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Parthenium argentatum A. Gray, *Taraxacum kok-saghyz* L.E. Rodin, AND *Scorzonera tau-saghyz* Lipsch. et Bosse AS ALTERNATIVE SOURCES OF NATURAL RUBBER: DO WE REALLY NEED THEM?
(review)

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Abstract

Natural rubber (NR) is a strategic raw material essential to the manufacture of 50,000 different rubber and latex products. In most cases, e.g., in automobile and aviation industries, it cannot be replaced by synthetic rubber alternatives. There are several important reasons why should we care about alternative sources of NR. Among them are a strong allergic reaction to products made from Hevea latex and a danger of spread of South American late blight (South American Leaf Blight, SALB) in Southeast Asia. The latter would cause irreparable damage to the production of natural polymer. At present, the only commercially significant source of NC is *Hevea brasiliensis* (Willd. ex A. Juss.) Müll. Arg. — an evergreen tree growing in tropical regions. It is not surprising that the research aimed at finding and creating alternative sources of NR by genetic engineering is intensively developing in Europe and North America. On this issue, there are numerous reviews of leading researchers in this field, in particular, the Dr. K. Cornish's team. Thus, back in 2000, one of the first detailed reviews devoted to the problem of alternative NC sources was published (H. Mooibroek et al., 2000). A year later, NR biosynthesis in evolutionarily distant rubber plants was described in detail (K. Cornish, 2001). This problem has been further developed in later works of this researcher (K. Cornish, 2017). Detailed reviews of alternative rubber producers have also been published by other leading groups in the field (J. van Beilen et al., 2007; S.C. Gronover et al., 2011; D.T. Ray et al., 2005). We have recently published two review articles describing in detail the biochemical and molecular genetic aspects of NR biosynthesis (A.Y. Amerik et al., 2018; A.Y. Amerik et al., 2021). In this review, we pay special attention to the historical aspects of this problem, which, in our opinion, have not received sufficient consideration in the literature, describe the state of the industry at the present time, and characterize three rubber plants that are promising producers of NR. As alternative sources of NR, two plants are receiving increased attention. These are Mexican guayule shrub (*Parthenium argentatum* A. Gray) and kok-saghyz or Russian dandelion (*Taraxacum kok-saghyz* L.E. Rodin). We certainly should also mention the undeservedly forgotten, but very promising alternative producer of NR tau-saghyz (*Scorzonera tau-saghyz* Lipsch. et Bosse), which, in our opinion, is currently not given enough attention. *T. kok-saghys* is the most promising alternative rubber plant. For biochemical and molecular genetic studies of the plant, modern molecular biological approaches were used, such as improved transformation protocols, RNA interference (silencing) approaches, and analysis of EST libraries to identify new genes. As a result, the key proteins responsible for NR biosynthesis, cis-prenyltransferase 1-3 (CPT1-3) (T. Schmidt et al., 2010) and CPT activator (RTA) (J. Epping et al., 2015), were identified. It should be noted that the intracellular concentration of CPT regulates NR biosynthesis in cells of *Taraxacum brevicorniculatum*, the closest relative of *T. kok-saghyz*. Transgenic lines in which expression of all three CPT genes was suppressed by RNA interference (RNAi) demonstrated almost complete suppression of NR biosynthesis (J. Post et al., 2012). However, more research is needed before *T. kok-saghyz* NR becomes a commercial alternative to *H. brasiliensis* NR. Research on *P. argentatum* is also rapidly developing. In particular, the work carried out in the laboratory of D.K. Ro should be noted. Researchers have identified and characterized a protein complex that includes CPTs and plays a key role in NR biosynthesis (A.M. Lakusta et al., 2019). Unfortunately, research on tau-saghyz (*S. tau-saghyz*) is not so successful. This species was critically undermined during intensive harvesting in the 1940s. Nevertheless, work on the restoration of this unique species, the concentration of NR in roots of which under favorable conditions reaches 40 % (dry weight), is currently being carried out at the Kazakhstan National University (S.K. Turasheva et al., 2016). Thus, there is a need for alternative rubber crops and technologies for processing raw materials into final products. Thermostable derivatives, e.g., epoxidized rubber from alternative crops can enter the market to significantly reduce the carbon footprint.

Keywords: natural rubber, *Hevea brasiliensis*, South American Leaf Blight, SALB, latex, allergy, *Parthenium argentatum*, *Taraxacum kok-saghyz*, *Scorzonera tau-saghyz*.

Natural rubber (NR) is one of the most important biopolymers synthesized by higher plants, which is widely used in industry and medicine. It has unique physical properties (elasticity, resilience, impact resistance, efficient heat dissipation) and is able to maintain plasticity at low temperatures [1-4]. Despite the scientific and technological progress in the development of rubber synthesis technologies, at present there is no synthetic rubber that would correspond to NR in terms of its main characteristics.

