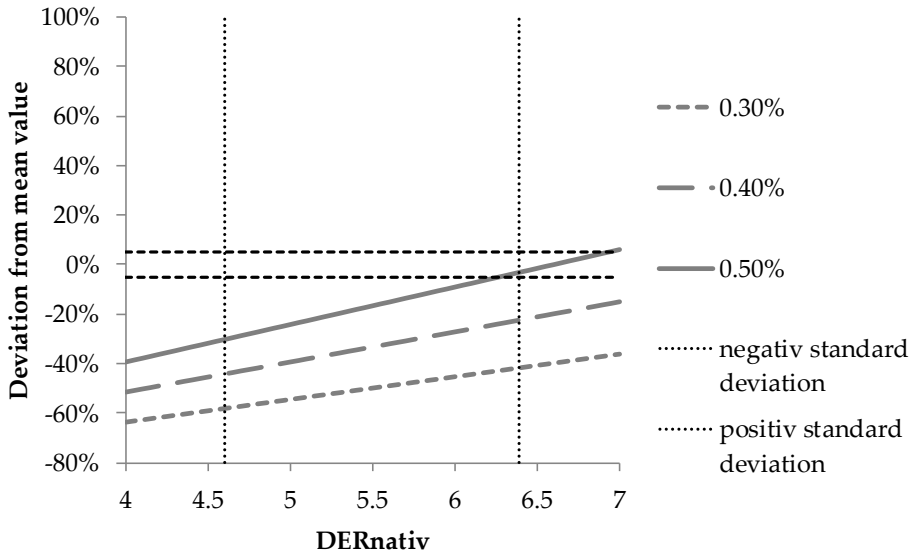


Figure 4. DER deviation derived by herbal raw content nature and definition range [50].

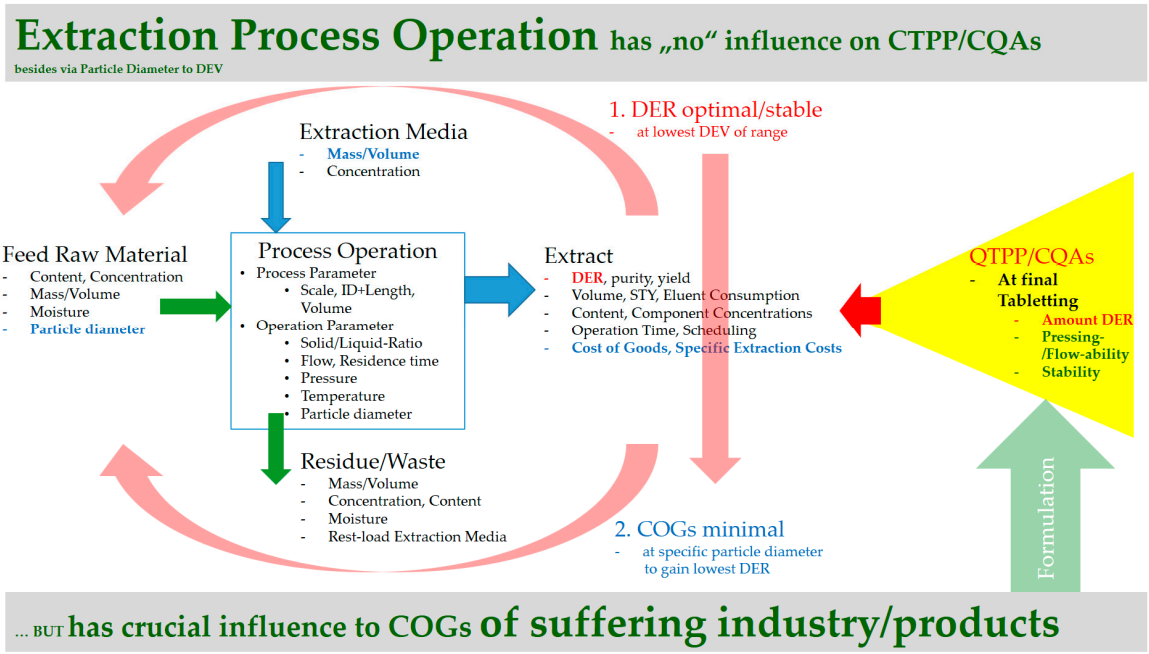


Figure 5. Analysis of root cause for Qbd-approach derived critical product quality attributes effects during manufacturing.

In order to improve other extracts towards quantified extracts, the following work steps are necessary:

- Analytical fingerprint, characterization, lead substances definition
- Efficacy study of lead substances range
- QbD approach to determine operation parameter and
- Submission of Design Space, i.e., new approval
- Economic optimal operation at maximal therapeutic value product

Fingerprinting is applied for any manufacturer with approval documentation in order to document batch specific recovery. Why not officially use this existing data for product and process improvement?

To empower quantified extracts towards standardized extracts, the following work packages are necessary:

- Analytical quantification (not characterization)
- Lead efficacy substance value (not range) i.e., efficacy studies
- Design Space by QbD approach much narrow i.e., robust process i.e., reliable product
- New approval

A discussion of the efforts and benefits of working out the final possible work flow step, approving a purified API:

- The steps described above, with efficacy based on single substances or well characterized substance groups
- Purification process development
- New approval

This results in high efficacy and high product quality (to be analytically distinctly proven) with the highest margins, and with less marketing necessary.

Consequently, it could be derived that the efforts are almost the same magnitude, which requires additional studies aiming at the potentially highest value product.

Financial support by funding organizations could be gained, if wished. The obstacles could be only missing or a lack of technology. This could be overcome by organizational means and/or co-operation, as those technologies are available, as described before.

5. Process Design Proposal for Efficient Manufacturing

Robust process operations generating reliable product quality given the natural variability of herbal raw feedstock is developed at the early stage of the process design and development. Therefore, efficient tools should be available for engineering tasks based on laboratory scale experiments. This tool box has already been proposed about a decade ago, and has been applied to many examples. It has also been developed further to extend technical readiness for daily project work [5,6,43–45,49–59]. In the following section, only a short summary is given to outline the general approach.

5.1. Modelling of the Extraction Process

The aforementioned extraction model assumes an average particle diameter of herbal raw feed material. Therefore, for a particle size distribution (PSD), uniform diffusion paths result. This is a simplifying assumption, which has to be proven at any industrial application first, as the particle size distribution is an easily accessible dimension. Due to this, the model is normally extended to a realistic particle size distribution.

This particle size distribution is implemented within the DPF-model by a summation of the different mass transfer amounts of each individual particle size class of a Q_3-distribution. Parameter γ_i is the mass amount of each class in relation to the total feed herbal raw amount.

$$\frac{\partial c_L(z,t)}{\partial t} = D_{ax} \cdot \frac{\partial^2 c_L(z,t)}{\partial z^2} - \frac{u_z}{\varepsilon} \cdot \frac{\partial c_L(z,t)}{\partial z} - \sum_{i=1}^{n} \gamma_i \frac{1-\varepsilon}{\varepsilon} \cdot k_{fi} \cdot a_{Pi} \cdot [c_L(z,t) - c_{Pi}(r_i = R, z, t)] \quad (1)$$

Fluid dynamic behavior is unaffected by this. The relevant characteristic numbers Péclet and Reynolds, as well as axial dispersion, are determined with the mean particle size diameter $d_{P,mean}$.

Regarding mass transport, the specific surface of the particles, as well as Sherwood and Schmidt numbers, are determined for each class with the following Equations (2)–(5).

$$a_{P,i} = \frac{6}{d_{P,i}} \quad (2)$$

$$Sc = \frac{\eta}{\rho_L \cdot D_{12}} \quad (3)$$

$$Sh_i = \frac{k_{fi} \cdot d_{Pi}}{D_{12}} \quad (4)$$

$$Sh_i = 2 + 1.1 \cdot Sc^{0.33} \cdot Re^{0.6} \quad (5)$$

Figure 6 exemplifies the experimental efforts of model parameter determination at the laboratory scale with increasing modelling depth for the rapid development over the last 10 years or so, starting with shrinking-core and pore diffusion effects taken into account [52,54], diffusion interference of different molecules by Maxwell-Stefan [55,60], shrinking and swelling mass transport kinetics of non rigid herbal raw matrices during extraction up to particle size distributions, and degradation kinetics caused by temperatures [46] up to a recent development, the spectroscopy-assisted model parameter determination [44,61].

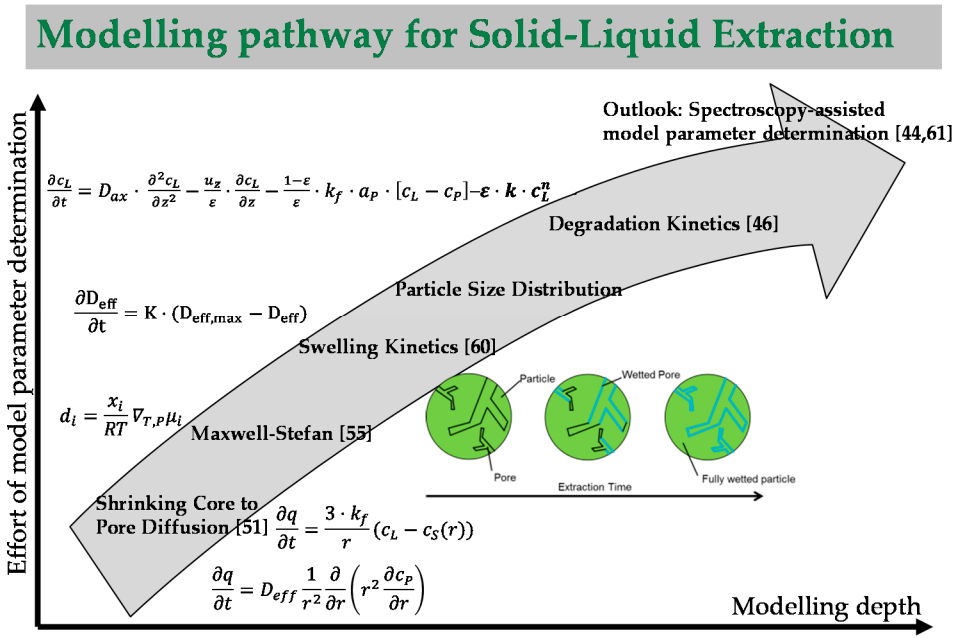


Figure 6. Effort of experimental model parameter determination at increasing modelling depth.

