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Phytoextracts

Proposal towards a new comprehensive Research Focus

Position Paper of the ProcessNet-Subject Division Plant Based Extracts – Products and Processes and the European Working Group on Phytoextracts – Products and Processes

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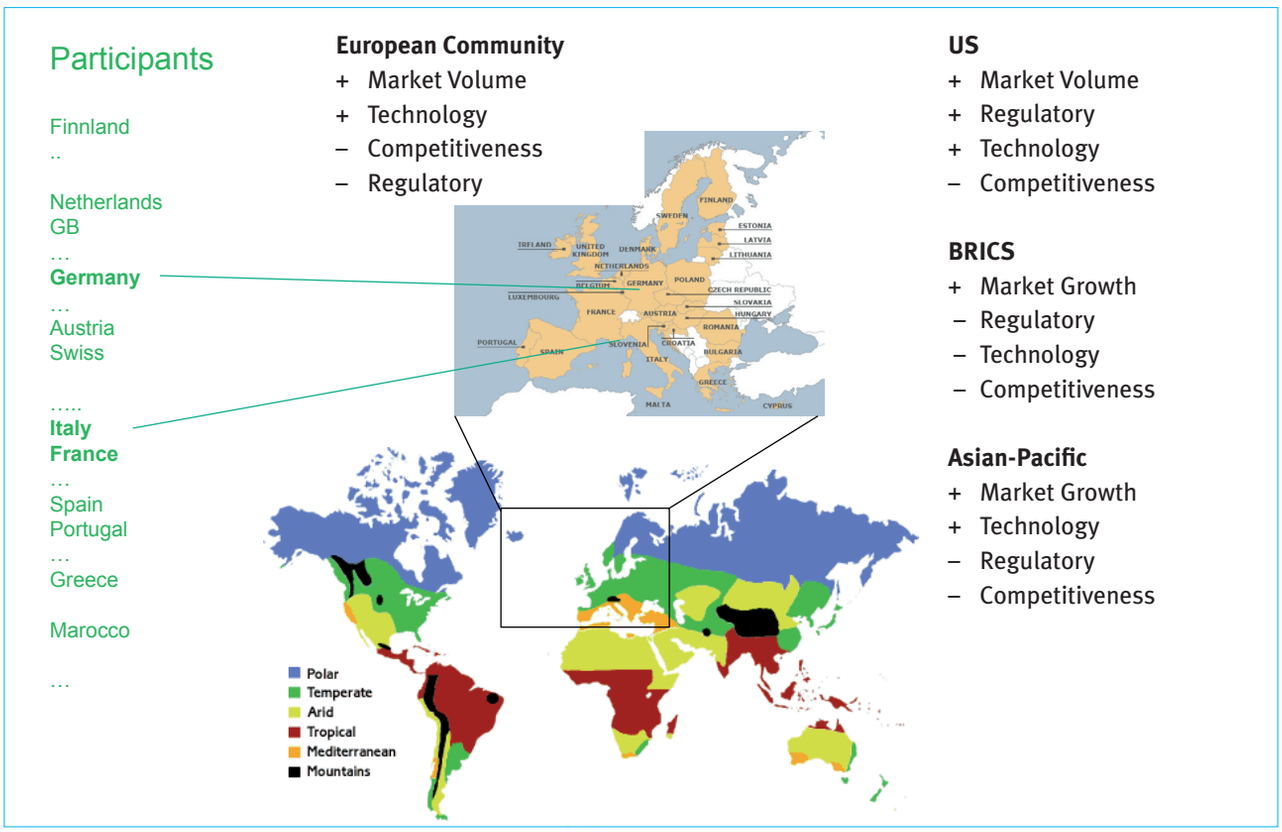

EU players within global phytochemistry market

1. Introduction

This positioning paper of the ProcessNet Subject Division replaces the earlier position papers from 2005 [1] and 2012 [2] due to the various activities and progress of the Subject Division over the past decade, which are also reported/documented in [3, 4, 5].

Historically, plant-based extracts form the basis of medical treatment in nearly all cultures. Additional application fields are their use as food additives, aromas, perfumes, cosmetics as well as agrochemicals.

According to the FAO (Food and Agriculture Organization of the United Nations) the worldwide trade volume for plant extracts was about 1 Trillion USD already in 2003/2004, and annual growth rates between 6% and 8% were reported for plant-based medical foods and phytopharmaceuticals.

In the USA, growth rates were as high as 15% [6].

The world market in 2011 was estimated to be segmented into [7]:

- Phytopharmaceuticals appr. 100 Billion USD with about 25% of total pharma market and double digit annual growth rates, which are a bit lower than growth of total pharma market, [e.g. 8, 9]
- Cosmetic, wellness appr. 200 bil. USD with double digit annular growth rates, in particular within the EU in Russia, Poland, in the Asean-pacific region besides Japan now China, and finally Iran, Irak in the Middle East, and i.e. trend being in anti-ageing, and [10]
- Aroma/Flavours/Parfume market of appr. 10 bil. USD with double digit growth rates, with trend in cosmetics [11, 12]
- Food additives, functional food, nutraceuticals appr. 500 Billion USD [13, 14, 15], and
- Agrochemicals with appr. 1 Billion USD worldwide.

Although plant-based preparations are well accepted by consumers, they are in stiff competition due to the increasing shift towards chemical defined actives. In addition, demands for sustainability in growing and collection of plant-derived raw materials from customer and regulatory side are increasing. For aromas, the natural origin meanwhile has in part become a precondition.

The **phytopharmaceutical** market is divided into that of prescription market – products which have to be prescribed by physicians because they are new or their risk/benefit profile has to be monitored and the non-prescription syn. over the counter (OTC) market – products which can be bought directly by consumers in pharmacies or drug stores.

Within the prescription market they experience a steady decline: while about 28% of all new approved medicinal products were of natural origin (extracts, purified natural compounds and partial synthetics) in 2000 their number declined to only 16% in 2014 [16]. Reasons are the rise of biopharmaceuticals, which are much more tailor made to reach selective targets as well as the competition with combinatorial chemistry combined with high throughput screening – a set of technologies which enables the industry to ensure a faster scale up from the point of target finding up the product launch [17].

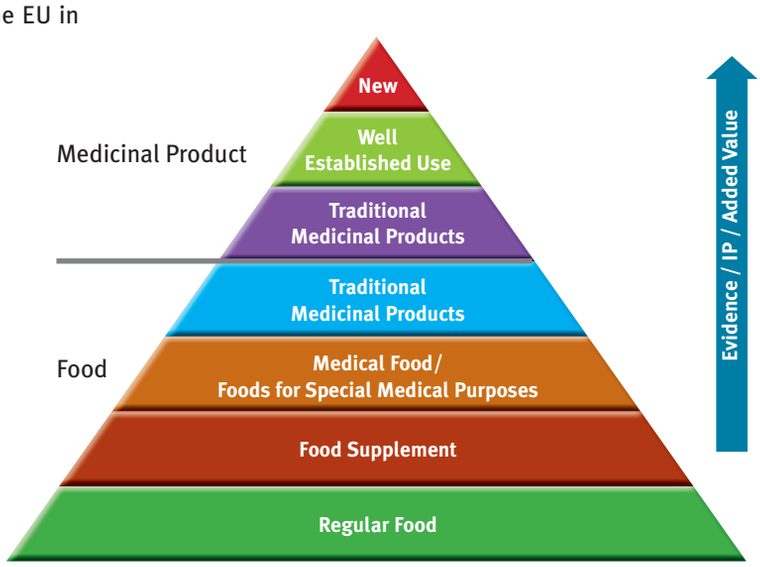

Figure 1: Trend in rising demand for higher standards [18]

Regarding non-prescription phytopharmaceuticals / food additives, which are mainly extracts rather than plant powders, about bn € 32 were globally spent in 2014 with combination products comprising 40% (growing) and mono products 60% in the US. The picture is opposite in Asia, where much more combinations are consumed. Top growth areas are Asia/Pacific and North America with top growth regions (› 20 %) being India, China, Japan, Malaysia, and South Korea, whereas US sales remain comparatively lower (6-8 %), but better than Europe (4-6%) [18].

Generally, non prescriptional mediciane is only used for non-serious illnesses, exemplarily you find the top 10 indications for phytopharmaceuticals in table 1.

Table 1: Top 10 Indications of phytopharmaceuticals and turnover in 2015 in Germany [19]

TOP 10 phytopharmaceuticals	Turnover m. €
other respiratory disorders	258
Cough	170
Blood circulation supporters	165
Stomach and digestion	125
Urologica and urinary passage	97
Tranquilizers and soporifics	94
Cold medicine and flue	86
Cardiovacular health	54
Muscle and joint pain	51
Liver and gall bladder	35

In Europe the market changed drastically mainly because of regulatory issues, e. g. the traditional herbal medicine regulation from 2004 which came into force in 2011 led the industry to switch from the phytopharmaceutical (mainly pharmacies) to herbal supplement (drugstores, groceries, internet) market. Further regulatory issues on the Supplement Market are e. g. the health Claim Regulation (many negative opinions by EFSA; evaluation of botanicals are still on hold) and Novel Food Regulation, which might lead to a switchback to herbal medicinal drugs (Traditional herbal medicinal products). Here the search for traditional herbal remedies which are already in use for a longer time in one member state and market this in the others can be a big opportunity [18].

Within Germany in special the stop of prescription and reimbursement in 2004 lead to a harsh slump in turnover. The sales figures are meanwhile again increasing after several years of steady decline (see table 2)

The OTC phytopharmaceuticals are the figures without homeopathic products which make up another nearly Mio € 500.

This shows that the biggest market within the EU recovers after a weak period, presumably caused by a lack of sufficient raw materials and changing regulatory demands.

Overall, the pharmaceutical market is developing into the direction of higher values regarding level of evidence, protection, and added value. Superior herbal extracts are becoming preferred over less expensive ones, Europe is losing further grounds to the Asian and US markets and Innovation is easier outside Europe [18].

Table 2: Development of German OTC Medicinal Product (in m. €) (Data IMS-Health in Zeitschrift für Phytotherapie) [19]

	2012	2013	2014	2015
OTC market overall	5,608	5,946	6,028	6,412
OTC phytopharmaceuticals thereof	1,230	1,301	1,291	1,369

An austrian group based study [20] points out, see figure 2, that the number of publications on phytopharmaceutica still increase the last years more than corrected by the general increase of publications.

