COMMERCIALISATION OF KNOWLEDGE

THE UNIQUE PROPERTIES OF NATURE'S WONDER – BETULIN

AIGARS PĀŽE, JĀNIS RIŽIKOVS, KRISTAPS STANKUS, INGUSS VIRSIS

Although Latvia is relatively small in terms of territory, it is the fourth most forested country in Europe. Forests cover 52% of the territory of Latvia, therefore, the wood processing industry in Latvia has historically been and still is one of the most important in the national economy. This obliges us not only to take care of forest management in accordance with the best sustainability practices in the Nordic countries, but also to strive to add as much value as possible to each cubic metre of wood obtained in the forest. Keeping pace with the European Green Deal, we are aware of the important role of biomass, including wood, in mitigating the effects of climate change, providing important options for alternatives of fossil resources in almost all areas. Therefore, in Nordic countries, as well as in Latvia, increasing capacity has been invested in the research and development of chemical processing possibilities and technologies for wood processing by-products. In addition, the splitting of wood by-products into individual compounds not only makes it possible to replace the use of petroleum refining products. It is a way to release extractives included in the bark, which have huge potential in the food, cosmetics, and pharmacy industries. One of the most promising components of extractives with a wide range of applications is betulin present in high yields in birch bark – plywood production by-product.

UNIQUE BETULIN IN UNIQUE BIRCH

The birch (*Betula pendula, Betula pubescens*) is a species of deciduous tree found in the Northern Hemisphere, one of the oldest in this climatic zone, which has reached its evolutionary perfection. Latvia is located in the central part of the birch growing area. According to the forest inventory statistical data, birch is the most common tree species in the country. Due to its physically mechanical properties, birch wood is unique, making it an excellent raw material for the production of board materials with an extremely wide range of applications. However, since ancient times, people have also widely used non-wooden parts of birch – bark, leaves, buds, discovering that they have excellent healing and antiseptic properties.

With the development of technology and knowledge, research has shown that the external, white layer or birch bark of Latvian birch contains biologically active substances, which make up about one-third of the birch outer bark mass [1, 2]. Birch outer bark extractives are primarily composed of lupane-type pentacyclic triterpenes, mainly betulin, betulinic acid, and lupeol. Very valuable biological activities have been identified for these three compounds, including those that allow their derivatives to be used in the treatment of various severe diseases in the future [3–10]. Betulin itself improves liver function [4], regulates cholesterol levels [5] and heals skin cells [6]. A betulin-related synthetic compound has shown good results in drug trials against HIV [7]. In scientific studies, betulin has also demonstrated immunomodulatory [8] and anti-inflammatory properties [9], as well as indicated a good potential in virus-like vaccine candidate against SARS-CoV-2 [10]. Compounds of birch outer bark extractives also have preservative, antioxidant, emulsifier and supramolecular gel-forming properties [11, 12]. Betulin has also been identified for a wide range of applications in the food and cosmetics industries. As a 100% natural, industrially sustainable raw material, in the future betulin could replace various synthetic emulsifiers, preservatives and antioxidants that are harmful to the human body. Indications for the potential use of betulin in

Main activity of the Betulin Lab is the development of methods for the production of betulin of different purity using various types of solvents and extraction methods

the chemical industry are also emerging. For example, in the production of adhesives and various polymeric materials [13, 14].

However, despite the fact that betulin as a chemical compound has been studied worldwide, the industrial production and use of birch outer bark extractives for the production of consumer goods has not been sufficiently commercialised to date.

BETULIN LAB

The "Latvijas Finieris" Group is the world's leading manufacturer and developer of birch plywood products, with supporting businesses also including the chemical industry and mechanical engineering. Every year more than 900 000 m^3 birch round timber arrives at the factories of the company around the Baltic Sea. Only about 1/3 of this volume becomes the final product – plywood. The rest consists of various by-products generated in the production

Betulin Lab technologies currently provide up to 210 dry tonnes of raw material for the extraction of betulin annually

process – sawdust, technological chips, grinding dust. There is also birch bark, which is mechanically separated in the technological process and makes up about 10% of the total volume of the veneer log. The added value and development of the possibilities for the further processing of these by-products has become particularly important in the last decade. As wood becomes an increasingly valuable resource in Europe, its maximum use and increasing of application possibilities is one of the key elements in a company's competitiveness. At the same time, it gives a significant contribution to achieving the goals of the European Green Deal and ensuring global climate sustainability.