Figure 6 shows the stepwise approach of model equation assembly based on stepwise experimental model parameter determination in laboratory scale in order to develop physico-chemical (rigorous) models, which are a priori predictive because of the effects of fluid-dynamics, mass transfer, phase equilibrium, and energy balances are separated from each other. This general approach was first proposed by Altenhöner for chromatography, and has successfully been transferred to solid-liquid extraction modelling [51].

Figure 7 clearly points out the two boundary cases of mass transfer, related to maceration and percolation process design. Either the mass transfer kinetics are slow such that enough residence time has to be provided in order to gain sufficient total extraction yield, or the capacity of the chosen extraction solvent limits the extraction yield because not enough solvent is provided by the operation parameter window chosen by process design, as shown in Figure 8.

Highly optimized extraction procedures with regards to solvent consumption, recycling effort, yield, robustness, and productivity are especially important for products in the low-price and OTC market segment. High-price products like APIs can normally compensate for unfavorable process designs due to their high margins. This is not desirable at all, due to the waste of natural resources on the one side, and on the other side, best in class processes will complicate market entry for competing

companies, so additional money might be spent to maintain the advance in manufacturing and knowledge instead of marketing effort.

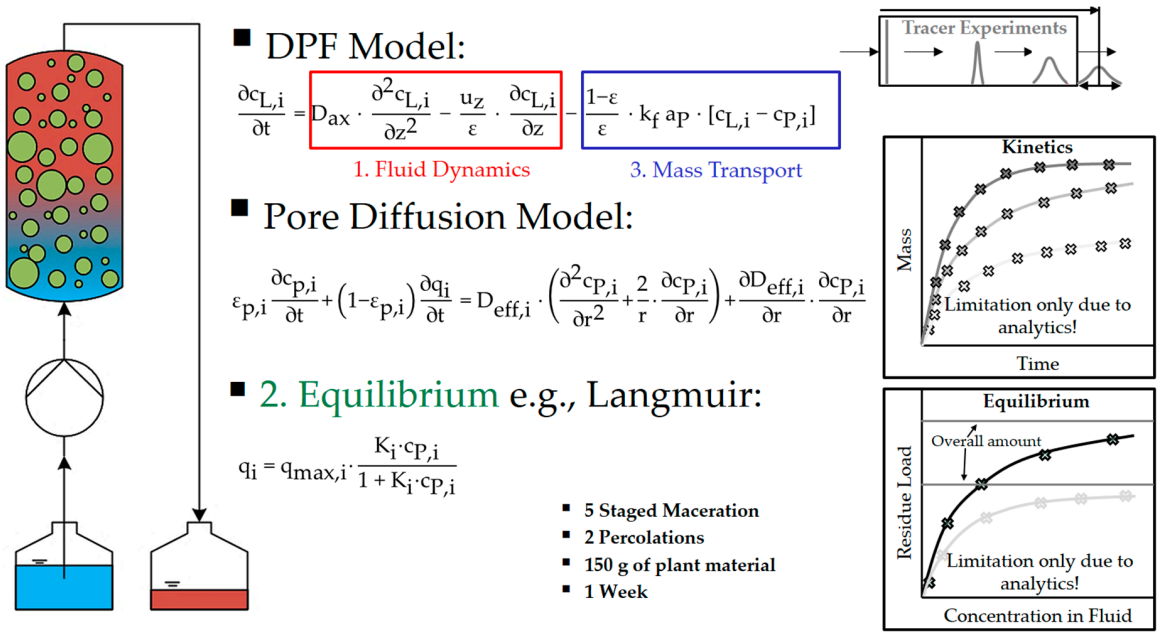


Figure 7. Equation assembly for experimental model parameter determination.

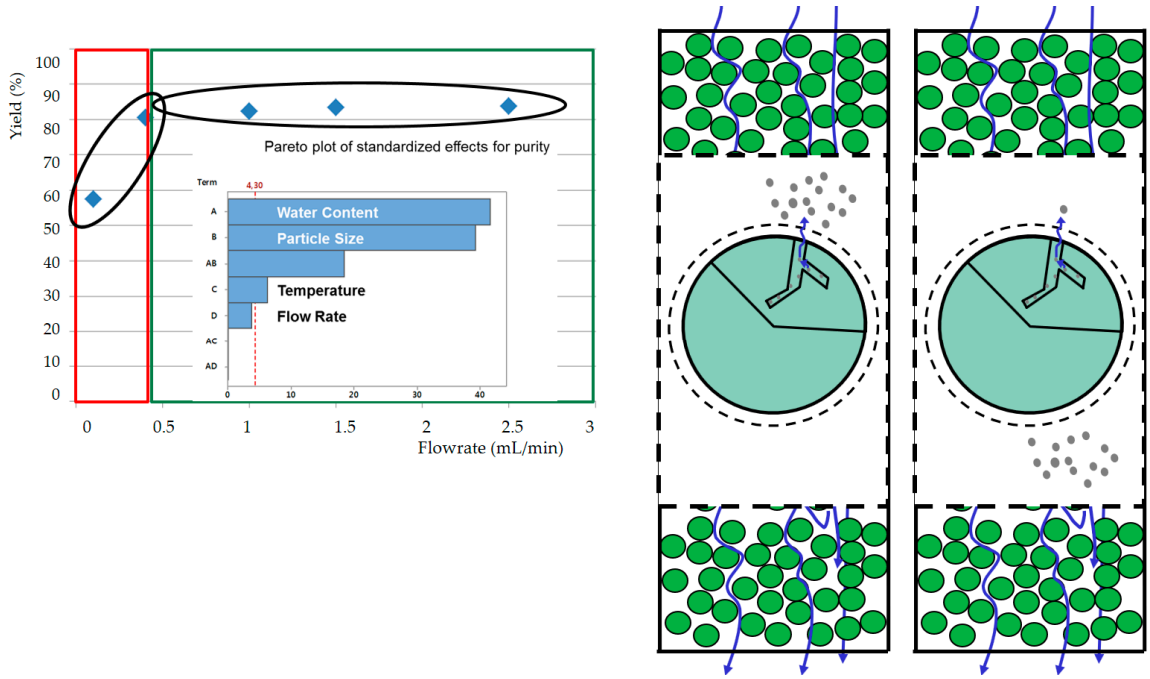


Figure 8. Residence time or solvent capacity limitation—maceration or percolation.

Tables 3 and 4 summarize as a review typical herbal raw material, which have been in process development and design, as well as process modelling and piloting studies, over the last years. From evaluation of this database, some general guidelines for process design and operation of resource-efficient extraction manufacturing can be derived:

1. If a targeted component is within the inner plant particle (e.g., yew, whitethorn, bearberry), then it is recommended that small particles be used to minimize the flow rate required to achieve high

extraction yields. In this way, diffusion limitations can be minimized, and a highly concentrated extract can be obtained.

2. Particle size is not significant if the target component is located on the outer surface (e.g., mugwort, salvia). As a consequence, high flow rates can be used to utilize the fast extraction kinetics. Overestimation of extraction kinetics can result in diluted extracts and a waste of solvent.
3. The extraction of oil requires breakage of oils seams of the particle. The phase equilibrium is practically immeasurable, because only solution mechanisms with extremely fast kinetics occur (e.g., fennel, caraway).

5.2. Resource Efficiency Optimization

The obvious way to reduce costs for solid-liquid extraction is to limit the solvent consumption by minimizing the total extraction time at constant yield. One possibility to achieve this is to shorten the diffusion pathway and to enlarge the specific surface area of the herbal raw material by grinding it to small particles. Other methods, e.g., ultrasound, microwave, or high pressure extraction are possible and have been applied at the lab-scale, but are currently not utilized in industrial production due to economic or technological challenges associated with scale-up [5,6,56].

The pore diffusion model of Section 3 is solved for each particle size class in parallel, and therefore, an individual diffusion path length is calculated for each class. The particle size distribution of the factions of yew needles which are utilized for model validation experiments are visualized in Figure 9. The coarse material shows a monomodal distribution around a median particle diameter of 1010 µm, while the fine material is distributed bimodally.

Figure 10 compares two different extraction progresses between measurements (data points) and simulations (continuous lines). Gray lines are the simulations with the particle collective characterized only by a mean particle diameter. If the fine material is simulated, the prediction with the simplified model assumptions is more accurate. The bimodal character of the distribution results, in the corresponding simulation (black line), in an area where the material is very rapidly leached out. In contrast, large particles delay the extraction and make the extraction progress much slower, as the simulations only with a x_{50}-value show. Simulating the extraction progress of the coarse material, all parameters besides particle size/particle size distribution and the mass of the herbal raw feed material are kept constant. In the described application, the simplified model fails totally to predict the extraction progress, whereas the detailed model, which considers particle size distribution, results in adequate prediction accuracy.

The sketched example exemplifies an extreme operation point. In earlier studies, the influence of varying particle sizes has been less drastic, and predictive simulations were possible [53,55,60]. The extracted particle collectives were distributed almost monomodally, and simulation using the x_{50}-values was an applicable simplification. Moreover, in the majority of those applications, the component of interest for extraction is located on the outer surface of the leaves, e.g., mugworth. Due to this, particle size reduces sensitivity, because diffusion paths within the particle play minor role. If complex particle size distributions are on hand and the active components are homogeneously distributed within the particles, then the particle size distribution of feed materials should be taken into account in order to improve the accuracy of the simulation's predictions. Notably, the PSD is quite simple to determine experimentally.