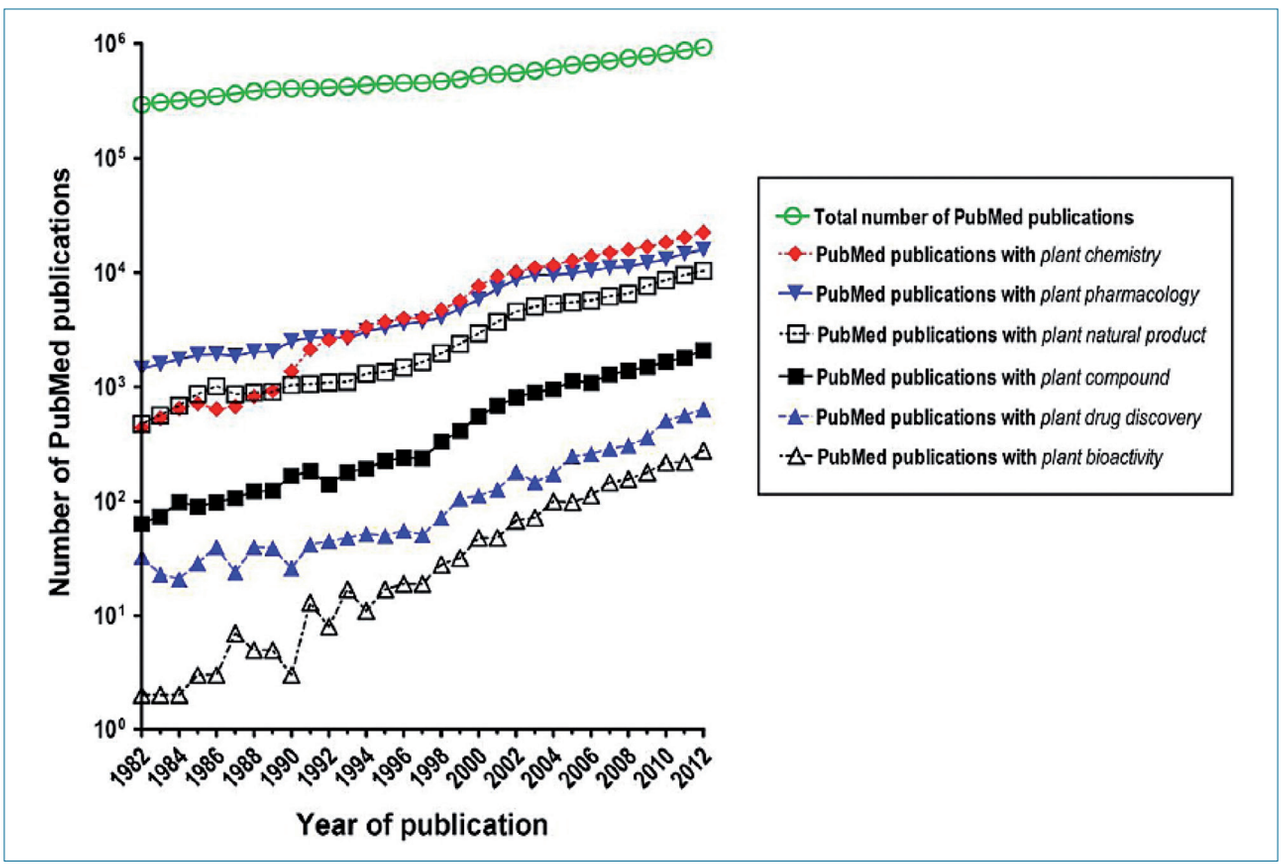

Figure 2: recent publications on phytopharmaca [Atanasov et al.] [20].

As well the market development of NEM (Nahrungsergänzungsmitteln) nutrition additives, to which many plant based extracts belong, is decreasing, see Figure 3.

Figure 4 examplifies shows, that the German NEM-market is almost constant with regard to sales/turn-over (sales price) [21].

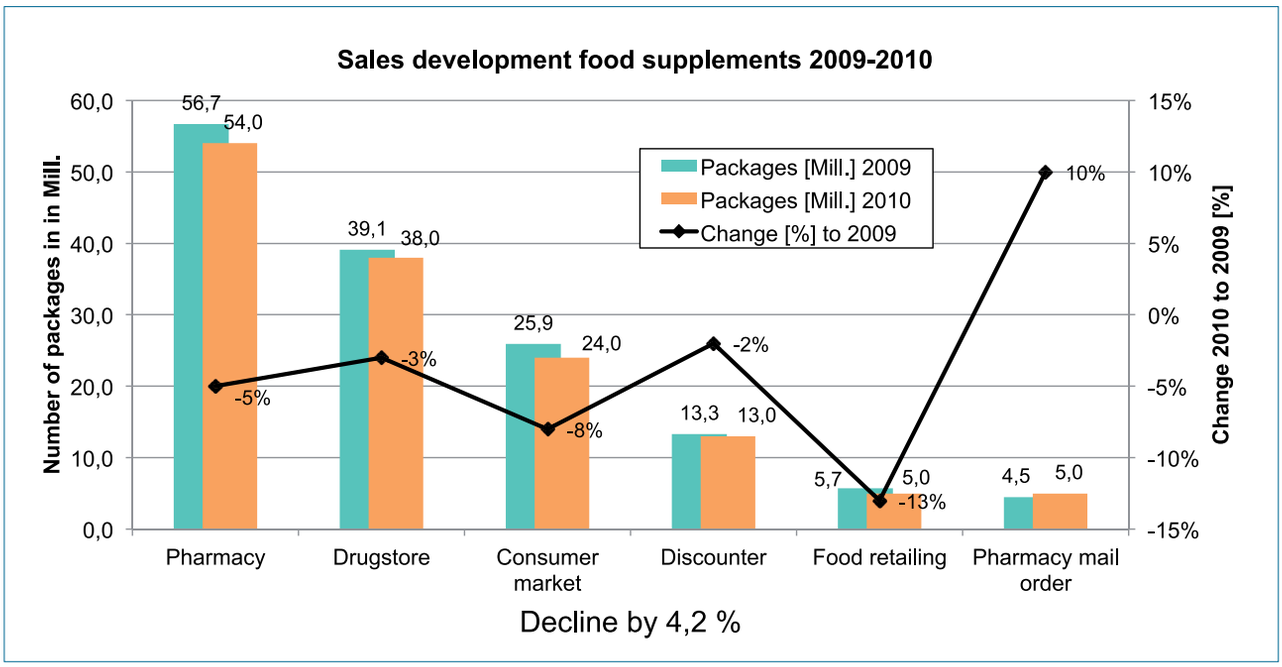

Figure 3: German market of NEM (Nahrungsergänzungsmittel) nutrition additives [21]

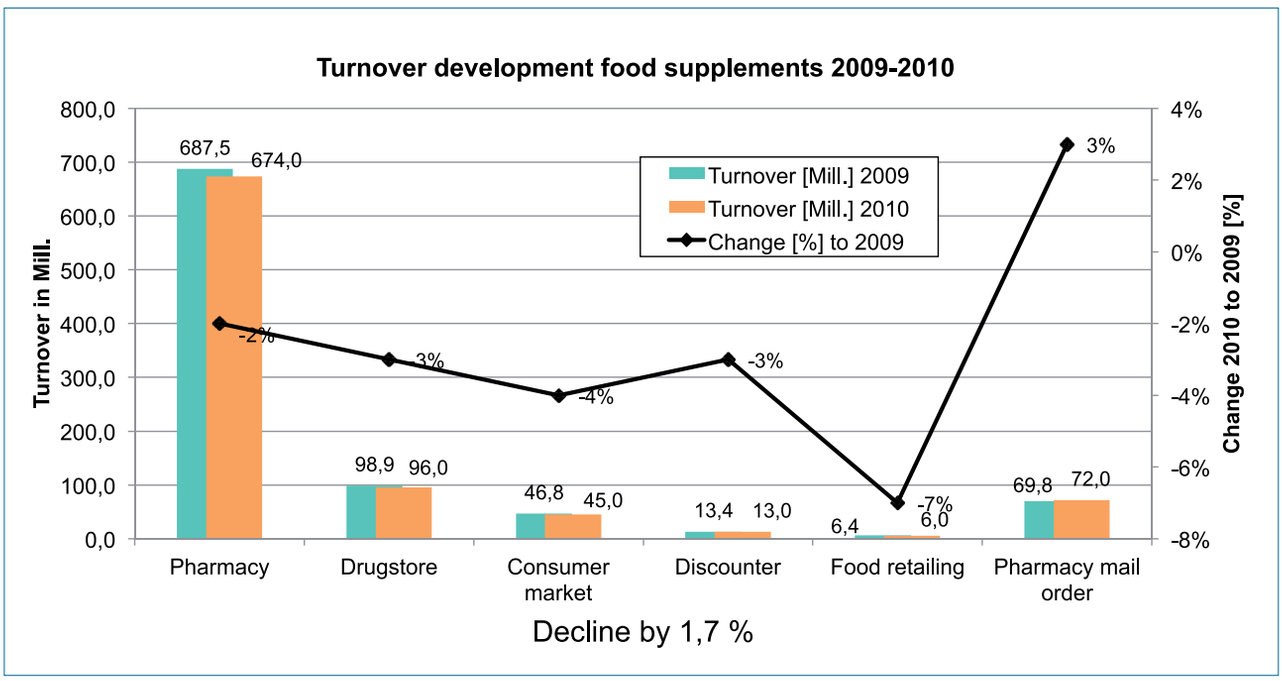

Figure 4: German market development of NEM (Nahrungsergänzungsmittel) nutrition additives with regard to sales [21]

This, however does not apply to the field of aromas. Due to the strong increase in demand from Asia (China), the supply with e.g. citrus aromas cannot be met in the foreseeable future. Key aromas cannot be produced synthetically. The same is valid for vanilla-extracts [2,22].

In addition, in the aroma field a "natural label" is a precondition, at least in part [22]. Also, many important compounds from the class of "secondary metabolites" cannot be synthesized, e.g. Mono- and Sesquiterpenes [2,22]. Natural extracts ad byproducts from food processing have a very important, if not a dominant position here.

Phytoextracts are also intermediary products for the purification of plant based natural products.

The use of purified natural products in the areas of pharma, food additives, and cosmetics is currently declining. The last big pharma product introduction having a natural product as API (active pharmaceutical ingredient) has been taxol in the 1990's [22,23]. A positive exception is the use of stevioside as a food additive, which has recently been approved for use as natural sweetener also in the EU [24]. Luo Han Guo (monk fruit) has also been awarded GRAS-status (generally regarded as safe) [25,26]. This is an indicator for the relevance of sugar replacement products without any or at least low calories and natural origin. Currently, other natural "no (low) calory" subsidiary products are being tested.

The European and worldwide situation

Worldwide market for botanicals is still growing and the share of supplement and functional food is gaining, total 108 bill USD in 2015 with 48% herbals, 17% cosmetics and 35% supplements&functional food. The annual growth rates are still larger than 15% in US.

The market in Europe is dominated by Germany 27%, France 22% and Italy 11%.

In 2014 consumers spent in US 6.4 mill. on supplements.

The US market for herbals is basically expected to continue as before. The regulatory situation in the EU is forcing manufacturers to consider going the herbal drug route to THMP primarily. Superior herbal extracts being preferred over less expensive ones. Europe is losing further grounds to the Asian and US markets. Innovation is easier outside Europe. [18]

Cosmetic market situation

The interest of consumers in natural cosmetic products continues to grow worldwide. An annual growth by nearly 10% (2014) is reported by the market research firm Kline & Co.

In Germany over the past decade the market volume for certified cosmetics has even doubled. Not only revelations on critical ingredients in conventional cosmetics have led to increased demand. For now products with natural claims but formulated with a high proportion of synthetic ingredients dominate the market (about 75% market share) – especially in emerging countries. However this situation is going to change rapidly. Natural ingredients will help the industry to conquer foreign markets with high quality and real green products. Reformulations replacing synthetic by natural ingredients will establish a strong natural concept. These efforts secure the binding of clients to reliable green labels [27].

Germany is the European champion in terms of natural cosmetics. In 2014, with a value of 1.009 billion EUR [28], sales exceeded the magic one-billion mark for the first time. Sales figures for the first half of 2015 indicate

a growth of around 8%. In contrast, the conventional cosmetics market is stagnating and continue to lose customers to natural cosmetics. People are well aware and educated to decide which ingredients they allow to come into contact with their skin.