In recent years, "Latvijas Finieris" has paid special attention to the possibilities of chemical processing of birch bark – up to now the least valued by-product of plywood production, which is mainly used in the energy sector as a fuel. For this purpose, a separate structural unit, Betulin Lab, has been established within the company's Chemical Products Plant, where research and technological development is carried out in close cooperation with the leading Baltic wood science centre – Latvian State Institute of Wood Chemistry (LSIWC). This creates powerful synergies between international expertise in wood chemistry, product development experience and access to extensive birch bark resources. Together with the leading scientists of the institute's Biorefinery Laboratory, who have invested many years in birch bark research, a pilot plant for processing birch outer bark into high value-added bioproducts was established in 2021 at the premises of Betulin Lab in Riga – the capital of Latvia. It includes experimental technologies developed together with LSIWC scientists for the production of extraction raw material – crushed birch outer bark, as well as for the extraction of betulin with a purity of 70–99.8%.

WE ARE SEARCHING FOR COOPERATION PARTNERS

Betulin Lab technologies currently provide up to 210 dry tonnes of raw material for extraction of betulin annually, but the potential volume which is available companywide is at least five times larger.

According to worldwide research, the most promising applications for the chemical properties of birch outer bark extractives are in the pharmacy, cosmetic and food industries, especially in food supplements

Betulin Lab technologies comply with the production of second grade pharmaceutical raw materials; cooperation has been established and the first supplies of the raw material for extraction have been supplied to one of Europe's leading medical companies, which soon plans to launch two pharmaceuticals that could potentially be used to treat rare skin conditions and severe burns. In order to help develop new research on the application of birch outer bark extractives, we are open to cooperation and the supply of raw materials to scientific institutions and companies that have their own extraction capacities.

However, the goal of the Betulin Lab pilot plant is not just to produce raw materials for extraction. Our main activity is the development of methods for the production of betulin and the production of betulin using various types of solvents and extraction methods. Therefore, we are looking for partners for further scientific research and commercialisation issues – potential interested parties in the use of betulin and other birch outer bark extractives in their industry. The competence of the Betulin Lab is to provide the partners with the required degree of

purity of betulin by developing and using the most appropriate extraction method for the specific application. According to worldwide research, the most promising applications for the birch outer bark extractives are in the pharmacy, cosmetic and food industries, especially in food supplements.
See www.betulin-lab.com

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From the left: Kristaps Stankus, Jānis Rižikovs, Aigars Pāže, Inguss Virsis

ABOUT THE AUTHORS

Dr. sc. ing. **Aigars Pāže** is a leading researcher at Biorefinery Laboratory and Member of the Scientific Council of the Latvian State Institute of Wood Chemistry.
Dr. sc. ing. **Jānis Rižikovs** is a leading researcher and Head of Biorefinery Laboratory, Chair of the Scientific Council of the Latvian State Institute of Wood Chemistry, Member of the Latvian Council of Science Expert Commission of Engineering Science and Technology.
Mg. oec. **Kristaps Stankus** is a project manager at AS "Latvijas Finieris" and manager of Betulin Lab.
Inguss Virsis is a wood by-products trade and logistic manager at AS "Latvijas Finieris" and client solution manager of Betulin Lab.

PATHWAY OF ANTIVIRAL DRUG DEVELOPMENT FROM A LABORATORY TO A COMMERCIAL PRODUCT: RELEVANCE OF ANTIVIRAL DRUGS IN MEDICINE

GUNA FELDMANE

Interest in antiviral drugs continues unabated as more and more new viruses in human and animal populations, as well as new infectious diseases are being discovered.