The extraction simulation shown in Figure 11 demonstrates this. Originating from a mean particle diameter of 1.5 mm, a yield of 80% is reached after 180 min of extraction. The same yield is reached after only 45 min if the particles are ground to 0.1 mm. Thus, the extraction time and the solvent consumption are both reduced by a factor of 4.

Table 3. Database of the physical properties of various herbal raw material for process design.

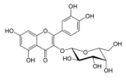
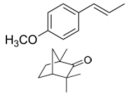
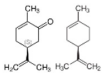
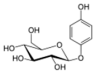
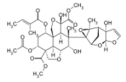
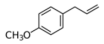
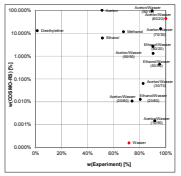
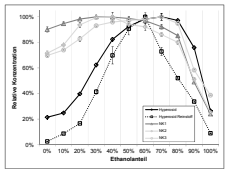
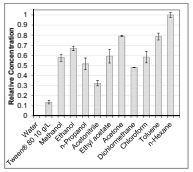
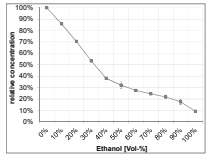
Category	***Taxus baccata* L.**	***Crataegus monogyna* JACQ.**	***Foeniculum vulgare* L. Mill.**	***Carum carvi* L.**	***Artemisia annua* L.**	***Arctostaphylos uvaursi* (L.) SPRING.**	***Azadirachta indica* A. Juss.**
Use	Pharma (cancer treatment)	Pharma (extract for cardiac insufficiency)	Aroma/fragrance	Aroma/fragrance	Pharma (Malaria treatment)	Pharma (extract for bladder infection)	Agro (pest control)
Target component	10-Deacetylbaccatin III (0.1–0.4% w)	Hyperosid (0.3–0.7% w)	Anethole (5.3%), Fenchone (2.9%) essential oil (~8% w)	Carvone, Limonene essential oil (~2% w)	Artemisinin (~0.4% w)	Arbutin (~15% w)	Azadirachtin
Molecular structure and weight							
	544.59 Da	464.38 Da	148.2/152.23 Da	150.22 Da	282.33 Da	272.25 Da	720.71 Da
Side component	Unknown	Unknown	Estragole (0.2%)		Unknown	Hydroquinone	Unknown
Molecular structure and weight							
			148.2 Da			110.11 Da	
Location	Needle Diffusion limitation	Leaf Diffusion limitation	Fruit Oil channels	Fruit Oil channels	Trichoma cells [62]	Leaf	
Solvent	Acetone/Water (80/20 *v*/*v*) [43] PHWE (120 °C, moderate decomposition) [46]	Ethanol/Water (70/30 *v*/*v*) PHWE (140 °C, no decomposition) [50]	Ethanol [60]		Acetone PHWE (80 °C, fast decomposition) [59,60]	Water (25 °C, fast degradation during maceration) PHWE (140 °C, no decomposition) [50]	Water (25 °C pH 4)
							

Table 3. *Cont.*

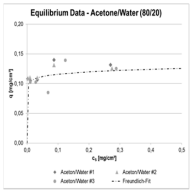
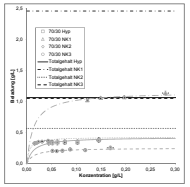
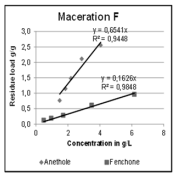
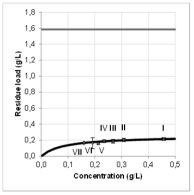
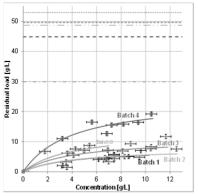
Category	***Taxus baccata* L.**	***Crataegus monogyna* JACQ.**	***Foeniculum vulgare* L. Mill.**	***Carum carvi* L.**	***Artemisia annua* L.**	***Arctostaphylos uvaursi* (L.) SPRING.**	***Azadirachta indica* A. Juss.**
Modelling	Pore diffusion	Pore diffusion	Broken Cells	Broken Cells	Film diffusion	Pore diffusion	
Equilibrium							
Optimization	small dp [60]	small dp [50]	Hydro distillation preferred	Hydro distillation preferred	high flow rate [6]	[50]	
Purification	Benchmark, lab-scale [43]	None	Conceptional	None	Benchmark, Lab-scale, Pilot-scale [50]	None	Lab-scale, Pilot-scale
Basic research	FTIR process control, Raman-mapping [61]	Lot variety [50]	Inline spectroscopy, APC, Raman-Mapping [63]	CLSM, FTIR	Process integration crystallization [50]	Lot variety, decomposition	

Table 4. Database of the physical properties of various herbal raw material for process design (continued).

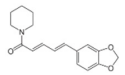
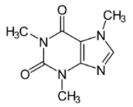
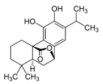
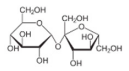
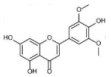
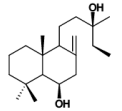
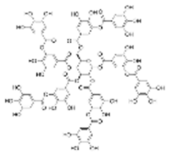
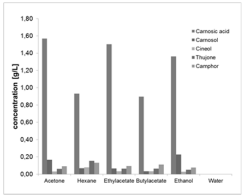
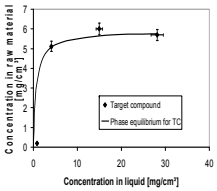
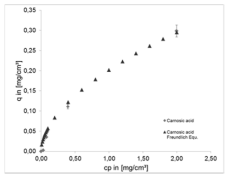
Category	***Vanilla planifolia* Jacks. Ex Andrews**	***Piper nigrum* L.**	***Camellia sinensis* (L.) KUNTZE**	***Salvia officinalis* L.**	***Beta vulgaris* L.**	***Zea mays* L.**	***Larix decidua* Mill.**
Use	Aroma/Food	Aroma/Food	Aroma/Food	Food (preserving agent)	Food	Food	Agro (pest control)
Target component	Vanillin (3–7% w)	Piperine (~6.5%)	Caffeine (3–6%)	Carnosol (0.1% w)	Succrose (14–20% w)	Tricin (55 ppm)	Larixol Larixylacetat
Molecular structure and weight							
	152.15 Da	285.34 Da	194.19 Da	330.42 Da	343.3 Da		306.49 Da

Table 4. *Cont.*

Category	*Vanilla planifolia* Jacks. Ex Andrews	*Piper nigrum* L.	*Camellia sinensis* (L.) KUNTZE	*Salvia officinalis* L.	*Beta vulgaris* L.	*Zea mays* L.	*Larix decidua* Mill.
Side component			Polyphenoles	Carnosoic acid (1.7%)	Ions (Mg, Na, K) Proteins		Tannines
Molecular structure and weight							
			>1000 Da	332.42 Da			
Location		Fruit	Leaf	Trichoma cells, Film diffusion limitation	Tuber		Bark
Solvent	Ethanol [51]	Ethyl acetate [51]	Water, Ethanol, US Extraction [56]	Acetone [60]	Water [54]		Ethanol/Isopropanol
							
Modelling	Pore diffusion	Pore diffusion	Pore diffusion	Film diffusion	Pore diffusion	Pore diffusion	Pore diffusion
Equilibrium							
Optimization	[51]		small dp	high flow rate [60]	small dp [9]		
Purification	None	None	None	Benchmark, Lab-scale [60]	None	Conceptional	None
Basic research	Raman-mapping, crystallization [64]	CLSM [51]					

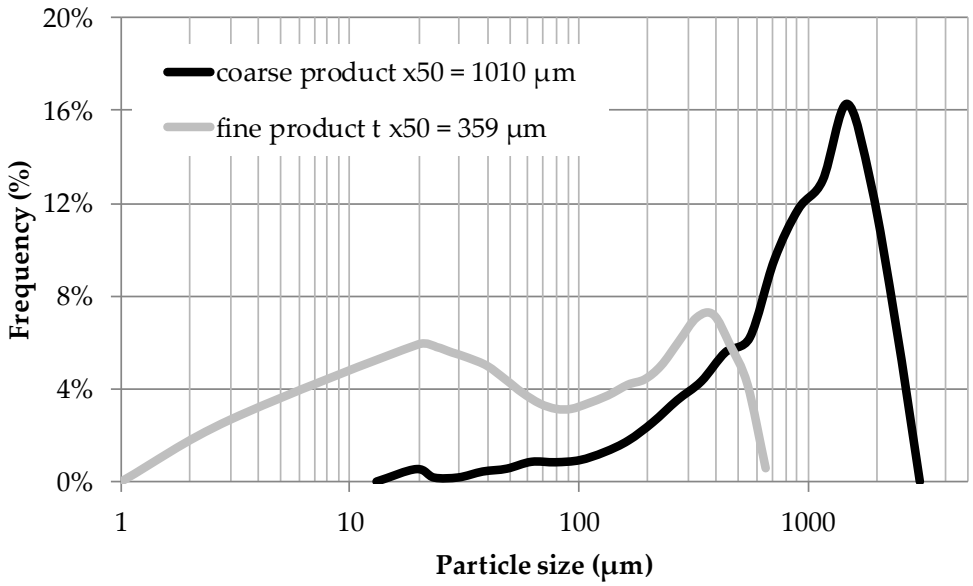


Figure 9. Particle size distributions of different feed herbal raw material batches.