In Europe, according to statistics from the European Cosmetics Association (Brussels, B), over 72 billion Euro is spent in cosmetics, in the EU member countries around 69 billion Euro. Germany, France, Great Britain and Italy are among the top consumers, generating over 60% of cosmetic sales in Europe.

The situation on the natural cosmetics market is similar. Germany has been the leader for years. Here, natural cosmetics have a market shore of almost 8%. Second place is taken by France, turnover generated in 2013 was around 410 million Eur. Third place goes to Great Britain. Also in Austria and Switzerland

natural cosmetics is booming. In each of these countries 80 million Euros is spent on natural personal care. In comparison, the total cosmetics market of the USA, Europe, China and Japan amounted to € 166 billion in 2015. according to Cosmetics Europe [29].

Natural products in the cosmetic industry

Botanicals are widely used in cosmetics, mainly as "active" extracts. There is a continuing trend to highlight the use of natural ingredients to support a positive claim. The increased usage elevate the demand for botanicals. Amounts used vary from fractions to substantial quantities in order for active ingredients to have an effect. Organic botanicals are also used in non-certified natural cosmetic products.

Fair production

Consumers increasingly want ingredients to be sourced fairly. However, products do not necessarily need to be certified to demonstrate fair production. Some manufacturers even choose not to list fair trade or other labels since the different certifications and standards can lead to confusion among consumers [30].

Innovation is needed

Manufacturers of cosmetics depend on product innovation to survive in the market. Novel natural ingredients are utmost important components of innovation. Most of the processes start in laboratories based on botanical samples. Most extracts are used in leave-on cosmetics, i.e. skin care products where active properties are the highest demand. Performance extracts are used less in rinse-off categories, such as hair care and bathing creams, but due to the large amount of these categories, quantities can still be substantial. The main applications for these products are the fields of:

- combating signs for ageing (anti-wrinkle)
- reducing environmental damage (moistursing, conditioning)
- anti-oxidants, cooling

Sustainable sourcing

Ensuring the sustainability of supply is increasingly relevant to buyers of botanicals, especially in Europe. This is especially important for wild collection. Due to large investments in product development, companies needs to rely on their supply chain which is the best case completely transparent. The Nagoya Protocol of the Convention on Biological Diversity (CBD) can be named here as main parameter. Based on all the stated facts in regards to sustainability – a green house or field production within Europe should be the most logical consequence. Besides controlled sourcing, documented treatment of the plants the short supply routes to the clients are another big benefit.

High-tech production

Being green is also valid for the production of extracts. Extraction with a low CO_2 emission, preventing the use of organic solvents and a reduced energy consumption are only some important parameters which needs to be considered [31].

The most favorable markets in the EU for the launch of new products are Germany, France and the UK.

Plant extracts in the agrochemical market

Introduction

Plant extracts were used as Plant Protection Products (PPPs) traditionally in many countries (e.g. nettle extracts against aphids). There is a distinction between insecticides, fungicides, plant growth regulators, nematodes and herbicides made of plants. During the 20th century highly active synthetics have been developed and with these the expectations of farmers regarding efficacy and economy of PPPs rose. Therefore pesticides with a natural background are mainly used as biopesticides in the Organic Farming. Organic plant protection consequently excludes the use of synthetics and genetically modified organisms. Due to the high value (costs) in comparison with chemical products, a use in the conventional agriculture is mostly not economically. A high advantage of natural products is, that they usually have a good degradability and do not cause residue problems, which are typical for chemical-synthetic products. Another advantage lies in the fact, that plant extracts often contain mixtures of slightly different molecules which are efficient against harmful organisms. Resistances are more likely to occur when single compounds are used as active ingredients.

According to the new European legislation (Regulation (EC) No 1107/2009) a Plant extract which is protecting plants or plants products against all harmful organisms or preventing the action of such organisms has to be registered as a PPP. But the demands of such registrations which were developed for synthetic products cause problems since the required studies are designed for assessing synthetic products and therefore not generally transferable one to one for plant extracts. Plant extracts often consist of mixtures of different compounds and might be classified as UVCB substances (Substance of Unknown or Variable composition). For example a radioactive labelling which is required for certain metabolism studies is often not possible.

The Market

In 2013 the EU citizens spent 22,2 billion € for biological produced products. In total the demand for biopesticides doubled in the last decade. Within the trend for eco-friendly products, the market for pesticides made of plants has grown within [32].

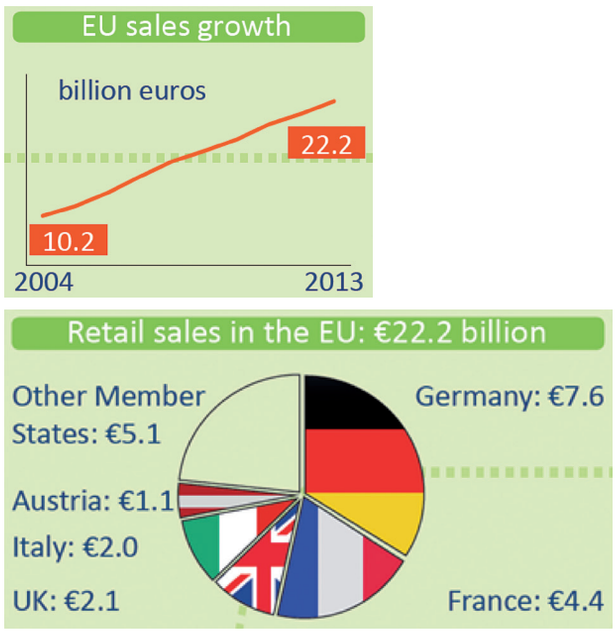

Figure 5: European Parliamentary Research Service Blog, published 2015

Until now only a few plant extracts are fully registered as PPPs within the EU. The first biological PPP made of a plant extract which has been registered in the EU in the 90´s was the product NeemAzal® T/S. The active ingredient is an extract made out of kernels of the tropical neem tree (Azadirachta indica) with Azadirachtin A as a leading compound. Azadirachtin is highly active against sucking and biting insects. NeemAzal® T/S has been registered during the last two decades in over 40 countries worldwide against a wide range of insects. The application is mainly on organic farms and in the home and gardening sector but a use in integrated pest management in combination with synthetics is considered to reduce residues and avoid resistances [33,34].

Another example for the use of a plant extract as an insecticide are extracts made out of the flowers of chrysanthemums. The components Pyrethrin, Cinerin and Jasmolin have a direct toxicity against sucking and biting insects. This also led to the development of synthetic pyrethrins with slight modifications that are used in conventional farming [35].

Vegetable oils are used as adjuvants in the formulation of both, synthetic and naturally derived active ingredients of PPPs to improve application properties, rainfastness, UV-stability or the uptake of active ingredients. Rapeseed oil is also listed as an insecticide in the EU. Rapeseed oil is used as a contact agent and is toxic and repellent against sucking and biting insects [36,37].

Potential

Biopesticides have a high potential, due to the increasing demand for biological products. Plant extracts, as an important part in the family of biopesticides, have therefore a good perspective on the market. Nowadays the potential is not developed at all. In the EU only a small percentage of the whole area for agriculture is used for Organic farming. There is still enough space for improvements.

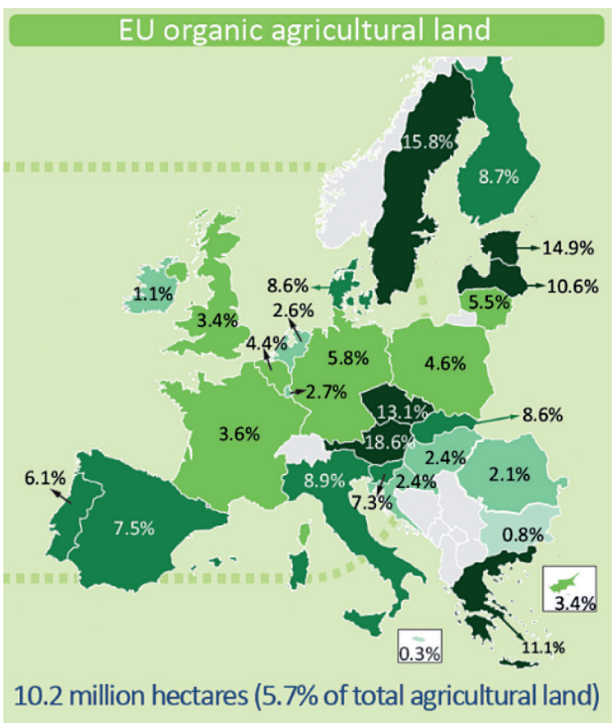

Figure 6: The map shows the share of land, in percentage, under organic farming out of the total utilised agricutural land. The source of the data is Eurostat.

Another big issue for a promising future is that the cancellation of chemicals by EU authorities, like neonicotinoids (insecticides) is in discussion [38]. Especially on the consumer market for home & garden, some countries will strictly ban all synthetics in the next following years. Within the new EU plant protection legislation EU member states are forced to develop “National action plans”. The aim of these plans is to reduce the use of synthetic pesticides and to protect farmers, customers and the environment from harmful effects. So the use of more green, environmental friendly and non-persistent active ingredients is also an ambition of the politics of the EU.

Production and use of herbal extract with supercritical CO_2

The usage of plant extracts is a fast growing market in many fields of human life. Botanical extracts are well accepted for cosmetics and perfumery, extracts find its use in flavourings for food or they do their job in functional foods or nutraceuticals. A further field of application is the use of plant extracts in phytopharmaka.

As an example the use of herbal extracts in dietary supplements in the US market reached in 2014 a volume of $ 6,4 billion and sales show an increase of 6,8%,

2014 was the 11th consecutive year of growth [39].

Supercritical CO_2 extracts are well established in the field of cosmetics where they offer the following advantages: sterility without need of any preservation, elimination of problems associated with germ growth as they are practically free from water, minerals, gluten and proteins. They do not contain production associated adjuncts as they are composed exclusively of extractives that allow simple declaration and meet the criteria of organic certification. Due to their high concentration, they are effective in small dosages.

In dietary food supplements, supercritical CO_2 extracts display a variety of well documented properties, anti-inflammatory, anti-oxidative, anti-microbial, anti-aging, immune stimulating, eye-health or digestive health properties and are similarly used as safe ingredients for prophylactic and adjuvant purposes.

In perfumery and aromatherapy supercritical CO^2 extracts are surprising and exciting components that enrich the gamut for creative experiences.

In food application whether used for boosting flavours, intensifying colour or improving activity, supercritical CO_2 extracts are inspiring tools for formulators.

The production of plant extracts require solvents. The use of extraction solvents is regulated in Europe by Directive 2009/32/EC [40].

Per the Directive: *"An extraction solvent is considered as being used in compliance with good manufacturing practice if its use results only in the presence of residues or derivatives in technically unavoidable quantities presenting no danger to human health."*

Only a small number of solvents are allowed, beside water, ethanol and CO_2 only ethylacetat and acetone and the gases propane, butane and nitrous oxide are generally recognized as safe solvents.

Single solvents as hexane are allowed for special uses.

For certified organic products only the solvents water, ethanol and carbon dioxide are allowed.

CO_2	CO_2/EtOH	EtOH	H_2O
Oils and Fats	Steroids Phopholipids	Flavonoids Phenols	Sugar Glycosids
non-polar		polar	watersoluble

On the extraction of plant materials the desired valuable ingredients determine the required solvent. For the recovery of pure lipophilic and less polar components CO_2 extraction is an established process for many years.