Since the 1970s, about 40 infectious diseases have been discovered, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), Ebola, chikungunya, avian flu, swine flu, Zika, and nowadays COVID-19 caused by coronavirus. There are hundreds of coronaviruses, most of which circulate among animals. Sometimes those viruses jump to humans. Four of the seven known coronaviruses that sicken people cause only mild to moderate disease. Three can cause more serious, even fatal, disease. SARS coronavirus (SARS-CoV) emerged in November 2002 and caused SARS. That virus disappeared by 2004. MERS is caused by the MERS coronavirus (MERS-CoV) identified in September 2012 and continues to cause sporadic and localised outbreaks. The third novel coronavirus is called SARS-CoV-2. It causes coronavirus disease 2019 (COVID-19), which emerged from China in December 2019 and was declared a global pandemic by the World Health Organization on 11 March 2020.

Particular attention is paid to the coronavirus group. Science and pharmaceutical industry are developing and testing the antiviral drugs. New antiviral drugs are being developed and the existing ones are being tested for new infections. The new products are both chemically synthesised ones and those of natural origin. Natural products tend to have a broader spectrum of action, which is particularly important when the virus is still new and poorly-studied.

In the middle of the last century, it became clear that nucleic acids, in particular one form of nucleic acid, namely double-stranded ribonucleic acid (dsRNA), have significant biological activities. This product was also first created by chemical synthesis, the resulting product being clearly definable, standardisable and uniform. In parallel, it was noticed that similar, ready-to-use dsRNA products also existed in nature. Double-stranded RNA forms are produced during the replication of single-stranded RNA viruses as a transient structure, the so-called replication intermediate. Viral (bacteriophage) mutants can be used to stop the replication process at this stage, allowing the intermediate to accumulate.

This particular form turned out to have specific biological properties, i.e. antiviral and immunomodulatory activity we are interested in.

Double-stranded RNA molecules, regardless of their origin and nucleotide sequence, are able to mobilise a number of cellular response mechanisms that result in a wide range of effects, including the establishment of an antiviral state and the modulation of immune response.

The very process of dsRNA formation in the cell results in dsRNA chain fragments of unequal lengths, so that the dsRNA molecules, once released from the cell, are more or less unequal in length and we obtain a heterogeneous population of molecules in terms of molecular mass. The product is therefore not easy to standardise and is not uniform enough to meet the classical requirements

for registration. Therefore, manufacturers are in need of partners who are willing and able to develop methods for determining the quality of the product acceptable for registration. However, as we move further into the clinic, it appears that chemically synthesised dsRNA molecules tend to be toxic and less suitable for the clinic, whereas those isolated from the natural system (bacterium-bacteriophage) are tolerant to the organism, well tolerated and cause virtually no adverse reactions. An explanation for this phenomenon remains to be sought.

HISTORY OF LARIFAN DEVELOPMENT

The history of Larifan dates back to interferon in the 1960s. When interferon, a protein with antiviral properties, was discovered in 1957, it was a major milestone in the fight against viral infections. At the beginning, there were high hopes and expectations placed on interferon, as it was believed that a universal antiviral agent had been developed that would stop all viral diseases and that it was a weapon in the fight against viruses in general. Unfortunately, the first steps did not live up to the hopes placed on them, as many and varied obstacles and limitations to obtaining interferon itself became apparent.

The next step in this direction was the search for optimal interferon inducers. It should be recalled that the Institute of Microbiology of the Latvian Academy of Sciences was one of the first research institutions in the then USSR to get involved in interferon and interferon inducer research already in the early 1960s. The ability to induce interferon synthesis in vertebrate cells (including humans) was found in a large number of compounds, both synthetic and those of natural origin, but mostly they did not meet the criteria for medicinal products. Various nucleic acid drugs attracted attention, in particular the double-stranded forms of ribonucleic acids (dsRNA). This is what Latvian researchers also chose to go with already in the 1970s. Different dsRNA-producing systems were selected. This period was followed by the development of a commercial product, Larifan.