With the development of the industrial production of synthetic rubber (SR), many innovations have been introduced into the technology that have a positive effect on the consumer properties of rubber. SC is an artificial elastomer derived from various monomers; it is synthesized using different raw materials (oil, coal, natural gas and acetylene). Some of the most commonly used synthetic rubbers are ethylene-propylene-diene, polyisoprene, polybutadiene, styrene-butadiene and iso-butylene-isoprene. They are widely used in the manufacture of tires, conveyor belts, belts, hoses, various seals, floor coverings and shoes. High-tech production of synthetic rubbers has also been created in Russia. When using various highly efficient catalysts - synthesis initiators (conventionally called lithium and titanium), polyisoprenes are formed containing up to 93-98% cis-1,4-units. However, both these types of SR are inferior in terms of microstructure homogeneity to NR, whose macromolecules contain up to 100% cis-1,4-units attached exclusively in the 1.4-1.4 type ("head to tail"). Imperfections in the microstructure of synthetic polyisoprenes manifest themselves primarily in their lower ability to orientate and crystallize compared to NR, which affects the strength and dynamic characteristics. Nevertheless, it should be noted that some types of synthetic rubber are superior to natural rubber in a number of technical properties [5].

The demand for NR is determined by two-thirds of the production of automotive industry. First, we are talking about tires for the primary equipment of new cars. A tire is made of a variety of materials, including several rubber components, each with a specific and unique purpose. NR is used in tire carcasses requiring high strength, while synthetic rubbers are used in tread materials to provide tire grip. At present, the share of NR used in the tire industry is approximately 50% of all types of rubber used [6].

The natural polymer is becoming more and more in demand with the development of high technologies. For example, the rubber components of aircraft tires, designed to operate with enormous loads and speeds at the smallest possible size and weight, are made only of NR. To produce oversized tires, NR is also mainly used. Another example of the exceptional use of NR is the production of mining truck tires and tires with solid steel cord in the carcass. However, compared to SR, NR is less resistant to oils, some chemicals and oxygen. It is also more susceptible to aging, erosion, and retains plasticity in a smaller temperature range compared to SR [7].

It should be noted that these shortcomings could be largely leveled by the epoxidation of NR [8]. Epoxidized natural rubber (ENR) is a molecular structure the NR rubber polymer. ENR has consumer properties (lower gas permeability, better oil resistance), which allow it to be widely used in industry [9].

The fresh latex is approx. 60% water, 35% cis-1,4-polyisoprene and 5% non-isoprene molecules. NR, in turn, is a hydrocarbon from the group of isoprenoids, in the structure of which the monomers are C_5H_8 isoprene molecules. The hydrocarbon component of NR contains up to 99.5% or more of 1,4-cis-isoprene units (Fig. 1). Also, in latex there are 5% of other organic compounds. These are mainly proteins, lipids, carbohydrates, and their distribution in the latex fractions is not uniform. Although these substances make up a minor part of the latex, some of them remain in the NR after processing and are considered to play a critical role in the properties of the NR. In fact, these impurities probably account for the better mechanical properties of NR compared to its synthetic counterparts, but they also cause unstable NR quality. More than 2500 plant species synthesize NR [10], but only a very few of them can produce economically significant amounts of high-quality polymer with a molecular weight of more than 10^6 Da [11-13].

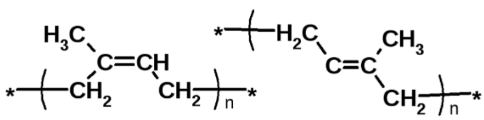

Fig. 1. The structure of plant polyisoprenes: rubber (left) is cis-1,4-polyisoprene, guttapercha (right) is trans-1,4-polyisoprene.

Interestingly, the group of plants synthesizing high molecular weight polyisoprene in the trans configuration (see Fig. 1) is very limited. These include *Palaquium gutta*, *Mimusops balata* and *Eucommia ulmoides.* The polymers they form (respectively gutta-percha, balata, and Chinese gutta-percha) [14-16] are not NR.

Even though many plants can synthesize NR, the only commercially significant source of NR currently remains *Hevea brasiliensis* (Willd. ex A. Juss.) Mull. Arg. (Brazilian rubber tree, hevea) [17]. The demand for natural rubber is constantly increasing. According to preliminary estimates, the world production of NR is expected to increase by 1.8% (up to 13.836 million tons), while during 2021, global demand was projected to grow by 8.3% (up to 14.028 million tons). According to forecasts, by 2023 it will amount to about 16.5 million tons per year and will grow in the future [18]. Of course, there are concerns that modern plantations of hevea trees will not be able to meet the increasing needs for this product. The process of collecting NR is very time-consuming and does not lend itself to mechanization. Plants begin to produce significant amounts of NR from the age of 5-7 years [19]. In addition, hevea can grow in a narrow climatic zone of tropical forests (Fig. 2) [17].

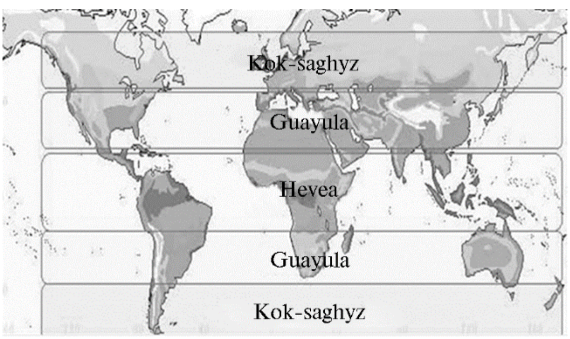

Fig. 2. Geographic distribution of *Hevea brasiliensis* (Willd. ex A. Juss.) Мьll. Arg., guayules *Parthenium argentatum* A. Gray and Kok-saghyz *Taraxacum kok-saghyz* L.E. Rodin. Figure is taken from article by K. Cornish [17].