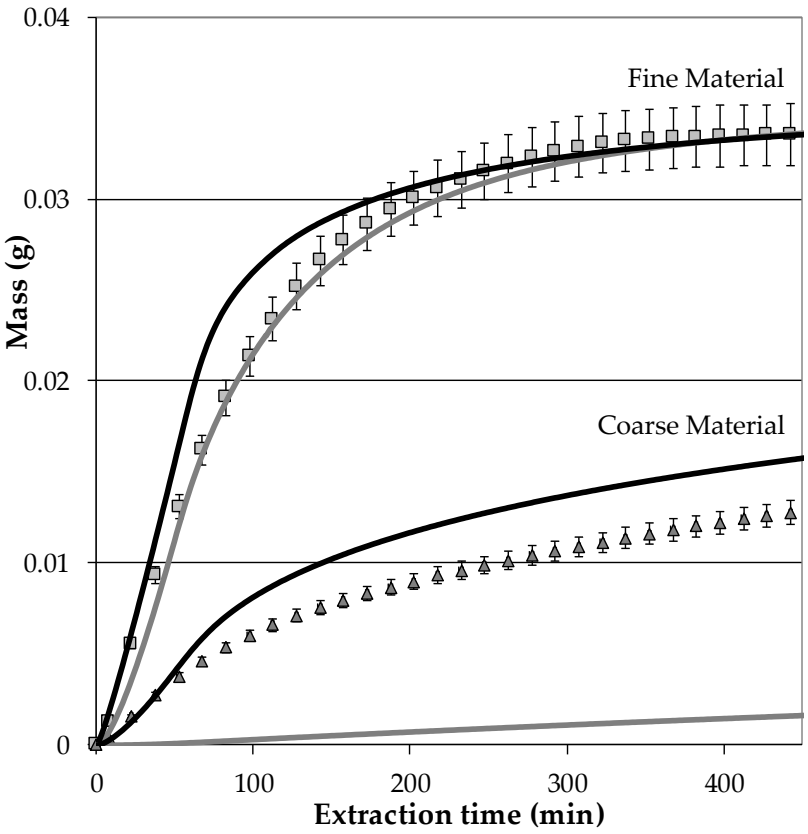


Figure 10. Extraction progress, simulation (continuous lines), and experiments (points) for two different particle size distributions, (black line: simulation with PSD and grey line: simulation with mean particle diameter).

Of course, the optimal process is almost never the sum of the single unit operation optima. Therefore, total process integration and optimization of the complete process chain yields the main profit, as proven in various studies, (e.g., [43,65]). These studies lead to the consequence that particle size, as an essential parameter for extraction, should always be integrated into manufacturing operations, as proposed in the following section.

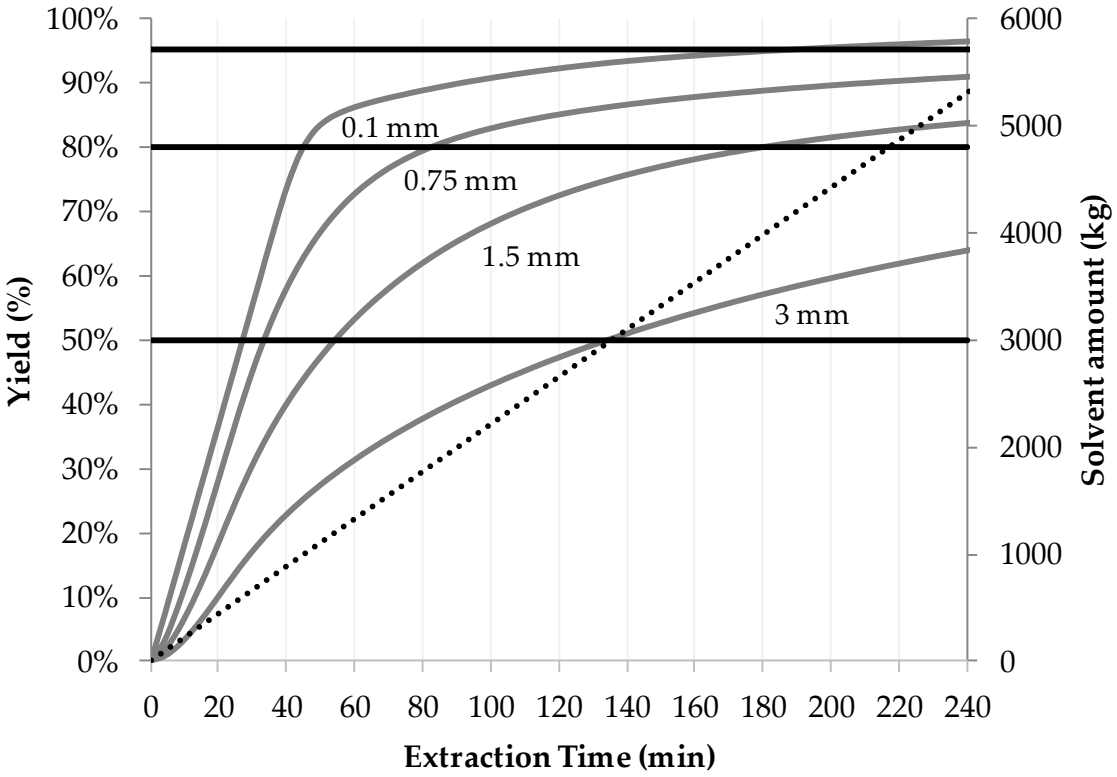


Figure 11. Yield and Solvent Consumption for hawthorn at different mean particle diameters [35].

6. Integrated Continuous Pre-Treatment and Extraction (iCPE)

One key parameter for fast and exhaustive extraction is a small particle diameter due to the higher specific surface area of the ground herbal raw material. The tremendous influence is shown by simulation studies in Figure 12. Different extraction curves considering mean particle diameters from 0.05 mm to 2 mm pare simulated. After 600 min of extraction, only about 20% yield compared to the overall amount of the considered target component is reached at 2 mm. The productivity of the extraction increases significantly with smaller particles; thus, a 95% yield is reached within 110 min using particles with a mean diameter of 0.05 mm. At the same time, the solvent quantity is reduced by 3%.

By applying small particle diameters in extraction, the productivity can be increased drastically, while extraction time and solvent consumption decrease. For that, a continuous operation mode is needed to avoid a bottleneck shift from a slow extraction towards an inefficient handling in between different batches.

6.1. Integrated Continuous Pretreatment and Extraction (iCPE) Process

According to the flow scheme, Figure 13, the herbal raw material is first chopped with a crusher, and then further ground with a ball mill. The particles are constantly blown out of the mill by a fan and transported to a zigzag separator. In the separator itself, a separation takes place, and the large particles are sent back to the mill, purging out a certain quantity. The small particles pass an in-line particle imaging system that controls the mill and the fan in order to get the desired mean particle diameter and distribution. The particles are blown into a percolation column equipped with a pivoted frit at each side. For column filling, the lower frit is closed; therefore, the particles are segregated into the column while the air passes through the frit (Step1). After loading is complete, the column is closed and extraction takes place (Step 2). In the meantime, another column, being in stand-by mode during Steps 1 and 2, is swapped into the filling-position, thus ensuring a continuous operation mode (Step 3).

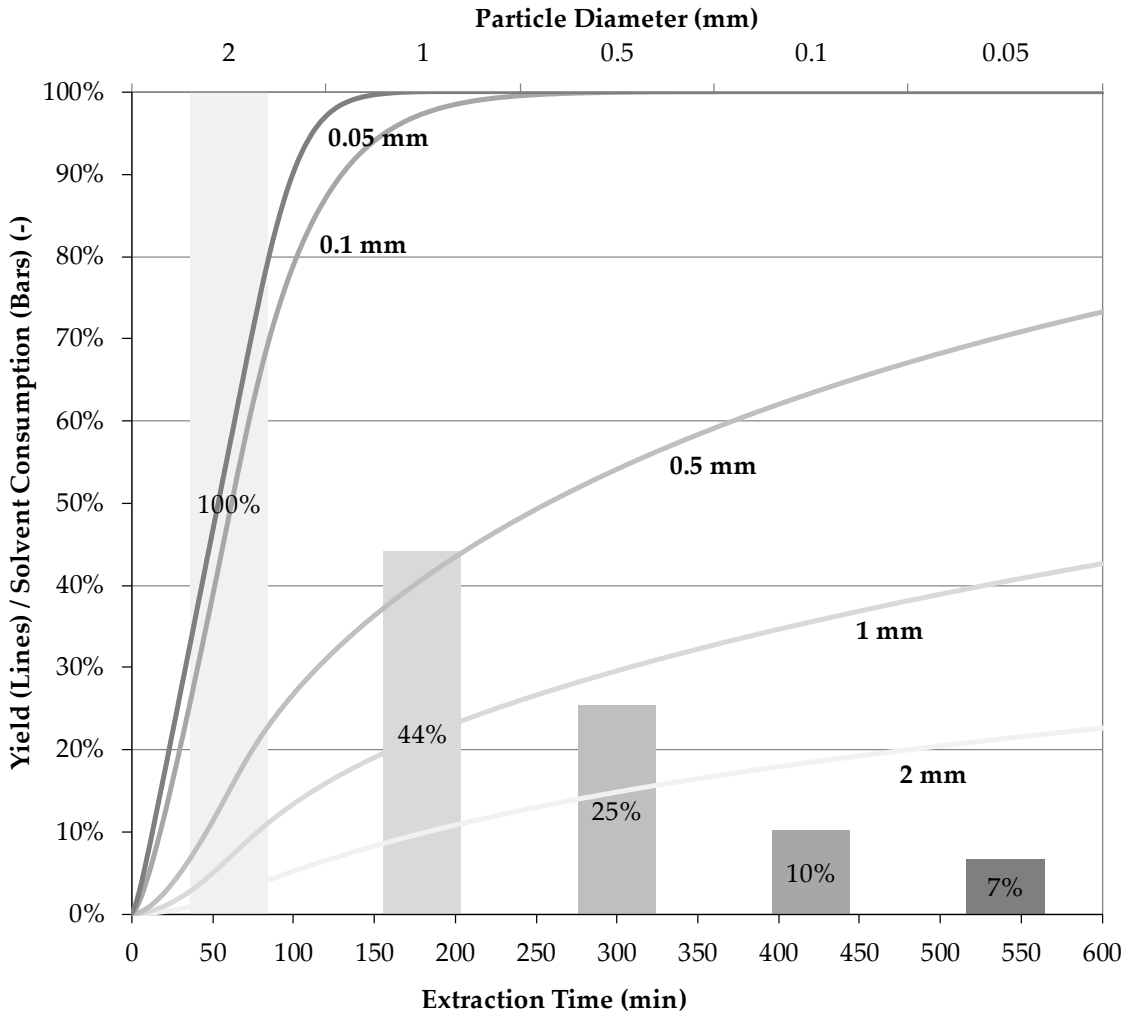


Figure 12. Simulated extraction curves and relative solvent consumptions for different mean particle diameters.