Latvian scientists tested different dsRNA producing cell-bacteriophage systems and chose *Escherichia coli* Q 13 – bacteriophage f2 mutant sus 11 as the most productive and convenient. The product was obtained through biotechnology. The production technology was developed, optimal media for cultivation of *E. coli* and bacteriophages were selected. At the moment, the company is still working in this system. The very first attempts for development of this type of product were taken in the USA already in the 1950s and in Czechoslovakia in the 1960s, but in different production systems, different technologies, and both were quickly swallowed up by what seemed to be an inability to solve the production problems.

In the 1990s, the production and further development of Larifan was taken over by the newly established company of the same name, SIA "Larifāns". The company gradually further improved and refined the production technology, tested and selected the optimal raw materials, improved the production line and modified various other technological nuances. Concurrently with the production of the active substance, the company is working on the development, production, and registration of new formulations containing Larifan. Thanks to the repeated support of the Investment and Development Agency of Latvia (*LIAA*), the company employees have participated in numerous international exhibitions, mainly in South-East Asia, seeking foreign markets. Some of these searches proved successful, which further enabled the development of export of the products.

ANTIVIRAL AND IMMUNOMODULATORY PROPERTIES OF LARIFAN AND THEIR APPLICATIONS

The dsRNA formulation developed in Latvia was further tested for both physicochemical and biological properties. The leading institutes of virology of the former USSR (now Russia) took part in the tests, and there was also long-standing bilateral cooperation with Eastern European countries (Czechoslovakia, Hungary, Poland, GDR, Bulgaria). Larifan was tested in virtually all models

of viral infections available in the territory of the USSR at the end of the last century in Latvia and at the Moscow Institute of Virology, both in tissue cultures and in experimental animals. Tests against herpes, influenza, papilloma, respiratory syncytial, rhino, tick-borne encephalitis, encephalomyocarditis, foot-and-mouth disease, vesicular stomatitis, Semiliki, Sindbis, Aujeszky, rabies, Omsk haemorrhagic fever viruses were carried out and all viruses were found to be sensitive to the antiviral activity of Larifan. In later years, further evidence of antiviral activity of Larifan was found for other emerging viruses such as Dengue fever, Japanese encephalitis (JEV) in mice and Zika in mice for which no data have yet been published.

As for another property of Larifan, its effect on the body's immune system responses, first of all, its ability to induce interferon should be mentioned.

Larifan has been repeatedly recognised as a highly active interferon inducer, which can have a significant impact on antiviral immunity. Antiviral immunity is mediated by non-specific factors at the early stage of infection, i.e. non-specific innate immunity is triggered before specific immunity has developed. Non-specific immunity consists of interferons and natural killers, which are the earliest responses and are activated within a few hours of the first exposure to the virus. This is why interferons are rightly called the first protective barrier encountered by any attacking virus. Specific immunity consists of immunoglobulins and T-lymphocytes. Immunoglobulins, or antibodies, neutralise the virus while it is outside the cell, while cytotoxic lymphocytes act on the intracellular phase by destroying the entire cell in which the virus is replicating. This process takes several days (on average seven days) while the non-specific immune response takes only a few hours.

Recently, it has become clear that interferon, and therefore Larifan as an interferon inducer, plays an important role in coronavirus replication. This is demonstrated by a large multi-country collaborative study (2017). It has been shown that in order for coronaviruses to start replicating, they first try to limit the innate immunity of the organism, i.e. they eliminate the above-mentioned protective barrier, namely interferon. Thus, the presence of interferon appears to be necessary to prevent coronaviruses from replicating. This means that the presence of interferon must be enhanced at the points where the virus comes into contact with the organism – i.e. at the infection entrance point. Topical action products containing Larifan are particularly useful for this purpose. They will work both before the disease (prophylactically) and at the onset of the disease. Further investigation of Larifan showed that, in addition to interferon induction, it also induces an increase in the synthesis of many other cytokines in the cell, such as interleukins (6,10, 23, etc.), TNF-alpha, GM-CSF and others.