It should also be noted that the production of NR is at particular risk because only a few closely related clones were used for the cultivation of hevea (unlike other agricultural crops) [17]. Thus, a single clone could form the basis of plantations with an area of hundreds of thousands of hectares. As a result, many phytopathogenic fungi infect genetically homogeneous plants, exposing hevea plantations to great danger. So, in Brazil, South American late blight (South American Leaf Blight, SALB) is a lethal disease for *H. brasiliensis* caused by the fungus *Microcyclus ulei* that has led to an almost complete cessation of NR production (Fig. 3).

Fig. 3. Symptoms of South American Leaf Blight (SALB, causative agent ascomycete *Microcyclus ulei*) **on leaves** (above) **and stem** (below) **of *Hevea brasiliensis* (Willd. ex A. Juss.) Müll.** Figure is taken from J. Guyot et al. [20].

The former leader in the supply of natural rubber currently produces only 1.5% of its global volume, while many times more is needed for its own needs. As a result, Brazil itself depends on imports of NR from Southeast Asia. Currently, studies are being conducted to obtain *H. brasiliensis* genotypes resistant to SALB, but it will take at least 25 years to replace existing plants with clones immune to the disease [17, 20, 21]. It should also be noted that repeated contact with some hevea latex proteins leads to allergic hypersensitivity of the first type [17]. Thus, the diversification of NR producers becomes a primary task to meet the needs for this polymer.

The purpose of this review is a comparative analysis of potential alternative producers of natural rubber that can replace the only commercially significant source of polymer to date — *H. brasiliensis*. Currently, *Parthenium argentatum* A. Gray (guayula) and *Taraxacum kok-saghyz* L.E. Rodin (kok-sagyz, Russian dandelion) are considered as such producers. *P. argentatum* is a perennial shrub growing in the Mexican Chihuahua desert and Southern Texas [22]. *T. kok-saghyz* is an herbaceous plant growing naturally in Kazakhstan, Southern Siberia, Uzbekistan and China [23, 24]. The review also pays attention to the perennial semi-shrub tau-sagyz (*Scorzonera tau-saghyz* Lipsch. et Bosse), a representative of the genus *Scorzonēra*.

T h e h i s t o r y o f n a t u r a l r u b b e r p r o d u c t i o n. The fact that NR can be obtained from some trees and used for various purposes was known back in the days of the ancient civilizations of Central and South America long before the appearance of Europeans there. The Aztec chronicles tell us that the NR was collected as a tribute from the conquered peoples and was used in religious ceremonies. It was also used to make balls and waterproof clothing. For Europeans, NR was discovered in 1743 by Charles-Marie de la Condamine, one of the first explorers of the Amazon, who compiled a fairly accurate map of it. He learned about rubber and quinine from local Indians and in one of the expeditions described the process of making rubber products and the treatment of malaria with quinine. The ability of NR to erase pencil inscriptions was noticed by Joseph Priestley, who in 1770 introduced the English word “rubber” into European usage. The unique hydrophobic properties of NR were due to the first attempts to use it in Europe for the manufacture of waterproof clothing and shoes [25].

However, the large-scale application of NR in industry was extremely difficult until in 1818 James Syme discovered that benzene can dissolve NR, and Charles Mackintosh used this discovery to create a special fabric containing a waterproof layer of NR. Raincoats made of this fabric were called mackintoshes [26]. It should be noted that products made of natural rubber had serious disadvantages. They became soft and sticky at elevated temperatures in summer and hard and brittle in winter. Therefore, interest in NR products fell until 1839 when Charles Goodyear, after 5 years of research that almost led him to bankruptcy, discovered that exposure to high temperature and sulfur stabilizes NR and leads to its unique properties being preserved over a wide temperature range. Later this process was called vulcanization [27]. It was vulcanization with subsequent modifications that expanded the possibilities of using NR on an industrial scale. Vulcanized NR (rubber) can be stored for a long time and transported to any point of the globe. Rubber quickly became an integral part in the aviation and automotive industry (tires), the manufacture of electrical appliances (insulators) and various medical devices.

Fig. 4. Collection of hevea latex (https://derevo-s.ru/drevesina/listvennye/geveya).

Large-scale harvesing NR in the Amazon basin began at the end of the 19th century near the Brazilian Atlantic port of Para and eventually spread to the east of the South American continent. The rapid development of the automotive, medical industry, and electric power industry has led to a rapid increase in demand for NR. For 12 years (from 1890 to 1910), the production of NR increased 6-fold [25].

Several rubber producers have been investigated as potential industrial sources of NR. These are different species of *Sapium* (caucho blanco) [28], *Castilla* (caucho negro) (29) and *H. brasiliensis* [17, 29-31]. It has been shown that it is the latter plant that produces high-quality natural rubber. A close relative of *H. brasiliensis*, the *H. guianensis* also synthesizes NR, but of low quality [32]. Hevea *H. brasiliensis* has been found only in the Putumayo River basin (a tributary of the Amazon). *H. brasiliensis* NR is obtained by cutting the bark (Fig. 4), but the collection of milky juice is possible only 6 months a year, since trees grow in lowlands prone to flooding during the rainy season.