Carbon dioxide is an odourless inert gas that is a major component of the atmosphere and a metabolite of living organisms. Like water it is GRAS approved unclassified solvent without USP/ICH residue requirement [41]. CO_2 under supercritical conditions is well established as modern solvent of choice replacing traditional organic solvents. Solvent power and selectivity can be adjusted by gas density and pressure.

Supercritical CO_2 extracts primarily contain lipophilic plant constituents and represent groups of secondary plant metabolites. Supercritical CO_2 extracts are therefore more specific for the botanical starting material as they exclude more common constituents of polar extracts like polysaccharides, flavonoid glycosides, polyphenols or proteins. The parameters for supercritical CO_2 extraction are uniquely defined and optimised for each type of extract. In a gentle environmentally friendly process active substances or sensitive flavours and fragrances are extracted under exclusion of oxygen from dried and powdered herbal materials. Results are selective extracts as replacement of steam distillates or total extracts as replacement of hexane extracts. Supercritical CO_2 extraction has the advantage of improved quality, without any formation of artefacts or residue problems and yields extracts that have more natural flavour, fresher more authentic fragrance and superior activity.

If the extraction of more polar components like steroids or phospholipids is desired then it is of advantage to mix some percent of ethanol in the carbon dioxide. With a content of 10 to 15% ethanol in CO_2 it is possible to extract phospholipids which are complete insoluble in pure carbon dioxide.

To recover the more polar herbal active substances like flavonoids or phenolic components a more polar solvent – pure ethanol – is necessary for extraction. Further increasing polarity of the desired extract requires the adding of water to the ethanol or to use water for extraction.

The art of producing fine herbal extracts starts with the selection of the ideal raw materials. Evaluation and analysis of herbal feedstocks identify important constituents that highlight the value of the extracts and provide a basis for strategic decisions for commercialization.

Conditioning of the gently dried material is the next important step, i.e. cutting, rolling, pelletizing and milling to the right particle size. Extensive knowledge for appropriate raw material preparation is essential for assurance of extraction efficiency and extract quality.

CO_2 under supercritical conditions is well established as modern solvent of choice replacing traditional organic solvents. Solvent power and lectivity can be adjusted by gas density and pressure or by the addition of ethanol as co-solvent. In a gentle environmentally friendly process active substances or sensitive flavours and fragrances are extracted under exclusion of oxygen from dried and powdered herbal materials. Supercritical CO_2 extraction has the advantage of improved quality, without any formation of artefacts or residue problems and yields extracts that have more natural flavour, fresher more authentic fragrance and superior activity.

The manufacturing of botanical extracts of exceptional quality and efficacy has the potential for important improvements in the quality of life of humans. In order to achieve an effective delivery of natural bioactive compounds the availability depending on the hydrophobic or hydrophilic nature of the compounds must be optimized. Efforts should be made in the field of micro- or nano-encapsulation or enhancement of bio-availability by utilization of suitable carriers.

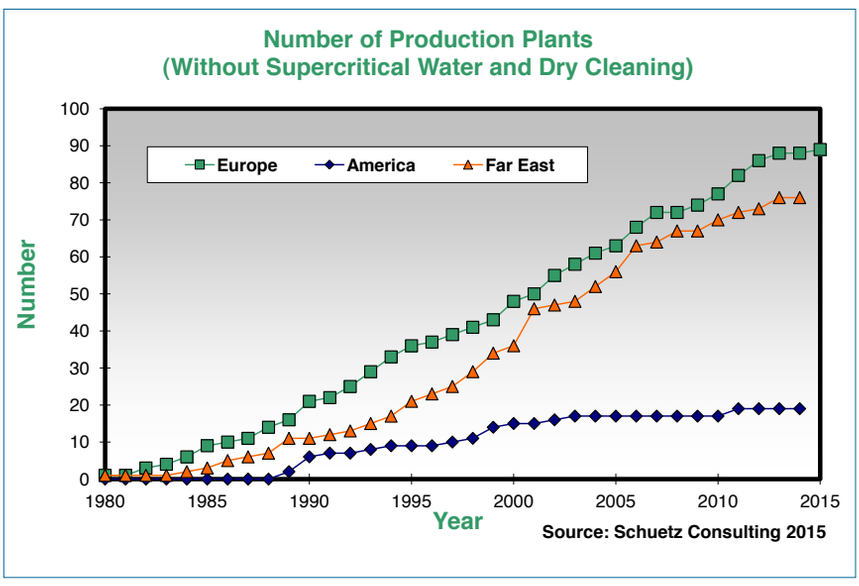

Figure 7: Production Plants worldwide

Market figures

Actually approx. 180 production plants using $scCO_2$ processes are existing and the global market is increasing constantly [fig. 1].

The preferred fields of application can be found in the food & beverage, cosmetic and pharmaceutical industries. Thus for the $scCO_2$-extraction of plant materials a growth rate of over 25 % from 2013 to 2018 is predicted, whereas alternative extraction technologies show significant lower rates [table 3].

Industrial Trends

Due to ongoing globalization, purification procedures gain more and more importance and the reduction of pesticides or odors by $scCO_2$ is of increasing interest. Additionally individual customer requirements are rising and product diversity, supplementary certifications and advanced process steps & services are essential.

Accordingly the application of ultra-high pressure of around 1000 bar enables the economic extraction of up till now challenging plant ingredients. Thus antioxidants like the Carotenoid luteine from calendula, anti-inflammatory triterpenes from barks or even anti-cancerogenic polyphenols from hops become extractable. Also continues rectifications or the creation of well defined powders are economically realizable by using novel critical fluid technologies.

Additionally now tailor-made solutions can be generated by using new technologies and coupling their respective capabilities adapted to product or process requirements. Therefore continues rectifications or the creation of well defined powders are economically realizable by using novel critical fluid technologies. For instance micro-particles and sustainable impregnations or encapsulations can be gained under $scCO_2$ atmosphere applying individually adjusted rapid expansion systems.

Conclusion

It becomes more and more important to add value to the processing capabilities by developing adjacent and innovative technologies adapted to the market requirements. Thus a good networking and acquisition of market know-how by e.g. taking part in international congresses or trade shows, cooperating with suitable companies and joining collaborative R&D projects with universities are crucial factors for successful business developments.

Table 3: Herbal/Botanical Extraction Technology Demand Through ($Billion) [42]

Extraction Technology	2010	2011	2012	2013	2018	CAGR %	
						2010-2013	2013-2018
Water Extraction	32,5	41,8	48,1	58,9	99,1	21,9	11,0
Drying	6,3	6,6	6,7	6,6	13,4	1,6	15,2
Cold Pressing	1,5	2,0	2,7	3,0	7,3	26,0	19,5
Steam Destilation	0,5	0,8	1,0	1,2	2,2	33,9	12,9
Enfleurage	0,3	0,3	0,5	0,8	2,0	38,7	20,1
Supercrititical CO_2 Extraction	0,1	0,1	0,3	0,6	2,0	81,7	27,2
Low-boiling solvent extraction	0,1	0,2	0,3	0,4	1,5	58,7	30,3
Total	41,3	51,8	59,6	71,5	127,5	20,1	12,3

SWOT (Strengths-Weakness-Opportunities-Threats)-Analysis on the relevance of phytoextracts and plant-based natural compounds

The competition with synthetic-chemical as well as bio-technologically produced molecules has recently been burdened by a manifold of disadvantages, while natural plant-based products show a number of intrinsic advantages. For new products these reasons are among others the following:

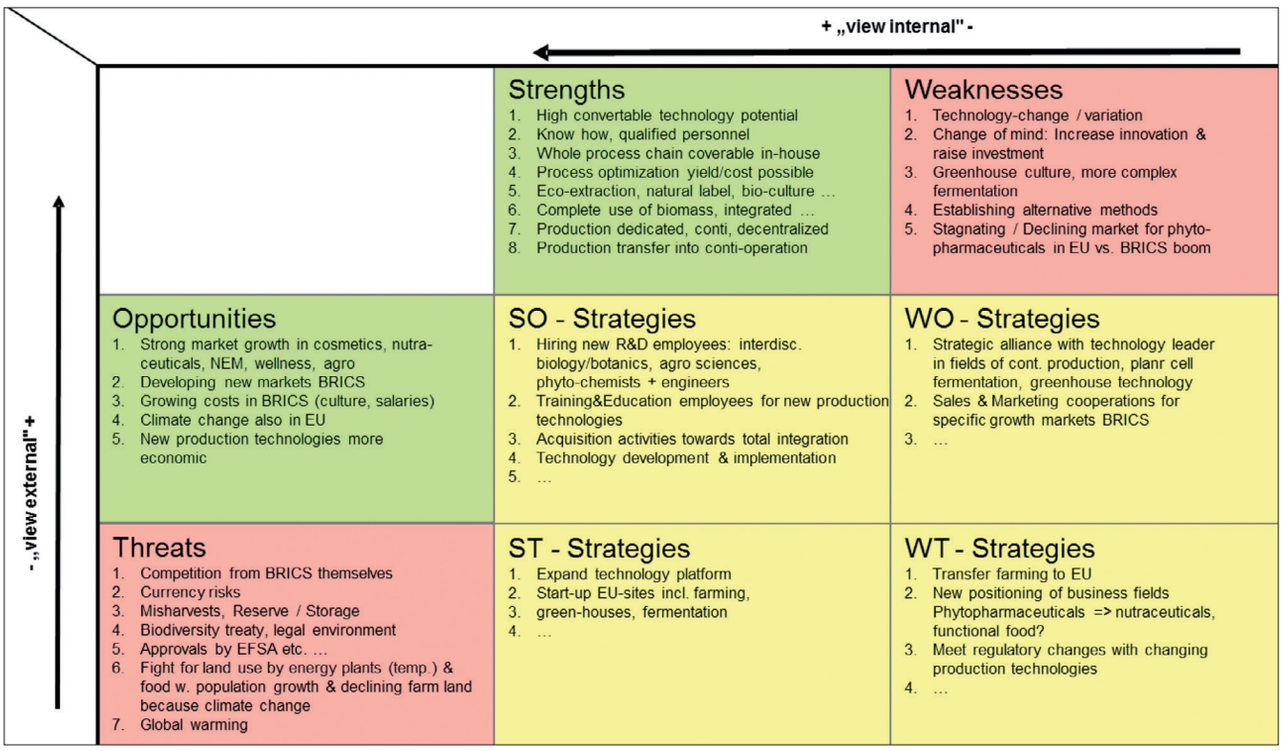

Figure 8: SWOT-Analysis Plant-based Extracts – Products and Processes

These strategic consequences can be derived from the total (a comprehensive) analysis of environment and capabilities for companies, academic research, and the subject group.

Underlying arguments are i.a.:

1. setting up a supply chain for plant-based raw materials can be very lengthy:

   a) Wild plants, which cannot be sustainably harvested in nature, need to be taken into culture.

   b) Raw materials from wild collected plants undergo high variations in quality, all the way to zero yield due to a miss-harvest.

   c) As a contingency, large raw material stock has to be built, associated with high cost tied up in the process.

   d) Biological growth is typically a basic requirement, as there are too many different plant protecting agents in use to ensure their absence analytically at acceptable costs during quality control.

2. Regulatory effort, especially for approval as a therapeutic is higher compared to chemically defined substances, however ...

3. for aromas and in part nutrition additives the hurdles for extracts are much lower than for chemical compounds not occurring in nature. Therefore, it will be

quite difficult in future to bring a new artificial sweetener to market. For the last one, Sucralose, it took more than 10 years. Also Stevia and monk fruit had to master significant regulatory hurdles, but are approved meanwhile!