Studies on the effects of Larifan on *ex vivo* (outside the body) cultured human blood lymphocytes show that Larifan acts as an activator of T and B lymphocytes as well as NK cells and stimulates the differentiation of T lymphocytes into activated effector cells. This means that antibody production is stimulated, which practically manifests itself as immunologic adjuvant activity and can be used in vaccinations to enhance vaccine efficacy. This is a direction worth developing even more so because as it has already been shown in the 1980s in models of influenza, herpes, and rabies infections that administration of Larifan both shortly before and after vaccination significantly increases the effectiveness of vaccines. In turn, the differentiation of T lymphocytes into activated effector cells means that activated lymphocytes become more aggressive against target cells, which is of particular importance in oncology.

This opens up new possibilities for further use of Larifan in the field of health protection.

In the context of today's pandemic, particular interest has been focused on coronaviruses and the means to fight them. The developers of Larifan have already submitted an application to the European Medicines Agency (EMA) on 15 May 2020 with a request to evaluate Larifan as a potential therapeutic against SARS-CoV-2.

The evaluation is still ongoing and in the meantime, on the advice of the EMA consultants, additional studies on the effect of Larifan on

SARS-CoV-2 in *in vitro* and *in vivo* systems are being carried out.
Shortly before the publication of this article, information was received from researchers with the following conclusion: "The inhibition of SARS-CoV-2 replication *in vitro* and the reduction of the viral load in the lungs of infected hamsters treated with Larifan alongside the improved lung histopathology, suggests a potential use of Larifan in controlling the COVID-19 disease in humans."
However, strong, interested and committed clinical research partners are already needed to bring the product to clinical use in diseases caused by SARS-CoV-2.

DEVELOPMENT OF NEW PRODUCTS CONTAINING LARIFAN

Over the years, SIA "Larifāns" has developed a product line that includes both systemic and local action products and offers them to the domestic market as well as for export. In addition to injectable formulation, the line also includes ointment, spray, lip balm, toothpaste, suppositories, pessaries, hygienic hand gel, jelly sweets, etc. Most of these are local action products, which have the advantage that the active substance can be delivered directly to the problem area. This is all the more important in case of new and understudied viral infections, keeping the potential to use these products also in SARS-Cov-2 cases.
The company products are already being exported to Estonia, Lithuania, Moldova, Turkmenistan, Uzbekistan, Vietnam, Russia, and exports to Georgia are regular and intensive. The company is still working on foreign markets and developing new products.
Overall, Larifan, first, acts directly on the intracellular stage of viral replication, i.e. to a major replication phase similar for many viruses, including coronaviruses and, second, due to interferon induction, activate the innate non-specific immunity, which switches on immediately after the first contact with the attacking virus. Thus, in the first hours, the first antiviral protection barrier is formed, which is non-specific against any virus, including emerging viruses.

ABOUT THE AUTHOR

Dr. med. **Guna Feldmane**, after graduating from Riga Medical Institute in 1957, worked for more than 40 years at the Institute of Microbiology and Virology of the Latvian Academy of Sciences. She founded the biopharmaceutical company SIA "Larifāns" and since its establishment in 1997 has been the chairman of the company's board. Elected State emeritus scientist. Developed and introduced the antiviral and immunomodulatory drug Larifan in medicine.

ON NEW TRENDS IN INCREASING THE EFFECTIVENESS OF FOOD SUPPLEMENTS

DMITRY BABARYKIN

> "Food supplements are concentrated sources of nutrients (i.e. mineral **and vitamins) or other substances with a nutritional or physiological effect that are marketed in "dose" form (**e.g., pills, tablets, capsules, liquids in measured doses). A wide range of nutrients and other ingredients might be present in food supplements, including, but not limited to, vitamins, minerals, amino acids, essential fatty acids, fibre and various plants and herbal extracts." (https://www.efsa.europa.eu/en/topics/topic/food-supplements).