Initially, NR was also obtained year-round, using trees of the genus *Castilla — C. elastica* and *C. ulei*, growing on non-flooded elevations. However, in this case, mechanical destruction and deep processing of wood were required, and as expected, the raw material base quickly dried up [29]. Thus, *H. brasiliensis* was finally chosen as the optimal source of NR.

In 1857, Thomas Hancock, the founder of the British company Thomas Hancock's clothing, proposed to create *H. brasiliensis* plantations. During the 1870s, three collections of *H. brasiliensis* seeds from South America were delivered to the Royal Botanic Gardens in London (Kew Gardens). One of them belonged to Henry Wickham, who lived at that time in the upper part of the Amazon in one of the largest right tributaries of the Amazon — Tapajos [17]. In 1876, he brought to London about 70,000 seeds, of which 2,700 germinated. A significant number of seedlings were sent to Malaysia and Ceylon, several to Indonesia and Singapore. Thanks to the hard work of the local population and British settlers, by 1907, about 10 million hevea trees had been grown on plantations in Southeast

Asia. In 1912, latex exports from Malaysia and Indonesia amounted to 8,500 tons, but this was significantly less than exports from the Amazon basin — 38,000 tons. Commercial production in Southeast Asia continued to expand, and in 1917, the Asian colonies of Great Britain, France and the Netherlands exported 370,000 tons of NR. This led to a sharp drop in prices for NR, which made its production in the Amazon unprofitable [25]. In the 1920s, Henry Ford tried to resume the collection of NR on Fordlandia plantations in the Amazon basin, but SALB (see Fig. 3), caused by the fungus *Microcyclus ulei*, nullified these efforts [20, 21].

It is not surprising that the United States was interested in an independent source of NR. An alternative rubber carrier — guayula (*P. argentatum)* was first used in Mexico and somewhat later in the USA. However, due to the depletion of raw materials in Mexico, the Mexican Revolution and the Great Depression, the production of NR stopped quite quickly. At its peak, it produced about 20% of the total amount of polymer consumed in the USA [10, 22].

The next attempt to find alternative sources of NR was caused by Japan's seizure of *H. brasiliensis* plantations in Southeast Asia in 1942 during World War II. This led to the fact that the countries of the anti-Hitler coalition lost their sources of NR. At this time, the production of SR began to develop intensively in the USA and interest in alternative sources of NR was again manifested. In addition to the already mentioned guaiula (*P. argentatum*) and Russian dandelion (*T. kok-saghyz*), rubber vine (*Cryptostegia grandiflora* R. Br.) [33] and golden rod (*Solidago leavenworthii* Torr. & A. Gray) [34] was considered as such sourses.. However, after the end of World War II, relatively cheap NR from Southeast Asia became available on the world market again. This circumstance, as well as the expansion of the production of synthetic rubber, led to the fact that by the mid-1950s alternative sources of NR practically ceased to be of commercial interest. However, some studies related to *T. kok-saghyz* were conducted in the Soviet Union until its collapse in 1991 [10, 35, 36].

Interest in guaiula resumed after the global spread of the deadly type 1 allergy to latex proteins of *H. brasiliensis* [37]. Studies have shown that latex from *P. argentatum* does not contain proteins that cause allergies, and products from it can be used by people who are sensitive to hevea latex proteins [38, 39]. But in general, *H. brasiliensis* remains the only commercially significant rubber carrier.

Synthesis of rubber in rubber carriers. Structurally, polymers produced by different rubber carriers are cis-1,4-polyisoprenes, the synthesis of which begins with the formation of two or three trans-initiator units [40-44]. However, the molecular weight, macromolecular structure, intermolecular bonds, and chemical composition of the molecule depend on the specific rubber carrier and affect the properties of NR [10, 44-46]. Plants produce many different cis-polyisoprenes, but NR only includes polymers containing at least 100 isoprene units, and at least 15,000 units are required for the polymer to be classified as high-quality NR [17].

NR is an elastic material that returns to its original size and shape after deformation. This is because NR can undergo deformation crystallization [47, 48]. Crystallization is a phase transition (from an amorphous to a crystalline state), accompanied by the release of heat, a change in specific volume and physico-mechanical properties. When rubber is stretched, crystallization occurs quickly and is accompanied by the orientation of the molecular links along the direction of stretching. Under the influence of special reagents (sulfur, peroxides, metal oxides, amine-type compounds), the vulcanization of rubber occurs with the crosslinking of molecules into a single spatial grid [27]. The strength characteristics of rubber, its hardness and elasticity increase, but the plastic properties, the degree of swelling and solubility in organic solvents decrease. The rate of vulcanization and the density of crosslinking critically depend on the components of NR that are not related to polyisoprenes. These components are specific to each rubber carrier, which leads to significant differences in the properties of the final product [17].

The synthesis of NR occurs in cytoplasmic rubber particles (Fig. 5) [49, 50]. Such particles are often formed in the multinucleated cells of the bark or roots, called laticiphras [51, 52]. This statement is true for the bark of *H. brasiliensis* and the roots of *T. kok-saghyz*. Interestingly, in *P. argentatum*, rubber particles are formed in the cytosol of parenchymal bark cells [53]. It is likely that the differences in the chemical composition of NR from different sources are due to the specific features of the cytosols containing rubber particles [54].