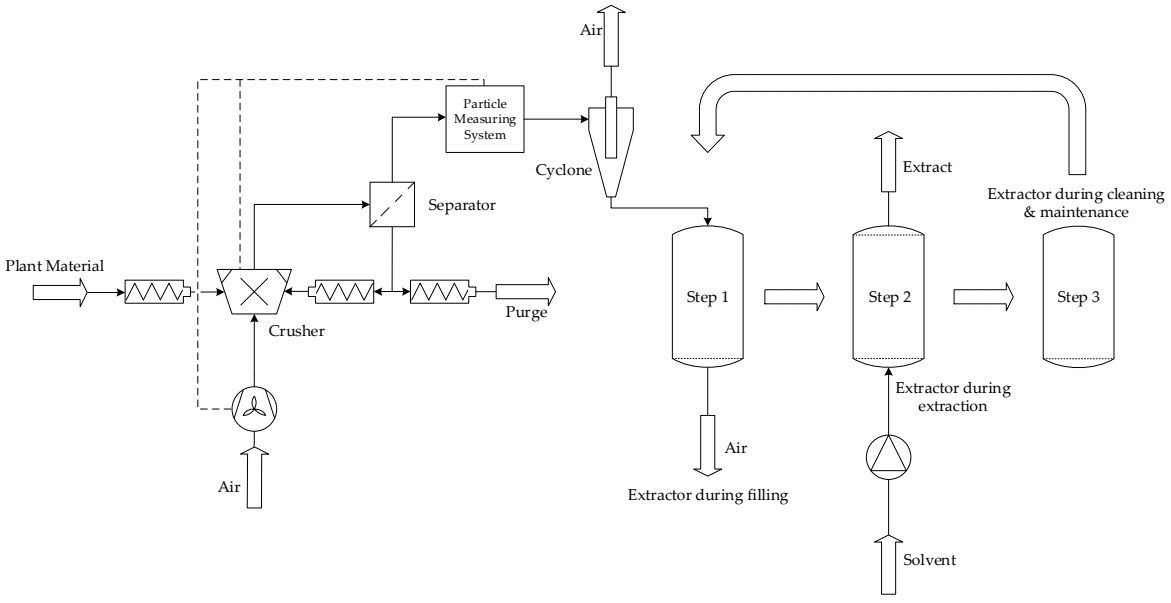


Figure 13. Process proposal for the Integrated Continuous Pretreatment and Extraction (iCPE).

6.2. Cost Calculation and Results of the iCPE Process

A comparison of four different processes is presented in Figure 14. The benchmark is based on a case study for the extraction of 10-deacetylbaccatin III from yew (*Taxus baccata* L.). The extraction takes place in one single 20 m^3 percolation column for 2 h, without milling. Afterwards, a 2 h period of refilling is required. In order to recycle the solvent (a mixture of acetone and water), it is partly evaporated with an agitated film evaporator. These two steps are considered as the standard apparatus for this special case [43].

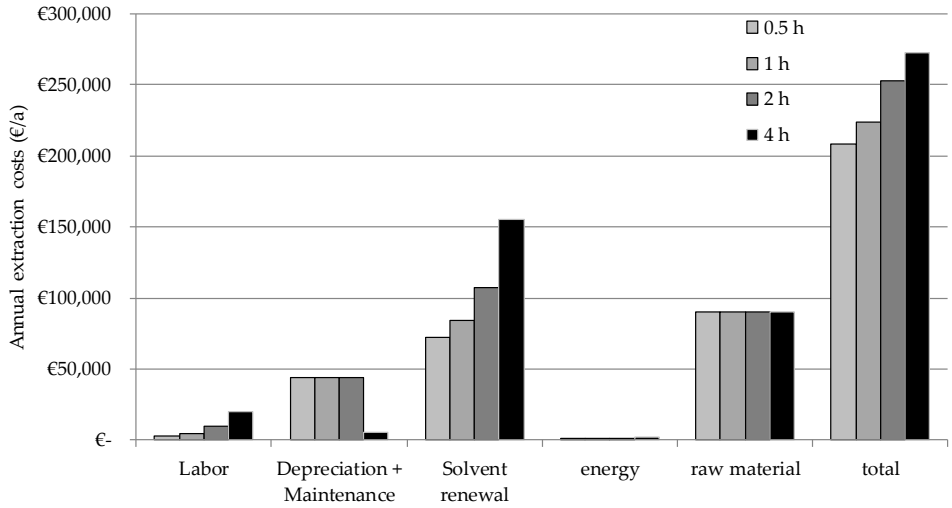


Figure 14. Annual extraction cost reduction by reduced extraction time for Hawthorn.

At three different scales, namely 10 m^3, 5 m^3 and 3 m^3 percolation columns, 2400 t/a of yew needles are extracted. It becomes obvious that the solvent amount can be reduced drastically, as extraction can take place much more rapidly when the particles are ground instead of just chopped.

This also results in lower operation costs, although 20% of the investment costs per year are considered as maintenance expenses compared to only 10% in the benchmark, because a smaller amount of solvent has to be recycled or replaced. The investment costs rise from the benchmark process to the alternative with 10 m^3 percolators, due to the high equipment costs of the mill. The need for smaller apparatus sizes in the 5 m^3 and the 3 m^3 case result in lower investment costs compared to the benchmark. Due to the smaller dimensions of the percolators, the number of batches rises from 375 in the benchmark process to 2500 in the 3 m^3 case. The same occurs with the total process time; that is, roughly 2600 h/a in the benchmark process and 7500 h/a for the 3 m^3 case, which has to be considered as continuously operating. It is obvious that the process proposal provides great potential for:

- reducing the solvent amount,
- minimizing costs for solvent storage, recycling and replacement,
- continuously running fully automated solid-liquid extraction,
- replacing established processes with state-of-the art technology with comparable or even lower CAPEX,
- reducing COG.

Potential for further intensification could be the focus on green extractions technologies [6].

7. Water-Based Green Extraction Processing

Conventional solid-liquid extraction of herbal raws, either for further isolating one single substance or to sell the extract as phytomedicine, often utilizes organic solvents. Despite the advantage of pressurized hot water extraction to extract non-polar substances [46], organic solvents will certainly

play an important role over the next decades. Especially for products which are less in demand, solvent costs dominate the whole process, as depicted in Figure 15.

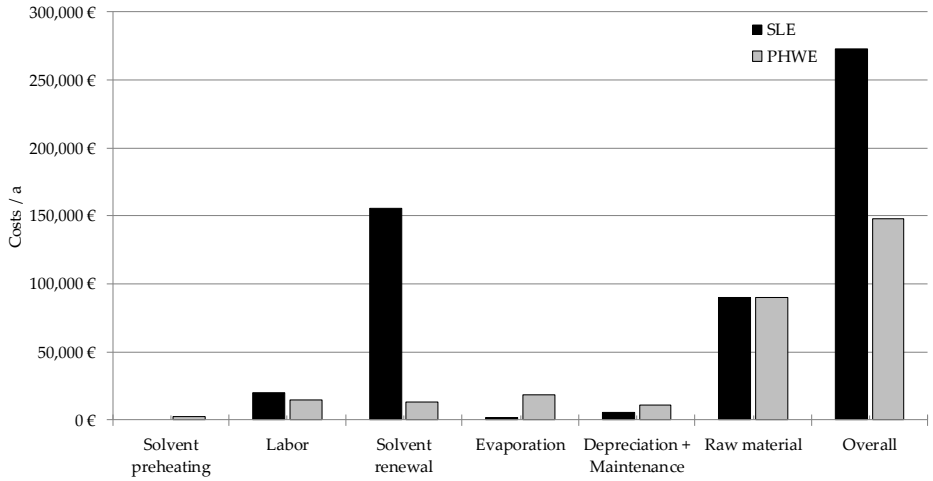


Figure 15. Annual Cost of Goods for hawthorn, Comparison SLE and PHWE [50].

The assumptions for the cost calculation are as follows:

- 30 t of leaves are extracted in 60 batches a year in a multi-purpose herbal raw. The costs for the herbal raw material is 3 €/kg and the yearly capacity of this product is 25%.
- An extraction equipment with 2 m^3 of volume is used. The investment cost is 200,000 €.
- The extraction takes place for four hours and the solvent ratio is 2.7 kg Solvent/kg Herbal raw material/h.
- The extract is evaporated for solvent recycling purpose. Steam is used (120 °C, 5 bar, 2.7 MJ/kg) to operate the evaporator. The costs are 13 €/t which is typical for a site infrastructure.
- 10% of the solvent has to be renewed after each extraction due to loss. Moreover, the whole solvent (20 m^3) is exchanged once a year to maintain a constant product quality. The solvent is priced at 3 €/kg.
- Labor costs are 100,000 €/a.
- The costs for yearly depreciation and maintenance are 2.5% each (multi-purpose herbal raw).