On the one hand, food supplements (FS) are a type of food and their production and turnover are regulated by relevant regulations. On the other hand, we are talking about healthy food products, which motivate the consumption of FS with the desire to improve health and quality of life. Traditional FS in the formulation of tablets and capsules for consumers often cause associations with medicines. Such a dual status of FS in the public consciousness is the ground both for their use by consumers instead of pharmaceuticals, and an incentive for the business of unscrupulous traders. The mention of its health effects in the product labelling is attractive to FS manufacturers and distributors, since it increases sales. But at the same time, it is alarming drug manufacturers and pharmacists who are afraid of losing customers due to their "switching" to FS. There is no denying that there is a certain conflict of interest between the pharmaceutical and food industries on a global scale.

There is also a third group of factors contributing to the well-known turbulence of public opinion regarding FS. The authorities that control the turnover of food in the mass media tirelessly inform that FS does not impact health (although it is not easy for the consumer to understand how the term "physiological functions" differs from the concept of "health"). This is explained by the logical desire of the authorities to prevent the population from using FS instead of medicines. However, scientific information about the safety and specific biological effects of natural substances, confirmation of their functionality in accordance with the requirements of evidence-based medicine appear much earlier than such information (health claims) enters the EFSA (European Food Safety Authority) database and other regulatory documents regulating food turnover. Such a situation contributes to the appearance on the Internet of countless unprofessional interpretations of information, "justifications" for the appearance of new "miraculous" FS, vulgarisation of scientific knowledge, complicates educational work with the population.

Unfortunately, the official position of the medical community is also to deny the health effect of FS, although sometimes doctors, based on their own experience, recommend their patients to take some FS. The indiscriminate denial of the health effect of everything that does not have the status of a medicine is met with misunderstanding on the part of the population, if only because such a position is in contradiction with the world experience of traditional medicine, from the depths of which pharmacology and pharmacy have grown, as well as the foundations of ideas about healthy nutrition, functional products, and FS.

If, in addition to the above, we take into account the extensive range of FS on the market, sales both in grocery stores and pharmacies, a huge turnover in monetary terms, it becomes clear why the main goal of using FS – improving the quality of life – is not always achieved.

What is the role of FS in the life of modern society, what are the trends in the development of new products, how do new phenomena (viral pandemics, climate change, etc.) affect this process, what are the prospects for the development of the relevant industry?

One of the arguments of those who oppose the use of FS is as follows. A balanced and varied diet will satisfy all the needs of the average consumer without additional intake of nutrients. Indeed, there is a wide range of local and exotic products on the market. However, there are a number of reasons for additional enrichment of the diet:

• the environment, the chemical composition of food change faster than adaptation and hereditary consolidation of the corresponding functional changes in the human body occur; for example, as a result of breeding, sweeter varieties of fruits become more widespread, the bitter taste of plants is levelled by reducing the content of such useful bitterness;

- the volume and range of consumed xenobiotics (medicines, cosmetic products, household chemicals, etc.) modifying biochemical processes is growing;
- phytochemicals reduce the risk of developing resistance of viruses and bacteria to medicines;
- the development of personalised nutrition based on taking into account individual nuances of the diet requires the presence of a whole "library" of relevant substances;
- an increase in life expectancy makes it necessary not only to additionally take certain nutrients (calcium to prevent osteoporosis), but also to "turn off"' some of them from the metabolism (iron at risk of Alzheimer's disease).

Humanity is facing new challenges that stimulate research on the development of new FS and functional nutrition. Thus, an increase in the exposure time of the skin to ultraviolet radiation due to climate change leads to an increase in the risk of developing skin melanoma. To reduce this risk, the use of sunscreens is clearly insufficient and requires the additional use of special food and FS. The fight against the coronavirus pandemic that has been going on for two years has shown that despite the indisputable importance of vaccination, it does not solve all the problems.

We can only welcome the reports of virologists about the need for widespread use of non-pharmacological products with antiviral activity, which will be an addition to periodic vaccination. In conditions of constantly mutating viruses, such products (in FS status) are very promising. Our long-term experience with black elderberry fruit extract, curcumin and other phytochemical compounds confirms this.