4. Access to raw materials is further reglemented by species conservation and biodiversity conventions (CITES, CBD etc.), which will negatively impact the dynamics of product development, and for existing products will result in higher costs [43].

   New research activities have additionally to respect the Nagoya-protocol, which demands a fair and well-balanced distribution of the advantages of the utilization. With regard to this aspect all rights on genetic resources and technologies must be compensated by a suitable finanziation th the countries of origin. In order to make a contribution to conservation of biological diversity and sustainable utilization.

5. There is significant competition for growth area with other and often heavily subsidized products, like corn (maize), e.g. for bioethanol production in the USA – which more and more swaps over to EU, eg. Germany's "Energiewende" approach based on Biogas as one pillar beneath wind and solar energy. This scenario will disappear sooner or later with the phasing out of the subsidies. However, competition with food production will become critical [44, 45]. It should be observed to use preferentially soil not easily usable for food production for phyto-plants.

6. The development of wealth in the so-called BRICS countries, which goes along with increasing consumption of food and consumer goods, together with the exponentially increasing population drastically impact the cost for agriculturally used areas as well as the wages in these countries [46,47,48,49,50]. This makes European activities competitive again, which therefore should be increased.

7. In addition, there is currently a need for optimizing a focused exchange between cultivation and application with regard to the optimal composition and concentration of the desired compounds to allow economic production processes and make existing processes more efficient. So far, such integrated production concepts have not been necessarily pursued in the historically evolved production, however the transfer from related production technologies is possible.

8. For revival and further development of products from phyto extracts and plant-based natural products innovative marketing ideas are also essential. Current life style product innovation cycles have been extremely reduced to the one year level, requiring correspondingly efficient total process development. Also, nutraceuticals, functional foods, and wellness products move through a boom phase (esp. in Eastern Europe, Asia, India, Middle East). If industry is able to react faster to customer needs technologically as well as with raw materials supply, then new markets for plant extracts can be opened in nutraceuticals, functional food, and wellness.

9. However especially on the production side big challenges exist for increasing value of these product groups, opening also opportunities due to the perspectives, as energy balances and, directly related CO_2 balances move into the focus of production processes. By an integrated development plant-based raw material productions represent neutral or even energy providing operations, at the same time absorbing CO_2.

10. Another core advantage lies in the fact, that plant extract products are intrinsically biodegradable and present no recycling or enrichment issues [23].

11. A clear decision has to be made as soon as no alternative exists to a chemical synthesis. Also hemi-synthetical approaches, linking extracts and their chemical transformation, have to be considered.

12. Plants, viewed as biocatalysts, could again present a direct competition to chemical compound synthesis, if the extraction and purification operations are developed energy efficient and free from or at least minimalized in use of petrochemistry. The France Eco Extraction Initiative [51] has worked out 6 rules, transferred to phyto extracts from the meanwhile accepted 12 rules of the Green Chemistry Initiative:

a) Favor innovations by natural biodiversity i.e. use sources of sustainable processes for access to plants

b) Preferential use of alternative, biodegradable solvents from agro-resources

c) Reduce energy consumption by means of innovative technologies and favor energy recovery if possible

d) Favor development of co-products by integration of residues from bio- and agro-refineries

e) Reduce single unit operations by technological innovations and favor safe, robust, and controlled productions

f) Prefer a product which is non-denaturing, biodegradable, without contaminants, and above all, certified with the label "(France) Eco Extract.

ProcessNet-Subject Division "Plant Based Extracts – Products and Processes

Development and production of plant extracts and plant-based natural products take place in multitude of small and medium enterprises (SME). In this set up, there is typically no interdisciplinary cooperation between agro-scientists, biologists, food chemists, natural product chemists, pharmacists, and process engineers. Botanists, biologists, and agro scientists are typically not participating in the development process like engineers. Interdisciplinary exchange or even an own discipline are non-existing. Therefore, a large potential is opening up for exploitation by simple means, if such an integrated technical approach could be established. See relating international discussions, e.g. [51,52].

Goal of the subject group is therefore to improve the currently still acceptable competitive position of domestic companies, and to lead them to a globally leading position in this growth market both technology and methodology wise and with regard to the product offering. Besides establishing German and European companies competitively as technology and know-how provider and, climate and diversity protection permitting, also establish them as plant cultivators.

By tradition, process development in general was not based on a systematic and engineering oriented approach, but more empirically driven by a pharmaceutical mindset with a view on small scale productions. For the fields of aromas and perfumes this is understandable, when the products are considered "commodities" and have little differentiation potential. The decisive steps for value generation are the production of the plant-based raw materials, the extraction of the actives, and the efficient as well as sustainable work up to the final products.

Likewise, the workup of the residual biomass needs to be comprehensively assessed, because many secondary metabolites are present only in low concentrations (ppm range).

Additionally after extraction of the target value component a most efficient cascade utilization of the residual biomass should be enabled. Due to this not only the value component could be manufactured at lower cost of gods but additionally in sense of bio-economy a sustainable utilization of raw material resources is made sure.

The systematic development in an encompassing approach allows to long term produce at more attractive prices, making it a concept for survival.

In addition, in the environment of a bio-based economy, modern cultivation as a relevant research initiative is gaining importance, allowing to

a. generate higher target compound concentrations with in proportion lower side components, not at least which simplifies work up of raw material waste

b. Furthermore primary interest is to switch to European crop plants [53,54] in order to guarantee on the one side via controlled cultivation and farming the raw plant product quality due to Good Agricultural Practice optimal and on the other side to minimize transporta-

tion efforts in order to minimize the carbon food-print as well/or to

c. move towards alternative, perennial, almost fully continuous production systems [55,56].

d. Breeding optimization of plant-based components is for many crop plant types which are already industrially utilized by far not exploited. Molecular biology, which scientific potential has been revolutionized the last 20 years, enables in general today faster and more selective methods in breeding of plants. Nevertheless, in cultivation of medicinal and aroma plants in Europe, largely the classical methods of combination and selection breeding (ie. cross-breeding and selection of wild species), Polyploidy and mutation breeding applied. Thereby, with aid of different breeding strategies first a broad variety of plant material is generated (by combination, polyploidy or mutation) afterwards the single plants with favored properties (i.e. high quality, high output, good resistance) selected. Application of genetic methods is in range of breeding research at some types applied, but never gained commercial application.

e. Europe has a long tradition in production and manufacturing of medicinal and aroma plants and international operating companies as well as with national funds financed research institutes are based. This convenient starting position should now be intensified by interdisciplinary activities of biology/botany, crop scientist and phyto-chemists in combination with chemical/biotechnology engineers, because a fundamental risky research with high innovation potential, but as well with an economical risk only can be carried by such a solid network – especially for SMEs.

2. Location Europe

Germany

For decades already Germany has stopped being the "pharmacy of the world". However, the prediction, that Germany will also in future not be able to take a leading role in the production of plant-based raw materials for standard products, because their production in low cost countries would remain to be more competitive, becomes more and more questionable. There the availability of land for agricultural use is drastically declining through urbanization, industrialization, wealth, population growth, and climate change, while the cost for agricultural land use and wages are rising significantly [46,47,48,49,50]. The innovations proposed in this document for Germany & Europe should help to actively change this situation. In addition, already today in cultivation and (primary) extraction of pharmaceutically used plants high quality requirements, like GACP (Good Agricultural and Collection Practice) and GMP (Good Manufacturing Practice) need to be fulfilled, which can only be fulfilled by adequately equipped agricultural companies (set ups). Especially the work up fresh plant constituents will therefore in future take place less and less in underdeveloped 3rd world countries. This tendency should also prevail in the non-pharmaceutical uses, once the requirements of REACH have been fully implemented.

Opportunities lie also in green house cultivation of plants, which due to legal permission (species conservation, CBD) become increasingly difficult to import. Large potential lies in the development of intelligent and integrated solutions, e.g. in cultivation, extraction and purification steps, coupled with e.g. green house cultivation and biogas systems for maximum utilization of materials and energy. The necessary clustering of technologies calls for interdisciplinary co-operations.

Focus should be, that Germany either exports the developed technologies for integrated extraction and purification into countries, where the respective plants are cultivated/grown, or to use the developed technologies to produce at home by using green-house cultivation or bio-fermentation.

Such cultivation technologies are economically acceptable for high value pharmaceutical products. For aromas and perfumes it will is important to find side products (residual/waste compounds) containing the desired components. Problem besides the typically low concentration is often the low microbiological stability. All of them are problems calling for efficient technologies to be investigated and which have to be established on a production scale.

France

Importance of valorisation of agroresources in France

Agro-resources are renewable raw materials whose transformation using industrial processes can create high-performance products with reduced environmental impact. A solution for the future, replacing petrol-based products.

Numerous raw plant materials are used in biorefining:

» **Starch-producing resources: maize, wheat, potatoes, etc.**
An example in wheat refining: by splitting straw, we obtain cellulose, lignin and pentose, used in making wood pulp, glues, detergents and emulsifying products. Wheat grains are transformed into flour, starch, glucose and proteins which are mainly found in syrup form or as fibres in food and feed. Starch is also used in the paper industry. Glucose syrups play an important part in biotechnology as fermentation substrates.

» **Oil-producing resources: sunflower, oilseed rape, etc.**
Trituration and the refining of oil-producing grains produces oils for biodiesel or biolubricants, and high-protein flour used in food and feed. After the oil is extracted, the residual elements, known as meal, are mainly integrated into animal feed.

» **Sugar-producing resources: beet, etc.**
Sugar comes from sugar cane or sugar beet, grown mainly in temperate climates. The subsequent production of saccharose (sugar) has numerous industrial applications including bioethanol (biofuel), food and feed, fermentation substrates and glue additives. The co-product of beet, called pulp, is used in animal feed. The co-product of sugar, bagasse, is used in energy production.

» **Protein-producing resources: peas, beans, lupins, etc.**
The use of protein-producing plants in biorefining is marginal. Their grains are rich in protein and so are mainly used in animal feed.

» **Lignocellulosic resources**
Lignocellulosic ressources include silviculture (forest) resources, herbaceous plants (miscanthus) and fibrous plants (hemp, flax), as well as several residual resources (agricultural, forestry or paper industry waste). Xylochemistry (wood chemistry) processes produce cellulose and hemicellulose, valuable to sugar chemistry, as well as lignin. Currently, lignin is used in paper, cardboard, softwood lumber and energy. New chemical applications with higher added value need to be developed.

» **Algal Resources**
Macroalgae and microalgae are valuable materials which are currently under-exploited. Today, microalgae are used in cosmetics, nutriceutics and fish-farming feed. In the medium term, microalgae will also be used in biofuel and synthons in the realm of chemistry.

French industries for plant and food extraction	
Cosmetic	Beauty Care Solutions Chimex
Food ingredients	Naturex Robertet
Aromas	Mane Charabot
Pharma	Pierre Fabre Servier Sanofi

Relevant French Associations

Association Chimie Du Végétal (ACDV)
www.chimieduvegetal.com/en

ACDV is the organisation representing players in the Plant-Based Chemistry field, with as primary role to represent and promote the sector and oversee the regulation of biobased products. It supports and accelerates the development of sustainable chemistry based on the use of plant resources in France and in Europe.