Totally water-based processes exemplify the Green Extraction [6,66,67] approach perfectly. Additionally, they are kosher and halal, directly GRAS, and therefore, represent ideal manufacturing technology for the market demands. A process sequence of PHWE and NF for concentration, followed by purification based on chlorophyll precipitation, liquid-liquid extraction for pre-purification and/or chromatography with final formulation by crystallization or direct lyophilisation seems to be the most direct and logical manufacturing technology approach for the future, efficiently generating reliable product quality under all marked regulation demands.

This could be systematically achieved by the QbD-(Quality by Design) approach, which is demanded by regulatory authorities like FDA and EMA [68–70]. A central part of such innovative approval documentation is manufacturing operation robustness gained by implementation of process analytical technologies (PAT) [44].

8. Inline Process Control in Phyto Extraction

Inline process control is established in the sugar industry for adequate payment of cultivating farmers due to the actual sugar content of beet with the aid of NIR directly on the tractor [71]. NIR is an efficient tool for water content determination [60]. FTIR- and Raman-mapping technologies are state of the art at e.g., JKI Berlin for cultivation origin determination. Moreover, those techniques,

as well as CLSM, have proven their usefulness in process design [53,61,63]. Techniques adopted in process development with PCA/PCS-analysis toward the individual component system have the potential to become key-enabling technologies for process control under modern PAT (process analytical technology) approaches within QbD-Process design and operation. Figure 16 exemplifies such a result for the extraction anethol and fenchone.

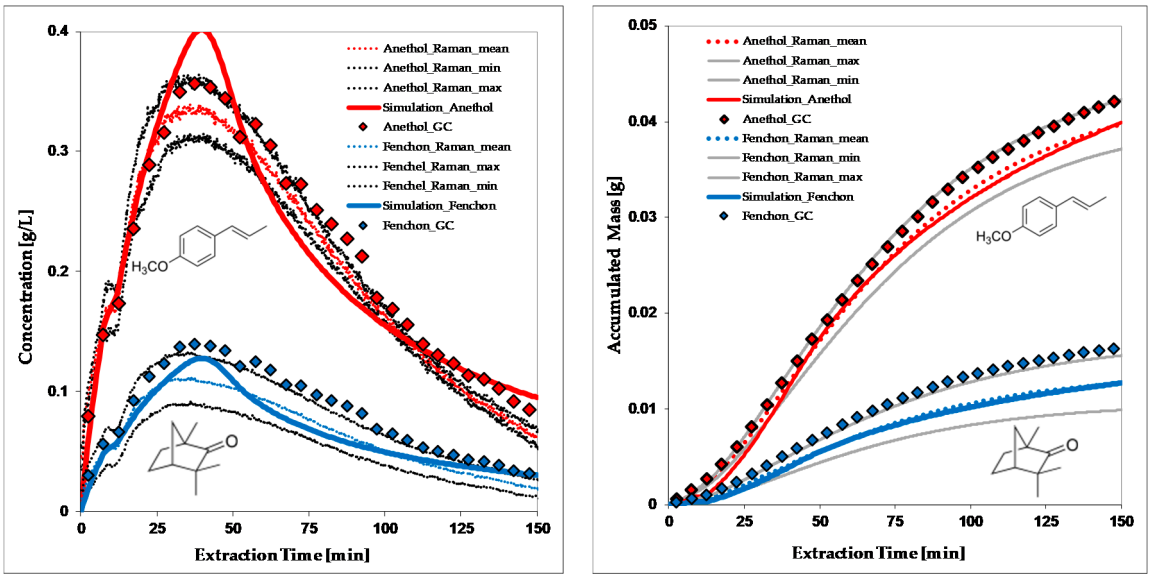


Figure 16. Concentration measurement by raman spectroscopy of anethol (dark grey) and fenchone (light grey) during extraction [44].

9. Options and Opportunities for Future Value Generation

Figure 17 displays a flexible modular manufacturing concept for herbal raw materials at a small scale, which, due to its continuous operation scheduling, may well act as a potential technical solution for SMEs on their way to becoming fully-integrated manufacturers. Only fully-integrated manufacturers with end customer access will be able to gain significant margins, as shown previously. One obstacle for SMEs is investment volume, which needs to be small and refundable for one single product. Here, typical scenarios for either 1 mi. € investment for a standardized extract at 10–50 €/kg dry extract cost or a higher value API at 50–100 €/kg product COGs at 5 mio. € is visualized, e.g., in a container design. In those scenarios, return on investment can be less than 3 years.

Business targets are moving due to changing markets and growing competition, as well as national regulatory decisions. The market demand increases, but industry does not move fast enough to ensure survival. Underlining this point is the fact that most companies do not invest in research and development at all, and are not seeking any product or technology innovation. Not to invest in their own future is not a strategic option. On the contrary, product innovation towards a higher market value is the only protection against increasing regulatory demands.

The market potential of natural products is hampered by efficacy constraints, because they too often lack sufficient definition and testing. QbD, instead of DER, definition is urgently required to cope with natural batch variability in manufacturing operation in order to gain defined products which are within specifications, and with less batch failures.

Manufacturing has not invested sufficiently in recent technology developments over the last 10–15 years of research. Detailed analysis points out that a process of industrialization of research and innovation is needed now to maintain and advance the natural products industry, and has the potential to solve the general challenge of manufacturing cost efficiency and product efficacy in combination with the robustness and reliability issues.

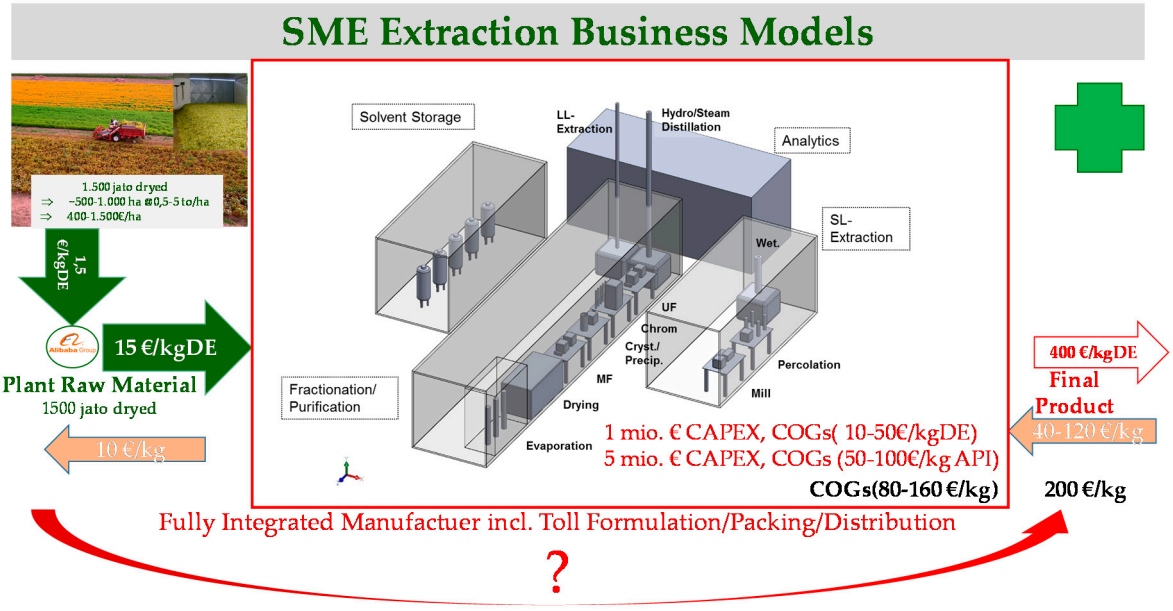


Figure 17. Business model for especially SMEs in phytomedicine manufacturing. CAPEX, capital expenditure; LL, Liquid-Liquid; MF, Microfiltration; UF, Ultrafiltration, SL, Solid-Liquid. (compare Figure 1).

One organizational approach could be the creation of regional agricultural cooperatives, as the sugar and hop industries chose to do, becoming fully integrated manufacturers with moderate investments, thereby gaining the full added value of the end product.

The cost scenarios analyzed show potential for dried extracts (DE) in the 10–50 €/kg range, as well as purified active ingredients (API) in 50–100 €/kg magnitude, which seems realistic within the typical sales price range.

As options for further growth, agricultural co-operatives are needed, alternative state supported infrastructures of technical centers, or medium-size single product manufacturers should be strengthened to enable fast direct access to the technology by first prototype centers. Besides the Clausthal Institute, in Europe, France, seems to be most advanced country for the implemention of such regional strategies, strengthening the local economy from agriculture to pharmaceutical, nutraceutical, aroma/flavors, and cosmetics manufacturing [72].

As a summary, infrastructure and technology exists and is accessible for industrialization, leaving no excuse for decision makers in industry [73].

For example, new active substances are urgently needed against infectious diseases. The development of new antibiotics against resistant microbes is laborious, and obviously does not offer the high commercial incentives expected by big-pharma. Therefore, a clear impulse for industry has to be set to change this situation in favor of research in this field of urgent societal needs by national and international funding organizations, part of which has already been started. Ideas and proposals for either API-substances or herbal sources could, in the meantime, be efficiently and within short timelines transferred to industrialization with the aid of modern process development and design tools, as well as modern manufacturing technologies, as discussed earlier in this contribution. Herbal raw material is still an indisputably innovative source provided by nature, which is far from being fully exploited and industrialized.

10. Conclusions

In conclusion, a suitable approach may be to switch to, or at least to put more emphasis on, standardized extracts, complete with efficacy studies and new approval processes supported by QbD-based process design, which enables process operation at its economical optimum. This is

beneficial, if not essential, to maintaining or regaining competitiveness in existing markets. Firstly, the batch variability of typical natural feedstocks can be accounted for in the process design.

Beyond that, it creates the technical basis for addressing increasing societal needs in the product development of innovative, plant-based antibiotics, and/or green and sustainable, resource-efficient manufacturing concepts with additional consumer benefits.