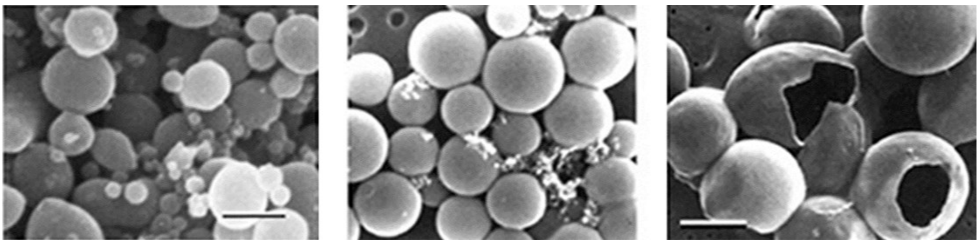

Рис. 5. Micrograph of rubber particles from *Hevea brasiliens* (A)**, *Parthenium argentatum*** (B) **and *Ficus elastica*** (C)**, obtained using a scanning electron microscope.** Scale bars are 1 μm (A and B) and 2 μm (C). The figure is taken from the article by K. Cornish [17].

Alternative sources of natural rubber and their comparative assessment. Although the genetic resistance of hevea to SALB has been studied quite actively recently, according to the forecast, it will take at least 25 years to create highly productive plantations based on plants immune to SALB [17]. Therefore, biodiversification of NR sources remains an extremely important task.

Currently, *P. argentatum* (guayula) and *T. kok-saghyz* (kok-sagyz, Russian dandelion) are considered as alternative rubber carriers. It should be noted that three rubber-bearing plants — *H. brasiliensis*, *P. argentatum* and *T. kok-saghyz* grow in different geographical areas, the Central and South America; northern Mexico and southeastern USA (mainly Texas); Kazakhstan, southern Siberia, Uzbekistan and Northwestern China, but together their ranges cover almost all the world's areas available for agriculture (see Fig. 2) [17]. Both alternative sources of NR are being intensively studied in the USA and Europe to ensure the security and price stability of the NR market. It is assumed that guayula will become a new or alternative crop for arid and semi-arid areas of the southwestern United States, north-central Mexico, and regions with a similar climate around the world [22, 25].

Guaiula (*Parthenium argentatum*). Among the potential alternative sources, NR gvayula (Fig. 6) stands out because, as already noted, it has a relatively long history of commercialization and even short-term periods of critically important intensive research (22). Unfortunately, not enough attention was paid to these studies in the future, as a result, the genetic material obtained and the experience of breeding work were lost.

Selection of *P. argentatum*. Fragmentary breeding studies of guayula during the XX century led to partial domestication of *P. argentatum*. The state of these works was analyzed twice, in 1991 [55] and in 2005 [56]. The selection of

P. argentatum is greatly facilitated by very high variability between and within the lines for each analyzed trait (in particular, the amount and quality of NR, dry weight, number of resins, yield of NR [11]. But at the same time for breeders of *P. argentatum* and *H. brasiliensis* are complex objects, since they are perennial plants, besides, relatively large areas are required to perform the corresponding programs. The guayula reaches the generative phase of development by about 2 years of age and reproduces mainly asexually — by apomixis [10, 11]. Thus, the selection is mainly reduced to the isolation of plants that give a higher yield of NR. Significant progress has been made in this regard, since several new lines that were completed as a result of work funded by the United States Department of Agriculture (USDA) produced five times more NR than the lines used in the 1940s and 1950s years [56]. Unfortunately, the success was not complete, since the descendants of the selected lines were unable to reproduce the results of highly effective parents [10, 56]. Nevertheless, such an approach certainly has potential. Similar studies performed on H. brasiliensis, over 40 years have led to an increase in the productivity of lines by 10 times — from 300 kg/ha per year to 3000 kg/ha per year [10; K. Cornish, personal communication].

Fig. 6. Guayule (*Parthenium argentatum*): plant in natural growth (A) and plantation cultivation of guayule (B). Figure is taken from articles by J. van Beilen et al. [11, 12].

Molecular genetic studies of P. argentatum. Wild guaiula is represented in nature by diploids ($2n = 2\times = 36$), triploids ($2n = 3\times = 54$) and tetraploids ($2n = 4\times = 72$). Interestingly, plants with the number of chromosomes reaching the octaploid ($2n = 8\times = 144$) were identified under cultivation conditions. It should be noted that diploids reproduce mainly sexually, while polyploids by facultative apomixis. Guaiula also has a sporophytic self-incompatibility system, and many plants contain B- or supernumerary chromosomes [57, 58].