Competitiveness Cluster Industries & Agro-Resources
www.iar-pole.com

The Industry and Agro-resource (IAR) Cluster promotes exchanges, decompartmentalisation and project launches. It assembles players from the whole value chain around a shared innovation problem. The IAR Cluster and its members are involved in developing technology and products to replace petroleum-based raw materials with agricultural, forestry and algal plant production.

The IAR Cluster supports project initiators, regardless of size, in terms of the initial idea, its development and the search for financing. The IAR Cluster provides the means to develop and test new technologies and products based on a renewable approach. In this way, it helps open up new markets and boost companies' competiveness in the area of agro-resources. The IAR Cluster enables member companies within and outside France to combine their strengths through operational partnerships. The IAR Cluster's actions fostering plant innovations can be seen today in the creation of the exceptional innovative structures now appearing in the landscapes of the Picardie and Champagne-Ardenne regions.

Competitiveness Cluster on fruits and vegetables
www.pole-terralia.com

Trimatec competitiveness cluster on green technologies
www.pole-trimatec.fr

Italy

Current Production of Aromatic and Medicinal Plants in Italy

Worldwide, the FAO data shows an overall increase in area and production for a group of products related to medicinal plants, between the end and the beginning of the decade 2000-2010. The biggest production expansion is represented by cinnamon, several citrus fruits (bergamot, bitter orange, cedar, etc.), poppy, other spices like bay leaf, dill, saffron, thyme, etc., anise, tea and pepper. In other cases, the static nature of the surfaces are associated increases in productions that show the most efficient production processes (i.e. mint, red pepper, hops and safflower). From 2000 to 2010, the worldwide production increased by 50%.

FAO data shows 77 million hectares and 330 million tons of worldwide production. The biggest item in terms of area is tea (3 million hectares); follow the various types of chili, citrus fruits (bergamot, bitter orange, cedar, etc.), the "other spices" (dill, thyme, bay leaves, etc.), and various types of "anise" (anise, star anise, fennel, coriander, etc.).

In these crops a leading role is played by India, particularly for: anise, spices, chilly, safflower seeds. China also is a major player above all in the tea and citrus fruits (next to Nigeria). Some productions show a high degree of geographical specialization like cinnamon (Indonesia), cloves (Indonesia and Madagascar), maté (Argentina), mint (China, USA, India and Morocco), pyrethrum (Kenya and Tanzania). In the case of the production hops is localized in Europe (Germany), but also in Africa (Ethiopia), as in the case of the carob (Spain, Italy and Morocco). Finally poppy seeds are mainly produced in Turkey and the Czech Republic.

In Europe, the statistics referring to 2010, report more than 36,000 companies involved in the cultivation of "medicinal, aromatic plants and spices" with an area of nearly 234,000 hectares. In the period 2007-2010 the number of European companies in the field increased significantly, as well as the cultivated surface areas (more than 50%!). In Europe there are over 36,000 companies involved in the cultivation of "aromatic and medicinal plants", with an area of nearly 234,000 hectares, most of which are located in Bulgaria (nearly 73,000 hectares), France (39 thousand hectares), Romania (21 500) and Finland (21 000).

A recent snapshot of the Italian supply chain showed a dynamic framework in the search of innovative technologies. In Italy accordingly to the results of the last Census of Agriculture (2010), there are 2,938 companies with an area under "medicinal, aromatic plants and spices" with about 7,191 cultivated hectares. Statistics showed a significant growth of both companies and above all the cultivated surfaces. This evolution is based on a significant expansion of production, which was characterized by the sharp decline in the number of micro-enterprises involved in the cultivation and for the simultaneous increase of the surfaces of the medium-large companies. A positive trend is finally confirmed by the data related to the organic sector, which showed an upward trend between 2000 and 2011 of the biological surfaces or in conversion to medicinal plants - once again in the face of a stabilization of agricultural land total bio - and a growth trend in the number of new notifications of organic operators of healing. The most important data of the sector, is certainly to emphasize the role of medicinal plants in the sector is of organic production.

In the agricultural phase, it can be estimated that the organic farms Relate universe census, represent 23% while the proportion of organic area affects more than 40%.

The Italian Economic Observatory showed that the also the organic cultivation of medicinal products with a high environmental value. The wholesale market of medicinal plants cultivated in Italy has a value of 120 million euro per year (2011) and is growing every year and much bigger the import of dry plants of about 600 million euros (such as ginseng etc.).

The consumption of medicinal plants from the pharmaceutical industry, food, liquor making, cosmetics and herbal is increasing worldwide. In Italy the processing and the marketing of finished products recorded in the last 10 years showed a significant increase. Nevertheless the Italian production of medicinal plants has to deal with the

price and the difficult competiton with Eastern Europe and those in developing countries, which together accounted for about 70% of consumed herbs in Italy. The largest producers in the world field of medicinal and aromatic plants cultivated in Western Europe are: Albania, Bulgaria, Croatia, Greece, Yugoslavia, Macedonia, Poland, Romania, Slovakia, Slovenia, Spain, Turkey, Hungary, Egypt, Morocco, Tunisia, China, India, Pakistan, Argentina, Brazil, Chile, Mexico, Central America, and others.

The fact that 70% of the national requirement is imported herbs, leads to infer that in Italy there should be a good chance to increase the cultivation of medicinal plants and many farmers see in the cultivation of these plants in the new opportunities they hope more profitable than the traditional ones. The feasibility in order to start the crops are: the knowledge of which plants grow, such as land and equipment are needed, how much manpower you must have available, such as machinery are needed, what are the costs of production and/or processing, such as are the yields and incomes and especially how to market the products.

Due to the large number of medicinal species required by the market, taking account of the various climatic and business situations it is very difficult to decide which species to grow and companies must evaluate each case what are the most suitable species. Crucial, and not always easily assessable, is knowledge of the sales possibilities and profitability; It can be a winning strategy to make contact with the marketing companies or with the processing industries which can buy dried plants or semi-finished products. It is essential to know the possible means of marketing and the minimum price that can be made or you will have to assume, in addition to the cultivation, processing in the company and sales in niche markets, which, in particular situations, may prove to be quite profitable.

The agronomic performance is strongly influenced by the crop species and the climate. For example, a hectare of chamomile provides an average of 6 q of dried flower, one hectare of mint around 70 kg of essential oil and a hectare of flax seed 10-15 q. In southern Italy, where the duration of the growing season is longer, the presence of irrigation allows increasing the green mass production and therefore to perform more cuts. Moreover in South Italy the higher temperatures reduce the drying costs.

The small Italian companies, individual or associated in cooperatives, should enhance the product directly dealing with the entire production chain, transforming and selling directly the raw material processed. This is easier operating in developed tourist areas where the tourism presence increases the chances of selling the product through outlets of local products, or at the hotels or directly to tourists.

Among the products that have the greatest economic value in Italy there are blueberry (fruit) with investments estimated at 15 million euro and the saffron stigmas (9.8 million euro). The main species by market value among the cultivable (and already partly cultivated) in Italy, as well as bilberry and saffron, red vine, ginkgo biloba, milk thistle, passion flower, chamomile, gentian and valerian. Of the latter only the passion flower is grown on surfaces and quantities compatible with national needs. Higher loan volumes for cultivable species in our country are: blueberry, red grape, gingko biloba, milk thistle, fennel, Passiflora incarnate, chamomile, onion, oregano, rosemary, licorice, wormwood, garlic, cilantro, lettuce , anise, sweet clover, artichoke, rhubarb.

In all industrialized countries is documented a renewed interest in traditional medicine, especially for remedies made from medicinal plants, which has revived the research in this area. The recent World Health Organization guidelines have highlighted the importance of ethnobotany and ethnopharmacology, with provisions encouraging each nation to recover on its traditional therapies [57].

Some important pharmacological active principles, previously unknown to official medicine, have been obtained thanks to ethnobotanical investigations have shown that particular therapeutic uses of wild plants (eg. Derivatives of salicylic acid, the active substance of aspirin, codeine, vinblastine, etc.).

More than 120 of structure known drugs that are still higher plants and extracts used in any manner in allopathic medicine. These molecules are extracted from less than 90 species, and considering that there are about 250,000 species of higher plants of our planet, we can expect that, with the progress of research, a much larger number of drugs can be identified in the plant kingdom [58].

Recently, a new problem has emerged for the large number of natural products that are imported in Western countries, as a result of migratory flows; In fact, migrants from different countries of the world carry in tow also their cultural traditions, including eating habits and medicinal remedies, mostly herbal. Many of these new supplements and herbal medicines, however, have a composition largely unknown, that may represent a risk factor for the health of consumers. Are known, for example, contamination of natural products with synthetic drugs, such as stimulants, diuretics or anorectic. In addition, Asians and Latin Americans are known to make extensive use of mushrooms (e.g. Psilocybe sp., Paneolus sp.)

Italian industries for plant and food extraction

Besides, some main companies such as Indena, Naturex, Martin Bauer, Real Aromi, Aboca etc., a big number of SME are known in Italy and abroad for the high standard of production quality (Bionap, Giotti etc.). Moreover huge extraction plants are working for specific applications like the Lavazza plant in Pozzilli for caffeine extraction. A big role is played by the liqueur industry (Bacardi, Martini, Pernod Richard etc.) that extract plants blend mixtures for vermouth and bitter liqueurs. Pharmaceutical industry has also own extraction plant as well as some big cosmetic industries.

Relevant Italian Associations

ASSOERBE
Via Francesco Ferrucci 22 - 20145 Milano
www.assoerbe.eu

F.I.P.P.O Federazione Italiana Produttori Piante Officinali
Via Spallanzani, 23 - 52100 Arezzo (AR)
www.fippo.org

Relevant European Associations

E.H.G.A. - EUROPAM
(European Herb Growers Association)

AESGP
(Association of the European Self-Medication Industry)

Food Supplements Europe and Botanical Task force

Herbal Medicinal Products Committee

EBF (European Botanical forum) created in 2004 by the **European Responsible Nutrition Alliance (ERNA)** and the **European Federation of Associations of Health Product Manufacturers (EHPM)**

3. State of Research and Technology

Research in phytoextraction is characterized by mostly independent activities of biologists, pharmacists, (phyto-) chemists, and engineers. Activities are either directed towards materials or technologies. Exchange of know how in joint projects or during symposia hardly take place. The industry side (especially pharma, food, cosmetics and the correlated engineering companies) protect their experience and know how against each other.

Technical transfer into apparatus design and process steps is mainly based on experience and trials with little variations and quick decisions on implementation or discontinuation. Laboratory and piloting experiments are run for selected raw materials only and in standardized equipment.

Many available and local raw materials are not considered for product development, because they do not fit into the classical set up or have not enough content of the target compounds.

The key task to be addressed first is to make users and manufacturers aware of the considerable advantages resulting from systematic approach towards a systematic and integrated process development, including process optimization, and offer support during their implementation.

In order to prepare properly for the future, like dealing with consequences from the climatic changes, and to be able to compete on an international level, it is mandatory to look at new cultivation concepts and work on their development. In particular the development of biotechnological concepts for the production of plant-based actives for the biopharmaceutical industry, biotechnology and pharma industry.