The key role of plants in the medicinal and pharmaceutical fields for thousands of years is undisputed; however, it has had its difficulties. Nevertheless, even today, innovative molecules with therapeutic potential are quite often based on plants, which, in principle, have been known for decades or even centuries. Being able to break down complex natural mixtures into individual molecules or groups of molecules by advanced analytical tools allows the characterization and testing for specific pharmaceutical/medicinal applications. Some of the best examples for successful applications in cancer and malaria treatments are Taxol and Artemisinin.

Maybe the variety of plants and their broad scope of beneficial applications in healthcare might be exploited to find solutions to one of the biggest threats to humankind in this day and age, i.e., the search for new antibiotic effects against MRSA.

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Abbreviations

a_F	Particle surface, m^2
CAPEX	Capital expentitures
c_L	Concentration in the liquid phase, kg/m^3
COG	Cost of goods
c_P	Concentration in the porous particle, kg/m^3
D_{ax}	Axial dispersion coefficient, m/s^2
DE	dry extract
D_{eff}	Effective diffusion coefficient, m^2/s
DER	drug extract ratio
d_F	Particle diameter m
DPF	Distributed plug flow
EMPL	employee
K_L	Equilibrium constant, m^3/kg
k_f	Mass transport coefficient, m/s
Pe	Péclet number
PSD	Particle size distribution
q	Loading, kg/m^3
q_{max}	Maximum Loading, kg/m^3
Re	Reynolds number
r	Radius, m
Sc	Schmidt number
Sh	Sherwood number

SME	Small and medium-sized enterprise
SP	selling price
t	Time, s
u_z	Superficial velocity, m/s
V	Volume flow, m^3/s
z	Coordinate in axial direction, m
ε	Voids fraction, -
ρ	Density, kg/m^3

References

1. Cragg, G.M.; Newman, D.J. Natural products: A continuing source of novel drug leads. *Biochim. Biophys. Acta* **2013**, *1830*, 3670–3695. [CrossRef] [PubMed]
2. Li, W.L.; Zheng, H.C.; Bukuru, J.; de Kimpe, N. Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. *J. Ethnopharmacol.* **2004**, *92*, 1–21. [CrossRef] [PubMed]
3. Atanasov, A.G.; Waltenberger, B.; Pferschy-Wenzig, E.-M.; Linder, T.; Wawrosch, C.; Uhrin, P.; Temml, V.; Wang, L.; Schwaiger, S.; Heiss, E.H.; et al. Discovery and resupply of pharmacologically active plant-derived natural products: A review. *Biotechnol. Adv.* **2015**, *33*, 1582–1614. [CrossRef] [PubMed]
4. Ditz, R.; Gerard, D.; Hagels, H.; Igl, N.; Schäffler, M.; Schulz, H.; Stürtz, M.; Tegtmeier, M.; Treutwein, J.; Strube, J.; et al. *Phytoextracts: Proposal towards a New Comprehensive Research Focus*; DECHEMA Gesellschaft für Chemische Technik und Biotechnologie e.V.: Frankfurt, Germany, 2017.
5. Bart, H.-J.; Pilz, S. *Industrial Scale Natural Products Extraction*; Wiley-VCH: Weinheim, Germany, 2011.
6. Chémat, F.; Strube, J. (Eds.) *Green Extraction of Natural Products: Theory and Practice*; Wiley VCH: Weinheim, Germany, 2015.
7. Veeresham, C. Natural products derived from plants as a source of drugs. *J. Adv. Pharm. Technol. Res.* **2012**, *3*, 200–201. [CrossRef] [PubMed]
8. Newman, D.J.; Cragg, G.M. Natural products as sources of new drugs over the last 25 years. *J. Nat. Prod.* **2007**, *70*, 461–477. [CrossRef] [PubMed]
9. Lopez, S.N.; Ramallo, I.A.; Sierra, M.G.; Zacchino, S.A.; Furlan, R.L.E. Chemically engineered extracts as an alternative source of bioactive natural product-like compounds. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 441–444. [CrossRef] [PubMed]
10. Mahmood, H.Y.; Jamshidi, S.; Sutton, J.M.; Rahman, K.M. Current Advances in Developing Inhibitors of Bacterial Multidrug Efflux Pumps. *Curr. Med. Chem.* **2016**, *23*, 1062–1081. [CrossRef] [PubMed]
11. Posadzki, P.; Watson, L.; Ernst, E. Herb-drug interactions: An overview of systematic reviews. *Br. J. Clin. Pharmacol.* **2013**, *75*, 603–618. [CrossRef] [PubMed]
12. Newman, D. Screening and identification of novel biologically active natural compounds. *F1000Research* **2017**, *6*, 783. [CrossRef] [PubMed]
13. Ramallo, I.A.; Salazar, M.O.; Mendez, L.; Furlan, R.L.E. Chemically Engineered Extracts: Source of Bioactive Compounds. *Acc. Chem. Res.* **2011**, *44*, 241–250. [CrossRef] [PubMed]
14. Ta, C.; Arnason, J. Mini Review of Phytochemicals and Plant Taxa with Activity as Microbial Biofilm and Quorum Sensing Inhibitors. *Molecules* **2016**, *21*, 29. [CrossRef] [PubMed]
15. Kalia, V.C.; Wood, T.K.; Kumar, P. Evolution of Resistance to Quorum-Sensing Inhibitors. *Microb. Ecol.* **2014**, *68*, 13–23. [CrossRef] [PubMed]
16. Borges, A.; Abreu, A.; Dias, C.; Saavedra, M.; Borges, F.; Simões, M. New Perspectives on the Use of Phytochemicals as an Emergent Strategy to Control Bacterial Infections Including Biofilms. *Molecules* **2016**, *21*, 877. [CrossRef] [PubMed]
17. Aparna, V.; Dineshkumar, K.; Mohanalakshmi, N.; Velmurugan, D.; Hopper, W. Identification of Natural Compound Inhibitors for Multidrug Efflux Pumps of Escherichia coli and Pseudomonas aeruginosa Using In Silico High-Throughput Virtual Screening and In Vitro Validation. *PLoS ONE* **2014**, *9*, e101840. [CrossRef] [PubMed]
18. Nascimento, G.G.F.; Locatelli, J.; Freitas, P.C.; Silva, G.L. Antibacterial activity of plant extracts and phytochemicals on antibiotic-resistant bacteria. *Braz. J. Microbiol.* **2000**, *31*, 247–256. [CrossRef]

19. Efferth, T.; Kahl, S.; Paulus, K.; Adams, M.; Rauh, R.; Boechzelt, H.; Hao, X.; Kaina, B.; Bauer, R. Phytochemistry and pharmacogenomics of natural products derived from traditional Chinese medicine and Chinese materia medica with activity against tumor cells. *Mol. Cancer Ther.* **2008**, *7*, 152–161. [CrossRef] [PubMed]
20. Europäisches Zentrum für die Prävention und die Kontrolle von Krankheiten. *The Bacterial Challenge, Time to React: A Call to Narrow the Gap between Multidrug-Resistant Bacteria in the EU and the Development of New Antibacterial Agents*; ECDC: Stockholm, Sweden, 2009.
21. DECHEMA e.V. Biobased World. Available online: https://www.biobasedworldnews.com/ (accessed on 22 June 2018).
22. Bundesministerium für Bildung und Forschung (BMBF). *Wegweiser Bioökonomie—Forschung für Biobasiertes und Nachhaltiges Wirtschaftswachstum*; BMBF: Berlin, Germany, 2014.
23. Jamshidi Aidji, M.; Morlock, G. *Effect Directed Analysis of Salvia Officinalis, Poster Presentation*; University of Giessen: Gießen, Germany, 2014.
24. Morlock, G.; Schwack, W. Hyphenations in planar chromatography. *J. Chromatogr. A* **2010**, *1217*, 6600–6609. [CrossRef] [PubMed]
25. Staniek, A.; Bouwmeester, H.; Fraser, P.D.; Kayser, O.; Martens, S.; Tissier, A.; van der Krol, S.; Wessjohann, L.; Warzecha, H. Natural products—Learning chemistry from plants. *Biotechnol. J.* **2014**, *9*, 326–336. [CrossRef] [PubMed]
26. European Medicines Agency. *Assessment Report on Echinacea purpurea (L.) Moench, Radix*; University of Ljubljana: Ljubljana, Slovenia, 2017.
27. European Medicines Agency. *European Union Herbal Monograph on Echinacea purpurea (L.) Moench, Radix*; European Medicines Agency: London, UK, 2017.
28. Council of Europe. *European Pharmacopoeia*, 8th ed.; Published in Accordance with the Convention on the Elaboration of a European Pharmacopoeia (European Treaty Series No. 50); Council of Europe: Strasbourg, France, 2013–2015.
29. Food and Drug Administration (FDA). *Guidance for Industry—Botanical Drug Development*; FDA: Silver Spring, MD, USA, 2016.
30. Food and Drug Administration (FDA). Dietary Supplements. Available online: https://www.fda.gov/Food/DietarySupplements/ProductsIngredients/default.htm (accessed on 21 September 2018).
31. Chinese Food and Drug Administration (CFDA). Verification and Issuance of Registration Certificates for Imported (Incl. from Hong Kong, Macao and Taiwan) TCM and Natural Medicine. Available online: http://eng.sfda.gov.cn/WS03/CL0769/98141.html (accessed on 21 September 2018).
32. Akerele, O. WHO traditional medicines programme: Progress and perspectives. *WHO Chron.* **1984**, *38*, 76–81. [PubMed]
33. Chaing, H.S.; Merino-Chavez, G.; Yang, L.L.; Hafez, E.S.E. Medical plants: Conception/Contratception. *Adv. Contracept Deliv Syst.* **1994**, *10*, 355–363. [PubMed]
34. Chotchoungchatchai, S.; Saralamp, P.; Jenjittikul, T.; Pornsiripongse, S.; Prathanturarug, S. Medicinal plants used with Thai Traditional Medicine in modern healthcare services: A case study in Kabchoeng Hospital, Surin Province, Thailand. *J. Ethnopharmacol.* **2012**, *141*, 193–205. [CrossRef] [PubMed]
35. Wagner, H.; Ulrich-Merzenich, G. (Eds.) *Evidence and Rational Based Research on Chinese Drugs*; Springer: Vienna, Austria, 2013.
36. Giovannini, P.; Howes, M.-J.R.; Edwards, S.E. Medicinal plants used in the traditional management of diabetes and its sequelae in Central America: A review. *J. Ethnopharmacol.* **2016**, *184*, 58–71. [CrossRef] [PubMed]
37. Govindaraghavan, S.; Sucher, N.J. Quality assessment of medicinal herbs and their extracts: Criteria and prerequisites for consistent safety and efficacy of herbal medicines. *Epilepsy Behav.* **2015**, *52*, 363–371. [CrossRef] [PubMed]
38. Pferschy-Wenzig, E.-M.; Bauer, R. The relevance of pharmacognosy in pharmacological research on herbal medicinal products. *Epilepsy Behav.* **2015**, *52*, 344–362. [CrossRef] [PubMed]
39. Russo, G.L. Ins and outs of dietary phytochemicals in cancer chemoprevention. *Biochem. Pharmacol.* **2007**, *74*, 533–544. [CrossRef] [PubMed]
40. Schuster, B.G. A new integrated program for natural product development. *J. Altern. Complement. Med.* **2001**, *7*, 61–72. [CrossRef]