A sufficiently large number of *P. argentatum* genes have been cloned that co-generate enzymes and proteins that participate in the biosynthesis of NK, including a gene encoding the major guayule rubber particle protein, RPP [59]. A gene encoding a protein with a molecular weight of 24 kDa has also been cloned, strongly associated with the so-called small rubber particle protein (SSRP). In vitro functional analysis using heterologous expression in *Escherichia coli* cells showed that the SSRP gene can participate in the synthesis of the polyisophene chain [59]. Several other proteins associated with rubber particles have been isolated and studied, but their functions have yet to be established [61]. The main protein associated with rubber particles in *P. argentatum* is cytochrome P450 with a molecular weight of 53 kDa. It is a member of the CYP74 family and has a high degree of homology with allene oxide synthase (AOS). It accounts for approximately 50% of the total protein of rubber particles. Despite the fact that it is catalytically active (converts 13(S)-hydroperoxy-octadecadenoidic acid into αand γ-ketolic fatty acids) and is the main protein of washed rubber particles capable of synthesizing NR, its role in this process is unclear. Moreover, it has no structural homology with cis-prenyltransferases [60, 61].

Significant progress has been made in molecular biological studies of the protein complex responsible for the synthesis of NR in *P. argentatum*. This complex includes cis-prenyltransferases (CPT) directly involved in the synthesis of the polyisoprene chain and proteins necessary for their activity (CBP/RTA) [62]. The transcriptome of the guayula diploid is available in the NCBI database (National Center for Biotechnological Information, GenBank: PI1478640) [63]. Transciptome analysis using tissues of roots, leaves, flowers, and stems (a total of 51,947 transcripts collected from 983,076 fragments) compared with previously identified sequences of the *Lactuca satнva* lettuce genome [64] showed that the genes of three CPT proteins (PaCPT1-3) and one CBP protein (CPT-Binding Protein, CPT binding protein) [62, 65].

In eukaryotic cells, a short oligoisoprenoid dolichol with several monomeric units from 8 to 18 is necessary for the transport of sugar molecules for post-translational glycosylation [66]. Therefore, all eukaryotes have at least one pair of CPT and SVR. The absence of one of these proteins is lethal to the cell. The yeast *Sacharomyces cerevisiae* has one SVR homologue (Nus1) and two SRT homologues (Rer2 and Srt1).

To study the function of the SRT/SVR complex, a double mutant *rer2 str1* was constructed, which is viable only in the presence of URA3 plasmid carrying the *RER2* gene [62]. On a medium containing 5-fluorotic acid (5-FOA), *Ura3* expression converts 5-FOA into a toxic derivative — 5-fluorouracil. Thus, only cells in which URA3 plasmid is lost and *er2Δ srt1Δ* mutations are complemented by the PaCBP/RaSRT1-3 combination can grow on media containing 5-FOA. Complementary analysis in yeast showed that PaCBP is necessary for the enzymatic activity of PaCPT1-3. The PaCBP and PaCPT1-3 genes alone or in combination were expressed in the double mutant *rer2Δ srt1Δ*. Indeed, it turned out that only PaCBP together with one of the PaCPT can complement a double mutant. Separately, PaCBP and PaCPT1-3 are not able to support the growth of yeast cells on media containing 5-FOA [62] (Fig. 7).

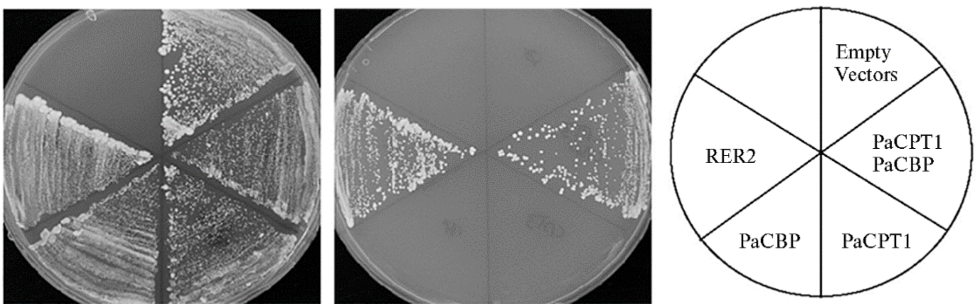

Fig. 7. Functional complementation of the *rer2Δ srt1Δ* mutant (*Sacharomyces cerevisiae*) with plasmids encoding PaCPT1 and PaCBP. The yeast strain *rer2Δ srt1Δ* is lethal but is maintained by expression of *RER2* in a URA selective plasmid. This strain was used to transform plasmids expressing both *PaCPT1-3* and *PaCBP*. Successful transformants were streaked onto selection plates with 5-FOA-xontaining medium to remove the *RER2*-containing URA plasmid. Yeast growth by selection for 5-FOA was observed only for PaCPT/PaCBP pairs or retransformed RER2 in the TRP plasmid. No growth was observed when PaCPT alone or PaCBP alone was expressed. The figure is taken from the article by A.M. Lokusta et al. [62].

Moreover, extracts from yeast cells growing on media with 5-FOA have been shown to exhibit cis-prenyltransferase activity. It should also be noted that the results of a two-hybrid analysis using the technology of split ubiquitin and coimmune precipitation convincingly showed that PaCBP and PaCPT1-3 interact with each other [62].

Cultivation of *P. argentatum*. Guayula is a perennial herb growing in the hilly areas of the Chihuahua Desert in Mexico and the Big Bend area in South Texas. The temperature in these regions varies from –18 to +50 °C. The high temperature does not seem to have a negative effect on the growth of the plant, but at values below +4 °C, the gum falls into suspended animation. Prolonged presence of the plant at negative temperatures can lead to its death [11]. One of the problems arising during *P. argentatum* cultivation is root disease, especially in stagnant water [67]. Well-drained limestone and sandy-clay soils with a relatively low content of nutrients are optimal for the cultivation of guayula. In general, the plant is quite unpretentious, it has been successfully grown in desert and semi-desert conditions, rainforest and middle belt with moderate temperatures and precipitation typical for these areas [11].