The following list of available options may elucidate possible opportunities:

Natural populations:

- – danger of extinction of rare plant types (lacking sustainability)
- – in part difficult access to raw material
  - ▸ lower logistic security
  - ▸ stockholding required
- – export prohibited or restricted
- – large heterogeneity in active concentration and variation
- – quality assurance impossible
- \+ low price for the drug

Field cultivation:

- – varying content and concentration of active compound
- – in part insufficient quality of content/ active compound
- – season dependent production harvest: requires stockholding
- – danger of miss-harvest NIR-online analytics
  - ▸ reduced safety in logistic chain
- \+ lower price of drug; scheduled availability
- \+ possible to set up quality-controlled processes
- \+ sustainability ensured normally

Production in closed systems:

- – higher production costs
- – unfavorable energy balance, if not included in an integrated process
- \+ lower cost for quality control; quality assurance simple
- \+ higher content of active compound through optimized culturing conditions
- \+ production independent of season, weather or climate; minimal stock required

Especially the pharmaceutical industry with their typically higher priced raw materials could substantially benefit from such a validated way of plant growing, and so differentiate itself from competitors, who are in part operating with materials of uncertified origin, lacking sustainability, and therefore operate with an instable supply chain.

In addition, due to the season-independent cultivation, freed resources and production slots can be used more effectively, while stock holding and the capital bound can be massively reduced.

Besides the already listed advantages, additional potentials are summarized as follows:

- development of cost efficient technologies for production of high value plant materials, extracts and phytochemicals
- adaptability to the specific requirements of individual cultures
- higher productivity compared with field cultivation
- potential to influence the compound spectrum through control and variation of culturing conditions
- production of extracts with optimized biological activity
- combination of the production technology with in vitro screening systems for fast process optimization and the development active agents/contents

4. Research Targets

The goal to enhance the competitive position of the national research institutes and companies shall be pursued by implementing a new interdisciplinary research focus in the areas biology/botanics, agrosciences, food chemistry, natural products chemistry (phytochemistry), medicine, pharmaceutics, and process technology.

This research focus should encompass all steps impacting the process to generate plant-based value products and active compounds. The relevant process steps are:

- selection of raw materials and their producing plants
- ensurance of sustainable wild plant collection ... or
- better: plant selection, cultivation and efficient growing methods
- disintegration
- extraction
- purification, possibly isolation
- formulation
- packaging / provision of raw material for subsequent further processing

Some of these steps will be discussed in more detail and supported by examples.

Finally, for each process step a concrete goal is defined, which will contribute significantly to creating competitiveness of the national research and development, and helps to improve economic conditions.

As overarching methodology the model-based complete process development is established. Innovative production technologies will conceptionaly be designed.

4.1 Raw materials

Raw materials, e.g. leaves, flowers, branches, bark, rhizomes, roots, seed and fruits, but also algae are very diverse in their consistency, thereby determining to a large degree the choice and design of apparatus. Active ingredient content is typically in the range of 0,03 to 5% dry weight (in special cases 8, sugar 18), varies significantly as a function of year and growth region.

Agrosciences and botanics should be able to contribute to a strong yield increase through plant selection and cultivation.

Beside analytics, the localization of the compounds of interest in the individual parts of the plant is of major significance, especially because they vary over the growth period.

The physical properties of the plant constituents also determine the procedure for processing and extraction, because for example in the case of wood and hard fruits significant problems can exist during sizing, transport and disintegration. In general, mostly leaves are extracted, while the share of extracts from bark or seed is small. However, at least in the field of the aroma and perfume industry many examples of extracts from seed (iris, vetivier, apiacea fruit,...), bark (sandal wood, ...) and peel (citrus, mangosteen,...).

Goal is to make all raw materials accessible for processing.

In 2015, a total of 268 industrial plants were grown in Germany on 2.472.000 ha overall (FNR, Gülzow), of which 2.204.000 ha were energy plants. According to the Federal Government's action plan for the non-energetic use of renewable raw materials an expansion of the cultivation area to 20.000 ha until 2020 is envisaged.

This ambitious goal, however, can only be reached, if additional wildgrowing plants can be cultivated successfully (e.g. traditional chinese medicinal plants), and species already in cultivation are further optimized regarding quality and resistance. Not least in this context it will be necessary to further increase the need for the corresponding renewable raw materials by developing new biobased products.

Of the pharmaceutical plants processed in Germany, only appr. 10% are cultivated here. The remaining amounts are imported and mainly come from wild collecting. This is manila based on the relatively high cost and time for cultivation, requiring at least 5 years for herb plants. Nevertheless, the growth of pharmaceutical and spice plants in Germany is continuously expanded, currently supported also by the initiative for advancing innovative biobased

products. A leading position with currently , › 1.000 ha of farming area is taken by camomille, followed by flax, peppermint, seabuckthorn, fennel, st. John's worth (Hypericum) and foxglove with about farming area from 100 – 500 ha each.

Further, echinacea, willow, valerian, ribwort, butterbur, salvia, anise and goldenrod are cultivated on area between 50 – 100 ha each. In contrast, the relevance of farming balm, arnica, artichoke, ginseng, whitethorn with farming areas ‹ 50 ha each is modest.

The harvested parts of the pharmaceutical and spice plants as leaves, flowers, branches, bark, rhizome, root, seed, and fruit, but also algae vary widely in consistence and therefore strongly impact the apparative lay out during the technical processing. For process optimization it is important besides the analytics to localize the individual value components in the different segments of the plants, as well as characterize the concentration changes during ontogenesis. The physical properties of the plant components determine the approach during processing and extraction, as wood and hard fruit can create significant problems during grinding, transport, and disintegration.

To localize the valuable plant segments vibrational spectroscopy techniques as infrared and Raman spectroscopy are successfully used, which in combination with microscopy allow to determine the distribution of plant ingredients on the cellular level. Also in cultivation and farming similar methods are used for non-destructive analysis of plant ingredients in leaves, fruit, or seeds.

4.2 Disintegration, Pre-treatment

Besides the process steps extraction and purification the disintegration and pre-treatment is decisive for the process economy. First, the products of interest have to be released from their matrix by a disintegration or at least become accessible. A product specific disintegration (i.e. only a cell component like the cell wall, or a plant component like flower leaves is desirable.) The often limited stability of the target compounds call for careful handling. From the manifold options, e.g. enzymatical, mechanical, chemical, electrical, ultrasonical, etc. no clear pattern exists as guide for the best suited disintegration process. In practical use almost always mechanical grinding is the method of choice. This is partly due to insufficient knowledge on the chemical structure (glycoside or other sugar derivatives), the location (on the surface, in specific cells, intra/extra-cellular), and the types of compounds in the plants.

Empirical approaches often lead to immature process developments and economically less attractive work up campaigns. Another specific criterion is the overall low degree of innovation in parallel with the very modest investment volumes.

Goal is design and improvement of disintegration processes well adapted to the product matrix.

4.3 Extraction

For assessment and conception of solid phase extraction the aspects solid phase preparation, selectivity, phase equilibria, kinetics, and capacity are decisive. Especially solid phase preparation and kinetics are closely linked.

Intraparticular diffusion is determined by particle- and product-size, as well as swelling degree or maceration of the starting material. Further impact on yield and purity of the products have the process parameters temperature, pH-value, state (liquids/supercritical), composition of the extraction agent and additives like tensides, as well as the control of the process. In general, during extraction the higher the yield, the unproportional higher the share of impurities.

A similar picture is found for the solvent or solvent mixture selection for the extraction of a key component or a selected product mixture. In an operating regime up to max. 100°C and pressures between 0,8 and 6 bar the most often used solvents are water, lower alcohols, ethyl acetate, acetone, hexane, and methylenchloride. The latter two have been traditionally used, but should be avoided for new processes (see MSDS), as they have known safety risks. By their use within a process all residual biomass has to be treated as hazardous waste. An innovative process is the extraction with supercritical CO_2 and near-/super-critical water. During solid phase extraction often fully empirically developed, company-specific solvent mixtures

are used, as for example the synergetic effects of different solvent components are widely unknown. Known, however is that pure components have lower solubility compared to a product extract containing several components, because accompanying substances (oils, salts, proteins, etc.) can act as solubility enhancers.

Key issue is the reduction of solvents used! In general, phyto-processes can be divided in either yield dominated due to the high raw material costs, or solvent dominated. Energy consumption has to be minimized. The effort of solvent recycling has to be reduced. Thermodynamics of phase equilibria is the basis for processes to separate/purify value products. Therefore, their solubility plays a major role during extraction of such value products. In the case of solid phase extraction

one has to account for the dissolution as well as a desorption of the value product from a solid phase, contrary to classical liquid-liquid extraction. Besides the equilibrium thermodynamics also kinetic effects play a major role.

The disintegration and the pretreatment of the solid significantly impact on the accessability of the active compound, as diffusion paths, swelling and pore size are relevant parameters. The steps disintegration and extraction/desorption cannot be treated independently of each other, which requires an interdisciplinary research approach of process technology and natural product chemistry, respectively biology/botanics. This can also be taken from Fig. 9, see ch.5.

Goal is the development of standard protocols for the extraction, adjusted (tuned) to compound classes and starting (raw) materials, above all, however, an intensification of the respective processes with the target of a significant cost reduction(› 50%) of overhead cost. A classification, which allows an easy correlation (sorting) of new substances, has to be developed systematically.

4.4 Apparatus design and process modeling

Today's apparatus are in essence based on a few traditional and "well-tried" designs. For extraction purposes, typically caroussel-extractors, stirred tanks, percolators and decanters are in use.

Known for their problematic handling are apparatus used for the removal of liquids: pressure filters and also ban-type filters.

Depending on the product especially factors like space-time-yield or product losses are critical for success. Selection and dimensioning of apparatus for disintegration of the plant material and for extraction occurs empirically until today.

More detailed knowledge of the botanical/biological and process technological basics shall contribute to make process development faster and safer. The number of laboratory experiments necessary to characterize the properties of raw materials and extracts should be kept low, and the necessary raw material amounts should be minimized by miniaturizing and automating laboratory apparatus through combination with on-line measuring technology. A model-based planning of experiments and evaluation of results to determine model parameters is indispensable. For the modeling of the process verified experimental data sets for defined systems as well as theoretical work (phase equilibria and mass transfer models) are required.

Goal is, besides apparatus development, also a standardization of the laboratory methods for further process concepts and the scale up. A model-based apparatus design as well as the total process development has to be developed, validated by mini-plant experiments.

Most of today's processes are batch type; continuous processes should be developed in future.

4.5 Formulaton and packaging

After production, the finalized extract is shipped to the customer for further processing. Therefore, packaging must ensure safe transportation and storage On the other hand, the extract has to provide to the customer a formulation, which is robust and reproducible for formulating a final consumer product. This is best achieved by early interaction with the customer during development. Failing to do so can result in difficulties during production.

Goal is therefore, to check into the product requirements (specifications) as specifically as possible and to verify those during the development process.