41. Food and Drug Administration (FDA). *Guidance for Industry. PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*; FDA: Silver Spring, MD, USA, 2004.
42. Food and Drug Administration (FDA). *Pharmaceutical cGMP for the 21st Century: A Risk Based Approach*; FDA: Silver Spring, MD, USA, 2004.
43. Sixt, M.; Koudous, I.; Strube, J. Process design for integration of extraction, purification and formulation with alternative solvent concepts. *C. R. Chim.* **2016**, *19*, 733–748. [CrossRef]
44. Sixt, M.; Gudi, G.; Schulz, H.; Strube, J. In-line Raman spectroscopy and advanced process control for the extraction of anethole and fenchone from fennel (*Foeniculum vulgare* L. MILL.). *C. R. Chim.* **2018**, *21*, 97–103. [CrossRef]
45. Sixt, M.; Uhlenbrock, L.; Strube, J. Toward a Distinct and Quantitative Validation Method for Predictive Process Modelling—On the Example of Solid-Liquid Extraction Processes of Complex Plant Extracts. *Processes* **2018**, *6*, 66. [CrossRef]
46. Sixt, M.; Strube, J. Pressurized hot water extraction of 10-deacetylbaccatin III from yew for industrial application. *Resour. Effic. Technol.* **2017**, *3*, 177–186. [CrossRef]
47. Uhlenbrock, L.; Sixt, M.; Strube, J. Quality-by-Design (QbD) process evaluation for phytopharmaceuticals on the example of 10-deacetylbaccatin III from yew. *Resour. Effic. Technol.* **2017**, *3*, 137–143. [CrossRef]
48. Wübbeke, J.; Meissner, M.; Zenglein, M.J.; Ives, J.; Conrad, B. *Made in China 2025: The Making of a High-Tech Superpower and Consequences for Industrial Countries*; Mercator Institute for China Studies: Berlin, Germany, 2016.
49. Sixt, M.; Strube, J. Systematic Design and Evaluation of an Extraction Process for Traditionally Used Herbal Medicine on the Example of Hawthorn (*Crataegus monogyna* JACQ.). *Processes* **2018**, *6*, 73. [CrossRef]
50. Sixt, M. *Entwicklung von Methoden zur systematischen Gesamtprozessentwicklung und Prozessintensivierung von Extraktions- und Trennprozessen zur Gewinnung pflanzlicher Wertkomponenten*; Clausthal University of Technology: Clausthal-Zellerfeld, Germany; Shaker: Aachen, Germany, 2018.
51. Kassing, M.; Jenelten, U.; Schenk, J.; Hänsch, R.; Strube, J. Combination of Rigorous and Statistical Modeling for Process Development of Plant-Based Extractions Based on Mass Balances and Biological Aspects. *Chem. Eng. Technol.* **2012**, *35*, 109–132. [CrossRef]
52. Kassing, M.; Jenelten, U.; Schenk, J.; Strube, J. A New Approach for Process Development of Plant-Based Extraction Processes. *Chem. Eng. Technol.* **2010**, *33*, 377–387. [CrossRef]
53. Kaßing, M. *Process Development for Plant-Based Extract Production*; Clausthal University of Technology: Clausthal-Zellerfeld, Germany; Shaker: Aachen, Germany, 2012.
54. Both, S.; Eggersglüß, J.; Lehnberger, A.; Schulz, T.; Schulze, T.; Strube, J. Optimizing Established Processes like Sugar Extraction from Sugar Beets—Design of Experiments versus Physicochemical Modeling. *Chem. Eng. Technol.* **2013**, *36*, 2125–2136. [CrossRef]
55. Both, S. *Systematische Verfahrensentwicklung für Pflanzlich Basierte Produkte im Regulatorischen Umfeld*; Clausthal University of Technology: Clausthal-Zellerfeld, Germany; Shaker: Aachen, Germany, 2015.
56. Both, S.; Chemat, F.; Strube, J. Extraction of polyphenols from black tea—Conventional and ultrasound assisted extraction. *Ultrason Sonochem.* **2014**, *21*, 1030–1034. [CrossRef] [PubMed]
57. Ndocko Ndocko, E.; Bäcker, W.; Strube, J. Process Design Method for Manufacturing of Natural Compounds and Related Molecules. *Sep. Sci. Technol.* **2008**, *43*, 642–670. [CrossRef]
58. Goedecke, R. *Fluidverfahrenstechnik*; Wiley-VCH: Hoboken, NI, USA, 2008.
59. Sixt, M.; Strube, J. Systematic and Model-Assisted Evaluation of Solvent Based- or Pressurized Hot Water Extraction for the Extraction of Artemisinin from *Artemisia annua* L. *Processes* **2017**, *5*, 86. [CrossRef]
60. Koudous, I. *Stoffdatenbasierte Verfahrensentwicklung zur Isolierung von Wertstoffen aus Pflanzenextrakten*; Clausthal University of Technology: Clausthal-Zellerfeld, Germany; Shaker: Aachen, Germany, 2016.
61. Gudi, G.; Krähmer, A.; Koudous, I.; Strube, J.; Schulz, H. Infrared and Raman spectroscopic methods for characterization of *Taxus baccata* L.—Improved taxane isolation by accelerated quality control and process surveillance. *Talanta* **2015**, *143*, 42–49. [CrossRef] [PubMed]
62. Duke, M.V.; Paul, R.N.; Elsohly, H.N.; Sturtz, G.; Duke, S.O. Localization of Artemisinin and Artemisitene in Foliar Tissues of Glanded and Glandless Biotypes of *Artemisia annua* L. *Int. J. Plant. Sci* **1994**, *155*, 365–372. [CrossRef]

63. Gudi, G.; Krähmer, A.; Krüger, H.; Hennig, L.; Schulz, H. Discrimination of Fennel Chemotypes Applying IR and Raman Spectroscopy: Discovery of a New γ-Asarone Chemotype. *J. Agric. Food Chem.* **2014**, *62*, 3537–3547. [CrossRef] [PubMed]
64. Lucke, M.; Koudous, I.; Sixt, M.; Huter, M.J.; Strube, J. Integrating crystallization with experimental model parameter determination and modeling into conceptual process design for the purification of complex feed mixtures. *Chem. Eng. Res. Des.* **2018**, *133*, 264–280. [CrossRef]
65. Helling, C.; Strube, J. *Modeling and Experimental Model Parameter Determination with Quality by Design for Bioprocesses: Biopharmaceutical Production Technology*; Wiley-VCH-Verl: Weinheim, Germany, 2012; pp. 409–445.
66. Chemat, F.; Vian, M.A. (Eds.) *Alternative Solvents for Natural Products Extraction*; Springer: Berlin/Heidelberg, Germany, 2014.
67. Chémat, F.; Vorobiev, E.; Lebovka, N.I. *Enhancing Extraction Processes in the Food Industry*; CRC Press: Boca Raton, FL, USA, 2012.
68. European Medicines Agency, Food and Drug Administration. *EMA-FDA Pilot Program for Parallel Assessment of Quality by Design Applications*; European Medicines Agency, Food and Drug Administration: London, UK, 2011.
69. Food and Drug Administration (FDA). *Guideline for Implimentation of Q9*; FDA: Silver Spring, MD, USA, 2006.
70. ICH Expert Working Group (ICH EWG). *Riskmanagement (Q9). ICH Harmonised Tripartite Guideline. Q9*; ICH Expert Working Group: Geneva, Switzerland, 2005.
71. Roggo, Y.; Duponchel, L.; Huvenne, J.-P. Quality Evaluation of Sugar Beet (*Beta vulgaris*) by Near-Infrared Spectroscopy. *J. Agric. Food Chem.* **2004**, *52*, 1055–1061. [CrossRef] [PubMed]
72. Chémat, F.; Fernandez, X. (Eds.) *La Chimie des Huiles Essentielles: Tradition et Innovation*; Vuibert: Paris, France, 2012.
73. Forschungsvereinigung der Arzneimittel-Hersteller e.V. (FAH). *(FAH). Trainings-Course on Phytoextraction—Process* Design and Operation, Experiments and Modelling October 2017 at the Institute for Separation and Process Technology; Clausthal University of Technology: Clausthal-Zellerfeld, Germany, 2017.