HiPerIn 2.0

Shaping the Next Generation of Bio-based High Performance Ingredients

Biotechnology in the Flavours and Fragrances Sector

HiPerIn 2.0 White paper

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CLIB networking biotechnology creating sustainability

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Cluster Industrial Biotechnology e.V.

CLIB (Cluster Industrial Biotechnology) is an international open innovation cluster of large companies, SME, investors, academic institutes, and universities, as well as other stakeholders active in bioeconomy. The cluster comprises over 100 members with a share of about 25 % international members. The overall goal of CLIB is to network stakeholders in Germany and beyond and to identify new opportunities for innovation, projects, and business. Through this, the cluster develops cross-sectoral biotechnological solutions for sustainable processes and products. CLIB is a non-profit association, with its members shaping the cluster's interests and activities. The cluster is involved in several associated programs which cover different aspects of bioeconomy and invites members to become involved. To this end, CLIB organises several events throughout the year: the annual CLIB International Conference (CIC), the CLIB Networking Day (CND), forum events, topic-specific workshops, and dedicated small partnering meetings.

HiPerIn 2.0

HiPerIn 2.0 is a project funded by the Ministry of Economic Affairs, Industry, Climate Action and Energy of the State of North Rhine-Westphalia (MWIKE). HiPerIn 2.0 reflects the rapid change in biotechnology and includes cross-cutting issues which had been identified and validated by CLIB and in an exploratory phase. The increasing digitalisation of biotechnology, the renewed concept of a circular economy, the end-of-life debate, the public perception of biotechnology, and increased regulatory requirements are cross-cutting topics which are of interest to many stakeholders. CLIB pursues the topics of biosurfactants, textiles, flavours and fragrances, and food / alternative proteins. Another focus in the HiPerIn 2.0 project is the support for project consortia and the identification of potential funding lines.

Zusammenfassung

Der Aromen und Duftstoffe (F&F) Sektor wird Prognosen zufolge bis 2029 auf über 36 Milliarden USD anwachsen, von denen heute nur 7 % biotechnologisch hergestellt werden. In diesem White Paper skizzieren wir im Rahmen des HiPerIn 2.0-Projektes eine SWOT-Analyse der Biotechnologie im F&F-Sektor. Die Stärken der Biotechnologie sind ein geringerer Kohlenstoff-Fußabdruck, weniger Landverbrauch, flexiblere Wertschöpfungsketten im Vergleich zu den derzeitigen Produktionsverfahren und die Möglichkeit neue naturfremde Moleküle zu designen. Lange Entwicklungszeiten und hohe Investitionskosten sind die Schwächen biotechnologisch hergestellter Nahrungs- und Genussmittel. Chancen ergeben sich aus den Forderungen der Verbraucher*innen nach natürlichen und nachhaltigen Lebens- und Futtermitteln und aus technologischen Fortschritten. Bedrohungen können ein Misstrauen der Verbraucher*innen, fehlende Investitionen und eine mögliche Priorität der grünen Chemie gegenüber der Biotechnologie sein. Aus dieser SWOT-Analyse werden Wachstumsfaktoren und die Relevanz für NRW abgeleitet und in diesem Whitepaper zusammengefasst.

Summary

The flavours and fragrances (F&F) sector is forecast to grow to over USD 36 billion by 2029, of which only 7% is produced biotechnologically today. In this white paper, we outline a SWOT analysis of biotechnology in the F&F sector as part of the HiPerIn 2.0 project. The strengths of biotechnology are a lower carbon footprint, less land consumption, more flexible value chains compared to current production methods and the possibility to design new molecules that are foreign to nature. Long development times and high investment costs are the weaknesses of biotechnologically produced food and beverages. Opportunities arise from consumer demands for natural and sustainable food and feed and from technological advances. Threats can be consumer mistrust, lack of investment and a possible priority of green chemistry over biotechnology. Enabling factors and relevance for NRW are derived from this SWOT analysis and summarised in this white paper.

Introduction

Flavours and Fragrances (F&F) are molecules altering the taste or smell of products. They belong to different chemical classes such as lactones, esters, acids, or aldehydes. The most important markets for F&F are the food and beverages market, with roughly 88 % market share, the cosmetics market, the home and personal care market, but also the pharmaceuticals market. In 2021, the global F&F market had a size of USD 25.89 billion and is projected to grow to over USD 36 billion in 2029.[1] The biotechnology share within the F&F sector is estimated to be around 7 %[2].