5. Road Map

The interplay of the interdisciplinary subject fields over the total value chain can be achieved through a backward integration from final formulated product via active ingredient purification to raw plant material farming/collection with harvest and extraction methodology, see Figure. 9

Plant-based Extract Production

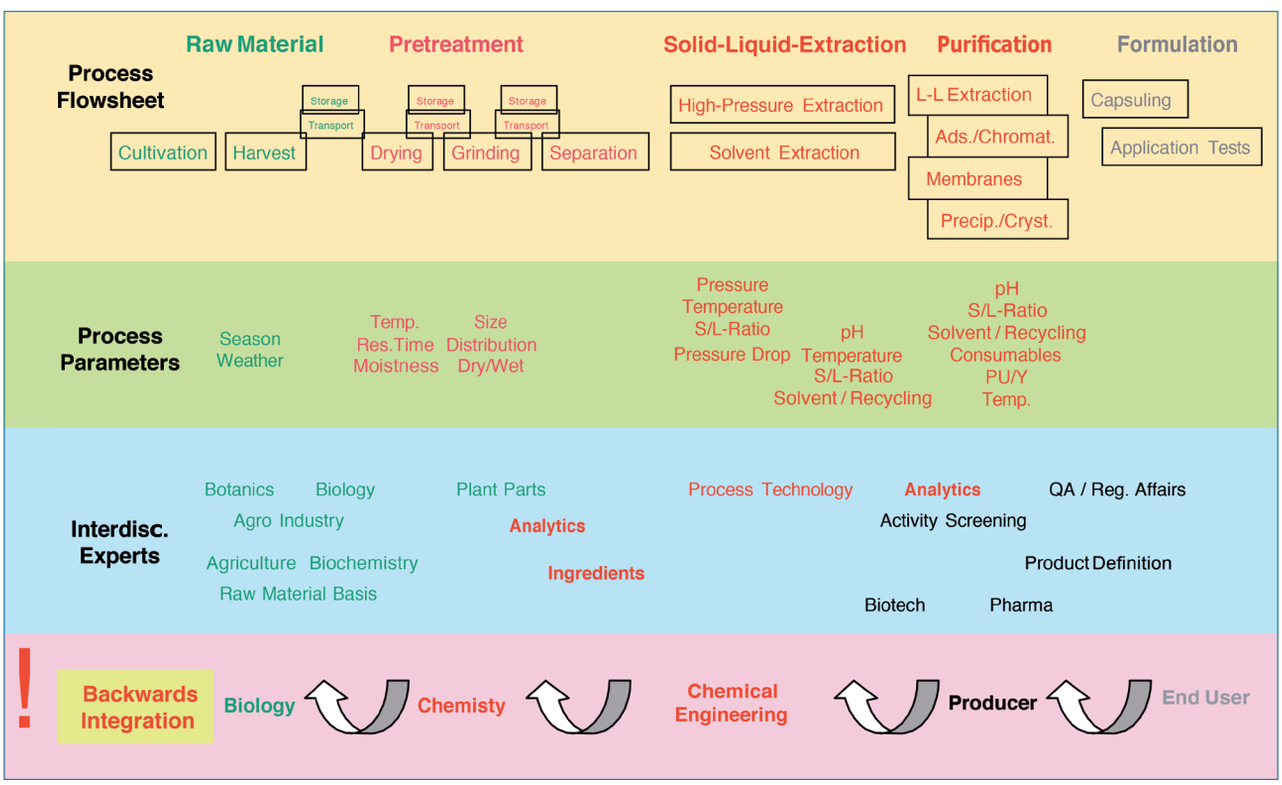

Figure 9: Process-orientated interdisciplinary realization of backwards integration

Conclusion:

1. The potential of phytoextracts with regard to market relevant products and efficient processes continues to be very high.
2. This potential can only be realized in an interdisciplinary coordinated research approach. The central support of the subject group is to be made visible by presentations and publications, the potential for interested companies has to be outlined to them to enable them to improve their own development potentials and use it for their products. This in particular is still one of the strengths of the German/European economy.

The time table, which the subject division has laid out for the next years in order to reach the goals, presented in the following table 4 as a road map.

Table 4: Road Map Working Group „Phytoextracts – Products and Processes“

2011	2016	2021	2026	2031
ProcessNetGerman Working Group	**EU Regulatory** Techn. harmonise as proposals • Agro/Pharma/Nutr./Flavors • SME Strengthening/Sustainm.			
meets GENP	**Standardized Measurement Cells** • Raw material choice • EU agricultural plants			
Clausthal Trainings Courses	**Green Extraction** • Methods and Light-house Applications	**New Productions Technologies** • decentral, flexible, regulated • KMU Strength, Product cycles		
Lecture Books	**Process Intensification** Methods and Light-house Applications	**Botanic → Modell → Process/ Aquipment** • ind. project work available		
	European Working Group • Foundation	**Analytics in ProcDev available** • CFLSM • FTIR, Raman • MS, NMR ...		**New Manufacturing Technologies** • European integrated
				Botanic → Modell → Process/ Equipment
				Data base Physical properties for ingredients (plant part&type)

Demand of European Phyo-based Industrie

I. Phyto-Pharmaca

» ~ 50 pure components on market

» ~ 150 plant types utilized

» most products as extracts OTC

» less block-busters like Taxol, Artemisinin etc.

» some like Gingko via mixture key-component ratio definition

1. Typical are problems like supply bootlenecks of raw plant material in sufficient quality due to harvest losses, too tight planned schedules or transportation and storage damages which leads directly to loss of end consumer groups, because they will in the marketing driven OTC environment not come back.

   ➞ This are basic management deficits, which could not be solved technically.

2. In general, phyto-pharmaca are cash cows withn the portfolio, therefore only the necassary regulatoray updates each 5 years are invested and are manufactured without any development budget. This leads at typicaly varying feed charges to enourmous challenges for production operation, because only one standard set of operation parameter is defined and deeper process knowledge is not available.

   ➞ In the meantime there are many studies available and process modelling is trained [Dechema Course on phytoextraction at Clausthal University of Technology since 2011]

3. Moreover the plant raw material is not utilized to any sufficient extent.

   ➞ Technology is available, See 2.

4. Plant-cell fermentation is in most cases of too high efforts and too time consuming to develop within more than 5-10 years, plant-based products are easily faster on the market. Complete new filling of cells is generally avoided. Only, Phyton's Taxol as a block-buster and a special Morbus-Chron niche product from carrot cells is on the market.

   ➞ It has to be waited whether new omics methods will speed up dedelopment

5. Miniaturization of extraction processes for predictive process design.

   ➞ Has been developed, see 2. And 3.

6. Demanded is determination of distribution behavior of plant ingredients in „single pot model" with plant cell membranes and a gastrointestinal membrane for fast prediction of bioavailable components

   ➞ Future research topic, but human pKs models are available, should be possible within 10 years.

7. PAT (Process Analytical Technology) for inline-analysis of extraction processes

   ➞ Is developed at the moment incl. QbD-methods, eg. DFG-project of JKI/Berlin and ITVP/TU Clausthal

8. Parametric defined release at manufacturing of plant extracts

   ➞ First proposals are available at e.g. QbD-methods published by ITVP/TU Clausthal

9. Fluid flow dynamics of extractor equipment and influence of internal geometry and dimensions

   ➞ Has been reported about 10 years ago. Could be worked on like project basis.

10. Homogenity at production of extracts in large-scale

    ➞ Corresponds with 2 and 7 and 8

11. Lyophilization instead of vacuum-beld drying

    ➞ Worked on e.g. BMWi-project at TU Clausthal

Technology readiness level colored:

already available 2016 | to be developed – 2021 | to be developed – 2031

12. Efficacy studies which enable IP protection to cover the costs via patents on the new processes
    - ➞ Has to be done, but so-funding is available for SMEs from regional governments
13. Fresh plants instead of dried raw material
    - ➞ e.g. at groups in Kaiserslautern and Clausthal
14. GHACP instead of GMP on field incl. extraction media and pomace to be deposited on field again
    - ➞ e.g. studies in Clausthal
15. Solid-liquid extraction process optimization and costs for optimization changes for decision on investments
    - ➞ e.g. see 2
16. Similarly to gingko example define ratios of key side components, execute efficacy studies and new approval for IP protection of efforts&costs
    - ➞ To be done, but see 2 and 12
17. SMEs and start-ups: Scale-up in 50 kg piloting-scale incl. technical infrastructure of manufacturing environment with non-manual handling and safety issues like ATEX-explosion proof, leakage prevention and water& air pollution protection
    - ➞ Engineering is available

II. Aroma, Flavors and Nutrition

- The market on aroma, flavors&nutrition additives is strongly diversified
- COGS are in most cases only in range of only xo€/kg
- Many products with small volumes 100-1000 kg/a.
- But as well for nutrition large volumes as aromes etc. for only x €/kg COGs

1. Exhaust vapors recycling in order to reduce loss of aroma at e.g. juice manufacturing and valorization of waste raw material
    - ➞ by e.g. capture unit operations
2. OSN organic solvent nano-filtration to be applied in manufacturing
    - ➞ Long-term stable and more selective
3. To have a standardized DSP (downstream processing) procedure for fermentation of fungi and algae etc.
    - ➞ Already worked on
4. Avoid new investments in (innovative) equipment of innovative unit operations like chromatography
    - ➞ see I.2.
5. Process intensification methods like MW, US, PEF etc.
    - ➞ led by french, Italian, german activities, strong European affiliation
6. Apply and adopt more often CO_2, Biosolvents, HPWE
    - ➞ Strong European activities, led by french and italian actions
7. Green Labeling for successful marketing
    - ➞ Led by french an italian activities
8. Biomass valorization, e.g. carrot, broccoli, artichoke etc. do have 30-80% plant material waste
    - ➞ French, italian and german activities within National an European bio-based economy programs
9. Reduce plant extractions via synthesis and fermentations
    - ➞ Since many years manifold activities at companies

Technology readiness level colored:

already available 2016 | to be developed – 2021 | to be developed – 2031

III. Agrochemicals

» Market is dominated by SMEs

» and driven by consumers reliant on bio-based labeling

» small volume low cost products

» niche at the moment but fast growing

1. Efficient total process design for SMEs

   ➞ See I.2.

2. Integrate process intensification methods for SMEs and scale-up infrastructure to fully integrated manufacturers

   ➞ Investment support needed

6. Options and Recommendations

The subject division wants to encourage academia and scientific organizations, active e.g. in the field of process technology to develop project proposals for the different fields, including all disciplines. This includes all aspects, starting with the farming, breeding, harvest and disintegration as pre-treatment of the plants, the solid-extraction, the enrichment of actives, and the dimensioning/sizing of equipment.

Regarding the financing of projects, the subject division proposes to exploit in the first stage the established ways of public funding.

The organizations involved in the preparation of this positioning paper, the ProcessNet-Subject Division Plant Based Extracts – Products and Processes, as well as their German organizations DECHEMA, VDI-GVC, GVT will argumentatively support the activities.

From the point of view of the subject division the topic phytoextraction deserves at least similar allocation of public funded capacities and resources as the established knowledge areas in process technology.

In individual cases, also direct funding by individual companies or a group of companies should be possible, e.g. to support project initiation.

Analogous to the research funding strategy in France, an explicit industry funding by setting up centers with regional focus in the "growth" regions to install/support services in process development up to the pilot scale including analytics is promising. Due to short distances and links this directly benefits the SME's in the region.

New and innovative products from plant-based renewable (re)sources for a variety of applications and markets are an interesting and valuable contribution to Europe's economic and ecologic future.

The breadth of potential products, the necessary technologies (in part already available, in other aspects yet to be developed), provide a great opportunity for a cohesive collaboration on a European level, because

... significant potentials and growth options for a "European" strategy should fit well into the scope of H2020

... an interesting mix of renewable raw materials from nature, although with variations in reproducibility opens many opportunities for "directed" cultivation of old and new plants for a variety of markets:

» as high quality food

» variable food additives

» pharmaceutical applications

A significant tool for future growth and success is the updated Road Map on the current status of focus activities.

This is complemented by the results generated from the Tutzing Symposium in September 2015 on these activities.

‹–›	‹+›
• limited space for plant cultivation & growing	• leading position in process design & equipment
• moderate varieties in plant species	• efforts towards process integration & conti moderately increasing
• lack of sufficient knowledge in using plant ingredients properly	• relocatable harvesting an processing
• less demand from consumers compared to other regions	

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