P. argentatum prefers regions where 280 to 640 mm of precipitation falls annually. It is shown that intensive irrigation is necessary for the maximum yield of NR. Interestingly, the formation of NR and resins increases in proportion to the availability of water. Even though a significant amount of water is required for intensive growth and production of NR, the plant is resistant to arid conditions, the periods of which can be long, but the synthesis of NR at the same time ceases [68].

The NR output varies greatly between lines. Moreover, in plants of the same line, it often differs markedly depending on the region, soil, and weather conditions. The season and the age of plants also affect the yield of NR and resins. In some varieties, the content of NR varied significantly depending on the time of year, in others the effect was not so obvious. For a set of eight varieties of *P. argentatum*, it was shown that the amount of biomass increases with the age of plants, but the dynamics of accumulation of NR and biomass differ [69]. Some studies show that old plants can contain very large amounts of NR. Thus, the biomass yield can reach 20 t/ha per year, whereas the NR is 2 t/ha per year (K. Cornish, personal communication).

Guayula synthesizes and accumulates rubber particles primarily in the epithelial cells of parenchymal tissue. The technologies for obtaining NR from the biomass of guayula are described in detail in the literature. Three methods of obtaining NR from guayula have been developed and applied. The first and oldest method is flotation. Crushed plants are placed in a large container with an alkali solution, wood tissue absorbs water and sinks to the bottom, and resinous rubber floats to the surface in the form of so-called “worms”. In the future, the rubber is cleaned of resins using acetone [70]. The second method is sequential extraction, in which the resin is first extracted with acetone or another polar organic solvent, and then the rubber is extracted with hexane [71]. The third treatment method is simultaneous extraction, which uses a mixture of solvents, usually acetone and hexane or pentane. After the initial extraction, acetone is added to coagulate high-molecular-weight rubber [72].

According to economic forecasts, for guaiula to become a competitive crop without subsidies, it is necessary to increase the yield of rubber and/or identify and develop commercial use of by-products of processing [73]. One of the potentially valuable by-products is the low molecular weight fraction of rubber, which accounts for about 25% of its total yield. These low molecular weight rubber compounds are of great importance as a special rubber not used in tires [73]. Another by-product of processing, the resins is characterized only partially, but mainly represents triglycerides of fatty acids and terpenoids. Resins are successfully used as preservatives for wood, raw materials for special chemicals (coatings and additives to rubber), as well as high-quality fuel without ash [11, 73].

Advantages and disadvantages of natural rubber from P. argentatum. The molecular weight and properties of NR from guayula are very close to those of NR from hevea. However, unlike NR from *H. brasiliensis*, natural rubber from guayula does not contain proteins capable of causing a severe allergic reaction [38]. This important pre-property has revived interest in NC from *P. argentatum*. For example, the companies Yulex (Solana Beach, CA, USA) and PanAridus (Casa Grander, AZ, USA) produce such NC, which practically does not contain allergenic proteins. It can be used for the manufacture of hypoallergenic gloves and other medical products, in which the strength and elasticity of NC is combined with the absence of dangerous allergenicity.

Isolated directly from the plant and dried, the NR of the guaiula can contain from 20 to 40% resin. If NR was extracted with solvents and then treated to remove the resin, then the viscosity of such NR is significantly lower than the viscosity of NR from *H. brasiliensis*. Selective coagulation is necessary to obtain a high-molecular fraction of NR from guayula, which is similar in properties to NR from hevea (74). NR from *H. brasiliensis* contains proteins and, consequently, reactive groups capable of crosslinking. This leads to the formation of branched polymer chains, and as a result, the viscosity of NR increases during storage for a long time. In contrast, irreversible chain cleavage induced by temperature occurs in the protein-free NR from *P. argentatum*. That is, such NR is less resistant to elevated temperature than NR from *H. brasiliensis*. Moreover, the triglycerides of unsaturated fatty acids present in the resin contribute to the oxidation of polymer chains. To prevent the oxidation process and increase the stability of NR from guayula, a combination of antioxidants and zinc dialkyldithiocarbamate [74] is used.

Kok-sagyz, Russian dandelion (*T. kok-saghyz*). An ideal rubber carrier should yield annually, grow rapidly, and produce a large amount of biomass. Plants yielding an annual harvest can be quickly planted and harvested depending on the needs of the product and the market situation. Kok-saghyz (*T. kok-saghyz*) meets these criteria to a greater extent than guayula.

T. kok-saghyz (Fig. 8) was discovered in Kazakhstan, in the Tien Shan valleys and was first described by the botanist L.E. Rodin in 1932 during the implementation of the strategic program of the USSR for the development of its own production of NR. The study of 1048 species from 316 genera and 95 families of the native flora showed that 609 species synthesize rubber and rubber-like substances.