F&F are usually used in small volumes in the end products and are often high prized. They are mainly produced chemically from fossil feedstocks or by extraction from natural sources. F&F can also be produced biotechnologically via fermentation of microorganisms, in plant cells or via enzymatic catalysis. For example, in 2019, 85 % of the global vanillin market was served by chemically synthetised, fossil-based vanillin and was sold for 10-20 USD/kg, while pure vanilla extracted from vanilla beans had a prize of over 25,000 USD/kg.[3] According to EU- and US regulation, F&F from extraction as well as from biotechnological processes can be classified as natural, if the feedstock is of natural origin[2].

The main drivers for the growth of the F&F sector are the growing cosmetics market and an increased demand for natural ingredients in personal care products. The pharmaceutical industry is also increasingly using flavours to overcome bad taste of orally taken medicines.[1]

[1] Flavours and Fragrances Market Research Report, 2022, Fortune Business Insights, Summary
[2] Bio-based flavours and fragrances, 2020, Advanced Technologies for Industry – Product Watch
[3] Ciriminna R, et al., Vanillin: The Case for Greener Production Driven by Sustainability Megatrend, ChemistryOpen, 2019.

The sector itself is heavily influenced by regulations and by customers' wishes. Even though an internal study performed in the framework of the project HiPerIn 2.0 showed that high-performance low-volume ingredients such as flavours in food and beverage products are only minorly perceived by the customer, non-acceptance of certain technologies or production processes can have a major influence on a market. This is true for biotechnology, which, although it has been used in the food industry for 13,000 years[4], most customers know little about.

The market is mainly controlled by few large internationally operating companies, such as Givaudan, International Flavours and Frangrances, Symrise and Firmenich, who together serve approximately 50 % of the global market. Many small and medium sized enterprises (SME) mainly work as experts in individual niches of the market. The large players within the sector have been acquiring SME or merging with other companies in the past years to expand their portfolio as well as to include biotechnology expertise in their company.[1]

[4] Li Liu, Jiajing Wang, et al., Fermented beverage and food storage in 13,000 y-old stone mortars at Raqefet Cave, Israel: Investigating Natufian ritual feasting, Journal of Archaeological Science: Reports, Volume 21, 2018.

SWOT-Analysis of the biotechnology F&F sector

To identify routes and strategies to strengthen the share of biotechnologically produced flavours and fragrances (F&F), the status of the sector has been analysed both based on desk research and based on the inputs given by experts coming from several members of CLIB active in the sector. The results of this analysis are summarised in this white paper. From this analysis, enablers of growth have been identified and the relevance of these insights for NRW have been summarised.

Strengths

The sector of biotechnologically produced F&F is set on a strong basis. The market for F&F is growing with many companies looking for biotechnological alternatives and new-to-the-market molecules. F&F are usually used in small volumes in products and natural compounds are often high prized. This combination can be advantageous for new technologies, which are initially often more expensive compared to established alternatives.

Biotechnology has several advantages over extraction from natural sources. Both EU and US regulations account substances produced via biotechnological routes from bio-based feedstocks, as for example sugars, as natural F&F. In contrast to natural F&F derived from extraction, biotechnologically produced substances are often more sustainable, as the feedstock can be sourced locally, and scaling of the production is easier, due to less land intensive and feedstock agnostic production. The supply and quality, and as a result also the price, are additionally more stable, as fluctuations in crop yield have less impact. For some compounds scaling of extraction is even impossible due to land scarcity and biotechnology is the only available route to produce large amounts of the compound that can be classified as natural.

Due to the limited supply of molecules from extraction, many F&F are currently produced chemically from fossil resources knowing to have an unfavourable carbon footprint and decreasing acceptance in society, especially in the strong F&F markets such as food & beverages and home & personal care. Biotechnological production routes omit these feedstocks and can even use non-food biomass or side streams to build strong value chains. For complex molecules, chemical synthesis routes often require multi-step syntheses and have to apply harsh or even hazardous conditions. Using engineered microorganisms or plant cells can shorten synthesis routes of these highly complex molecules to “single-step” synthesis.

Biotechnological synthesis is in addition more precise compared to extraction. Natural extracts are often mixtures of several molecules and can contain allergens. In contrast, fermentation or enzymatic catalysis produces defined molecules, that omit allergy-causing side-products and can even be produced enantiomer-specific, which is especially important for bioactive compounds.

Exploitation of the developments in synthetic biology will also allow companies to produce new-to-nature F&F, that show improved or even new properties regarding taste, smell, or processing, or possess secondary functionalities such as being antimicrobial, anti-inflammatory, or anti-allergic. This is especially true for savoury aromas, which see a growing market in vegetarian and vegan meat-alternatives and are hardly available through extraction.