It should be noted that as the popularity of FS increases, new trends appear in terms of the demand for new ready for use formulations of these products. As noted above, capsules and tablets in consumers often cause associations with medicines, which, if it is necessary to use FS regularly, reduces customers' compliance. There is an increasing need to use such formulations that provide the possibility to consume active substances in a wider range of dosages and bring FS as close as possible to the taste and appearance of conventional food. Therefore, there is a growing demand for powders in sachets, liquids in 50–100 ml vials, boluses, bars, spreads, etc.

The consumer does not proceed from the formal definition of FS (affecting organism functions), but sees them as means to improve health and the quality of life. Otherwise, the motivation to use FS disappears. Of course, the degree of this influence is determined by many factors, but the strategic trend in the development of the food industry is the manufacturing of more effective functional products. This task can be solved only in collaboration with scientists and doctors. With this in mind, in 2001, a private Institute of innovative Biomedical Technologies was founded, bringing together scientists (biologists, doctors, chemists, technologists) and an experimental manufacturing unit "FitoBALT" under a common roof. Taking into account the requirements of the time, the creation of highly effective dietary supplements and functional products requires new approaches to their creation.

Our twenty years of experience in the development and production of innovative dietary supplements indicates the feasibility of modifying algorithms in this area.

Changing approaches concern all stages of the creation of FS. For example, the use of plant extracts as raw materials is regulated by the requirement of their standardisation, i.e. it is assumed that extracts from different manufacturers, but standardised by the active substance, will provide the same effectiveness of finished dietary supplements. However, this does not always happen. Concomitant compounds are also of great importance for the biological activity of phytochemicals, the content of which depends on the plant variety, growing conditions, and other factors. However, regulatory documents do not require an assessment of the actual effectiveness of the finished product.

This problem is closely related to the question of the interaction of various biologically active substances that make up FS. For example, in order to enhance the immune-stimulating effect of echinacea, the manufacturer combines this ingredient with another well-known immunomodulator – licorice, hoping to provide synergy of the effects of these ingredients. However, in addition to the desired synergy, you can get the opposite effect (antagonism) or the absence of any interaction of the ingredients. When combining not two, but more substances, there are even more outcome options. The problem is that it is theoretically impossible to predict the biological activity of mixtures of phytochemicals, and the manufacturer's information about the effectiveness of the finished FS is to a certain extent declarative. The way out of the situation is seen in testing the product on live objects *in vitro* and/or *in vivo*. At the current level of knowledge, *in silico* methods are still far from practical use.

How appropriate is it to use highly purified phytochemicals in the production of dietary supplements? Unlike pharmacological products, the benefits of this are not obvious in relation to FS. Purification of raw materials leads to a significant increase in the cost of FS. In addition, the biological activity of chemically pure plant ingredients will differ from that of an extract with a greater or lesser degree of purity. This is clearly seen in the example of herbal teas.

In recent years, technologies have been rapidly developing to increase the functionality of plant derivatives by fractionation based on molecular weight, using ultrafiltration. Thanks to this technology, it is possible to obtain combinations of phytochemicals with the necessary functional properties from juices and extracts. We used ultrafiltration to vector modify the functionality of vegetable juice.

DEVELOPMENT OF RED BEET ROOT JUICE FRACTIONATION TECHNOLOGY USING ULTRAFILTRATION

The aim of the project was to develop a FS with the ability to stimulate iron absorption in the intestine in iron deficiency anaemia by activating cellular mechanisms of iron ion transport. Initially, the juices of 24 species of vegetables were screened in order to select the source of raw materials for processing. Juice samples were evaluated for their ability to stimulate iron absorption of the chicken's intestinal mucosa *in vitro*. Red beet (*Beta vulgaris*) was chosen as the most active plant. The specific activity of juices of 14 varieties of red beet was screened. As a result, one variety was identified whose juice efficiency significantly exceeded other varieties. With the help of preparative chromatography, the juice fraction was isolated and its molecular weight limits were established. Further fractionation was carried out by ultrafiltration using semipermeable membranes with appropriate parameters.