Weaknesses

Using biotechnology to produce F&F also has some disadvantages that the sector needs to overcome in the future.

Despite the rapid growth of *omics*-data and knowledge of organism engineering, the development of biotechnological processes still takes long periods of time.

This is not only due to the engineering of the production strain and scaling of the fermentation, but also due to the difficult optimisation of downstream processing to purify the product suitable for markets such as food, beverages, home and personal care, which require highly pure products. These long development times do not meet the urgent need of the market to transform from fossil- to bio-based production or to exploit new molecules.

In addition, the development of biotechnological processes requires a considerable investment, as the construction of new facilities is both a lengthy and expensive endeavour. There are fermentation and downstream capacities available in toll-models, but the last years have proven that these facilities are quickly outgrown by the demands.

These disadvantages of biotechnology often result in the chemical process being more favourable, especially for rather simple F&F molecules.

Although an advantage in many cases, the small volume of F&F in the final product can also be a weakness. The frequently more sustainable and climate-friendly production, especially compared to extraction, and the smaller carbon-footprint of biotechnologically produced F&F contributes little to the overall carbon-footprint of the final product, which limits the drive of B2C companies to substitute existing products. Thus, biotechnological processes and products often need to show a unique advantage over existing processes to be implemented.

Opportunities

Looking on current trends and development, there are many chances for biotechnology in the F&F sector.

Growing concerns about health, sustainability and climate change have already started putting pressure on fossil-based products. Demand for natural, clean, and sustainable products will favour biotechnologically produced F&F, which are

natural according to regulation and compared to extraction often more sustainable and cleaner.

The market for extracted F&F is expected to shrink due to increasing land shortage and harm to ecosystems and biodiversity by wild harvesting. Classical chemical synthesis is not answering the demand for natural and sustainable products. Already today, the importance of naturalness is very high in the food and beverages market and will become more important in the personal care market in future.

In the recent past, concerns about global and non-flexible value chains have arisen particularly strongly. Local and agnostic value chains will be of economic and social importance and favour biotechnological processes, which can use several carbon-feedstocks, are sourced in the respective region, or can be switched if certain feedstocks become unavailable.

Furthermore, development times for new processes are rapidly decreasing, as more and more knowledge and technologies are developed in synthetic biology, genetic and process engineering, and downstream processing. Examples are the directed evolution, for which Frances Arnold won the 2018 chemistry Nobel prize, or the CRISPR-technology for gene editing, for which Jennifer Doudna and Emmanuelle Charpentier received the chemistry Nobel prize in 2020[5]. The deep-learning platform AlphaFold[6] predicting protein structures was an additional milestone. Recent trends and examples are also summarised in a review by Aravind Madhavan and colleagues from 2021[7].

[5] https://www.nobelprize.org/prizes/lists/all-nobel-prizes-in-chemistry/
[6] https://alphafold.ebi.ac.uk/
[7] Aravind Madhavan, et al., Design of novel enzyme biocatalysts for industrial bioprocess: Harnessing the power of protein engineering, high throughput screening and synthetic biology, Bioresource Technology, Volume 325, 2021

Inside and outside of the F&F sector a growing number of biotechnological processes are being developed leading to an overall increase of knowledge, experience, workforce, and awareness for biotechnology in society. Sustainability efforts of other sectors, such as the paper and pulp sector or the sugar industry, will enable mutually beneficial cooperation between the sectors to use side and residual streams and thus decrease the carbon footprint of biotechnologically produced F&F further.

The F&F market itself is also expected to growth. Biotechnology will open doors for new-to-nature molecules with secondary properties, such as being non-allergenic or preservative. Additionally, the growing market for vegetarian and vegan meat-alternatives will ask for new flavours creating a completely new market.

According to some experts in the sector, the precise production of defined molecules by biotechnology will not only exploit new functionalities but might also simplify approval of these new molecules compared to chemically synthesised or extracted compounds.

Threats

Despite the promising chances emerging for biotechnology, the sector needs to monitor several developments risking the growth of the biotechnology share in the F&F sector.

The lack of suitable facilities and investment is a huge hurdle for all biotechnological developments and a slow capacity build-up might handicap the development of the biotechnology sector for F&F.

Another major risk is an inertness of the sector itself. The F&F industry is currently largely chemical-based. Therefore, many industry players favour green chemistry using biomass or C1 gas streams together with sustainably produced hydrogen to

transform to fossil-free production. Biotechnology needs to show their unique advantages over green chemistry to grow its niche and identify the cases in which a combination of biotechnology and green chemistry is most appropriate, even though the property as natural F&F is lost, if chemical synthesis is used.

Regulation will also play a pivotal role in the further development of biotechnology in the F&F sector. Especially regulations on using feedstocks competing with food usage (e.g. sugar from sugar beet), regulations on genetically modified organisms and new technologies for genetical engineering (e.g. CRISPR) and regulations on the calculation of sustainability and life cycle assessments (LCA) will have a massive impact on the fate of the sector.

The growing market for organic products both in the food and in the personal care market in combination with the stronger rejection of products coming from genetically modified organisms may shrink the market share for biotechnologically produced F&F. Additionally, the growing market for “sensitive” or “non-allergenic” products contains very little to no F&F, especially in the personal care market, which might decrease the market size of F&F in total.

These threats need to be addressed jointly by industrial, political, and civil stakeholders to take advantage of the opportunities.

Enablers of growth

The market for biotechnological F&F is based on solid strengths and shows numerous opportunities for the near future. The industrial production of vitamin B2 (riboflavin) has already proven, that biotechnological processes using genetically engineered organisms can surpass chemical synthesis for products used in the food sector[8]. Nevertheless, weaknesses and risks need to be monitored and overcome so that the chances can be realised.

To exploit the potential of biotechnology to its fullest, efficient, and safe methods to genetically modify organisms need to be applied. This will only be possible if social acceptance and regulations follow scientific insights. Education and information, as well as scientifically substantiated decisions are crucial.

Biotechnology can be used as a powerful toolbox to shape the market. In combination with sustainable agriculture and local production facilities, biotechnologically produced F&F can strengthen regions and create value independent from global supply chains. The virtually limitless options of combining enzymes and microorganisms will open a market for new-to-nature molecules with new functionalities. These molecules can have a unique advantage over natural extracts and over chemical synthesis, as for example in taste, smell, or their secondary functionalities such as antimicrobial, anti-inflammatory, or anti-allergic. One example already on the market are glycosylated fragrances, that are released slowly when in contact with human skin and thus cosmetic or personal care products retain their smell longer[9]. With these unique advantages they will strengthen the biotechnology share in the sector.

[8] Averianova Liudmila A., et al., Production of Vitamin B2 (Riboflavin) by Microorganisms: An Overview, Frontiers in Bioengineering and Biotechnology, Volume 8, 2020
[9] https://4gene.de/en/services/cosmetics-fragrance/

As the F&F sector is heavily driven by the regulatory framework and the acceptance of the customer, these chances can only be exploited, if not only research and development resources are used and facilities and measurements for fast scale-up of technologies and processes are guaranteed, but if politics and society are also involved.

First strategies to increase the share of biotechnologically produced F&F are the development of molecules for products that are already close to 100% bio-based and where bio-based F&F can close the final gap to allow for a “100 % bio-based”-branding, for which a green premium prize is accepted. Products with low volumes and complex structures are also favourable early targets, as the competition with alternatives produced via green chemistry is less strong.

Relevance for NRW

The F&F sector is a global market largely dominated by multi-national industry players working and cooperating across continents. Nevertheless, North Rhine-Westphalia (NRW) can be a promising location for biotechnology companies producing F&F.

NRW has a strong basis both in academia and in industry. There are numerous excellent research institutes including universities, universities of applied science, Max Planck Institutes, and Fraunhofer Institutes. Both the chemical and the food industry located in the Rhine-Ruhr area is well established with many large enterprises, well established SME and start-ups emerging from the transfer and innovation centres at the research institutes or moving to NRW due to the excellent infrastructure. The biotechnology stakeholders in the region are well connected through several networks such as the Cluster industrielle Biotechnologie e.V. or the NRW-specific network BIO.NRW forming an ecosystem

for innovation. Thus, NRW combines all relevant stakeholders and prerequisites to overcome challenges and exploit chances in the F&F sector.

The biotechnology F&F market can open a new market of new-to-nature molecules, that can drive the whole sector forward. If NRW combines its excellent research with industry expertise and enables fast scale-up by offering facilities, funding, and suitable frameworks, both new biotechnology companies, as well as established companies can benefit from the chances in the F&F sector.

To take full advantage of the opportunities, societal acceptance for the new technologies and products needs to be fostered by educating and informing the citizens and by putting in place appropriate framework conditions.

Especially for the structural change within the former Rhenish lignite mining area, the F&F sector can be one relevant market to maintain the excellence of NRW in future.