The biological effects of the obtained beet juice fraction were studied *in vitro, in situ*, as well as *in vivo* on animals with experimental models of iron deficiency anaemia and other pathologies. Clinical observations were also carried out in humans. As a result of the conducted research, the manufacturing of two FS with relevant functional properties was developed and organised – correction of haemoglobin blood level in people with iron deficiency anaemia, as well as pronounced stimulation of capillary blood flow, which is very important not only for the sick, but also for healthy individuals, including athletes.

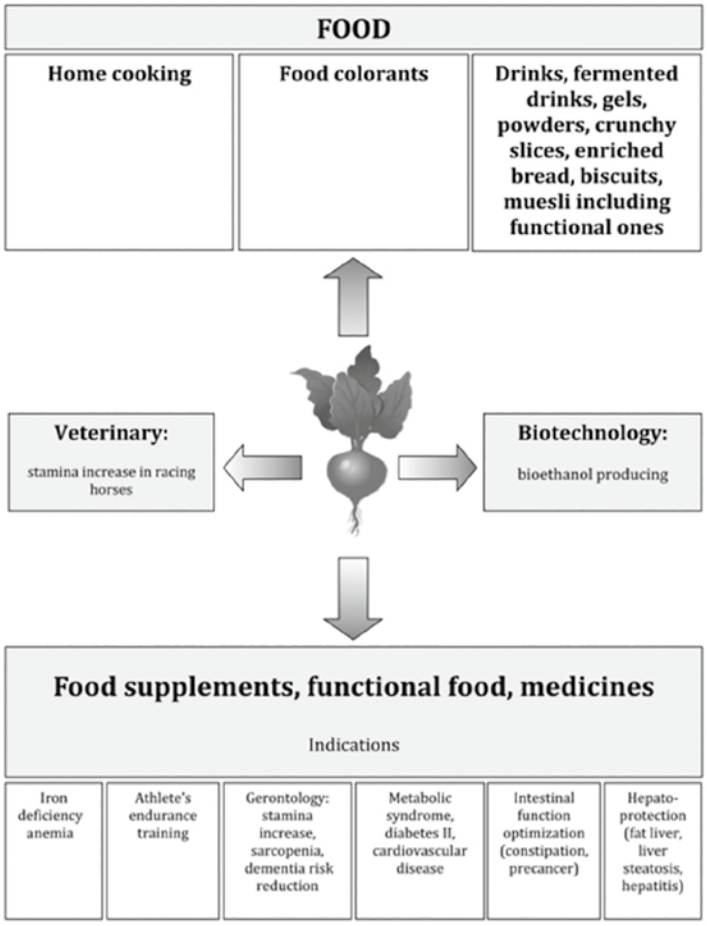

Fig. 1
Red beetroot processing and developed product's health effects (Babarykin D. A. et al. Red Beet (*Beta vulgaris*) impact on human health. *J. Biosci. Med.,* 2019, Vol. 7, pp. 61–79)

Fig. 2
BetaVUSAN. Fractionated by ultrafiltration red beetroot juice. It has a pronounced ability to stimulate capillary blood flow and restore blood hemoglobin levels in iron deficiency anemia

Fig. 4
KUMAT-antivir. Composition of plant extracts effective in respiratory viral diseases

Fig. 3
Don't sleep. Natural caffeine free energy drink. No sugar added

It should be noted that the described research algorithm made it possible to create not only innovative healthy food products, but also to develop a technology for waste-free processing of red beet (Fig. 1).

Fractionation by ultrafiltration, ultra-grinding, reducing the allergenicity of plant raw materials, increasing the bioavailability of the most important ingredients of products, increasing the safety and nutritional value of fast food, developing methods to reduce the glycaemic index of food, improving the safety of processed meat products, stimulating the creation of waste-free food technologies – this is only a small part of the directions for intersectoral research that will lead to the creation of new conventional and functional products, food additives that contribute to improving the quality of human life, preserving the environment and climate. Undoubtedly, these goals can be achieved provided that the expected effects of the developed healthy food products are scientifically proven.

ABOUT THE AUTHOR

Dr. biol. habil. **Dmitry Babarykin**, associate professor, is the Chairman of the Board and Director of Operations of the Institute of Innovative Biomedical Technology Ltd.