The development of koksagyz occurs in harsh conditions of a sharply continental climate on saline soils, with a lack of moisture and strong winds [72]. Based on koksagyz seeds collected in places of natural growth, a collection of plants was created at the All-Union Institute of Plant Breeding named after N.I. Vavilov (VIR, St. Petersburg), a botanical description and determination of the intraspecific diversity of plants were carried out, which made it possible to select the best genotypes for cultivation. The biological and morphological features of the plant were studied and it was found that the crop is moist, requires at least 420-600 mm of precipitation per year with their uniform distribution, needs highly fertile soils (floodplains of rivers, cultivated peat bogs, black steam). Agrotechnics of culture for various types of soils were developed, diseases and pests were studied, breeding work was carried out [36, 72, 75, 76].

The roots of wild koksagyz accumulate from 4 to 12% of high-quality rubber synthesized in laticifera — elongated secretory cells found in the leaves and stems of those plants that produce latex and rubber as secondary metabolites [51, 52].

T. kok-saghyz was actively cultivated in the USSR from 1930 to 1952. In

1941, 67 thousand hectares of plantings covered about 30% of the country's need for NR [11]. With the outbreak of the Second World War, there was an acute shortage of NR, and several countries independently began to implement emergency programs to develop technologies to produce NR from *T. kok-saghyz*. Among them, the USA [77], Great Britain [78], Germany [79], Sweden and Spain [80] should be mentioned. If the best result in the USA was 110 kg/ha, then in the USSR it was possible to exceed the indicator of 200 kg/ha [36].

Fig. 8. Plants of kok-saghyz (*Taraxacum kok-saghyz* L.E. Rodin): A — general view, cultivation in the soil; B — roots of a plant grown in the soil: C — growth of kok-saghyz plants under phytotron conditions (aeroponics cultivation) (authors' photo).

Unfortunately, the cultivation of *T. kok-saghyz* is laborious and expensive. The seedlings of the plant are very small, it is difficult for them to compete with the weeds, which makes constant intensive weeding necessary. After the resumption of supplies of cheap NR from Southeast Asia to the world market after the end of World War II, the cultivation of *T. kok-saghyz* in the USSR continued until the early 1950s, but then these works were stopped in the USSR for economic reasons [36].

Selection of T. kok-saghyz. For kok-sagyz to become economically competitive, the rubber content in latex needs to be increased. The main goal of all breeding programs is to increase the yield of rubber per unit area. It should be noted that the programs for the selection of koksagyz were carried out from the moment of its description, study, but were conducted inconsistently, with long time intervals. In addition, breeding was complicated by the fact that this species has a system of self-sterility (self-incompatibility) that prevents self-fertilization [81]. The genetic material used in the USA during the implementation of the emergency rubber program was essentially improved samples of wild type koksagyz, obtained from the USSR. If in the most productive plants the yield of NR was about 5-6% of the dry weight of the roots, then in most cases it did not exceed 2-3% [10, 36]. It is noteworthy that, according to published data, in the USSR, the yield of NR reached 15% (82). In 1953, by the method of multiple crosses, it was shown that the size of the koksagyz crust and the accumulation of NR in them could be significantly increased [83]. Based on these studies, it was assumed that the selection of cocsagyz would potentially increase the yield of NR to 15-25% [84].

The yield of rubber can be increased by increasing the biomass and/or the content of rubber in it. An increase in the rubber content is more desirable since this increases the efficiency of plant processing. The increase in biomass is associated with additional costs associated with harvesting, transportation, and processing. To turn *T. kok-saghyz* into a commercially attractive product, it is necessary to significantly improve its agronomic properties, for example, the growth rate. This is possible by crossing *T. kok-saghyz* with the common dandelion *T. officinale*. In experimental fields in New Zealand, the yield of *T. officinale* dry roots was 6-9 t/ha after 6 months of growth [85]. Thus, theoretically, a hybrid of koksagyz and ordinary dandelion could produce NR in a quantity of about 1200-1800 kg/ha.

Several features make *T. kok-saghyz* an exceptionally attractive model system for studying NR biosynthesis, including for breeding purposes. It has a very short life cycle (6-8 months) compared to other rubber carriers. For example, in the case of *H. brasiliensis*, it takes an average of 7 years to assess the phenotype of a plant by its ability to produce NR. For the shrub *P. argentatum*, the same period is 2 years. Moreover, *T. kok-saghyz* can be genetically modified relatively easily (for example, transformed to produce transgenic plants). The analysis of the NR content in the roots of kok-sagyz can be carried out already 3-6 months after transformation [41, 42].

Molecular genetic studies of T. kok-saghys. To use *T. kok-saghyz* as a model organism in the study of NR biosynthesis, modern molecular biological approaches are required - improved transformation protocols, the use of RNA interference (silencing) to suppress gene expression and EST (Expressed Sequence Tag) libraries. In molecular biology, the expressed sequence label (EST) is a short cDNA subsequence. EST identification is carried out quickly, and now there are about 74.2 million EST in publicly available databases (for example, GenBank as of January 1, 2013, all types). Earlier, we described in detail molecular genetic approaches to the study of NK biosynthesis in *T. kok-saghyz* cells [42].

The key enzymes in NK biosynthesis are cis-prenyltransferases associated with rubber particles (rubber transferases, CPT, RT); they synthesize the polyisoprene chain and can be isolated into a separate subfamily (CPT) [62]. CPT classes differ in cellular localization, the ability to bind substrate molecules, and the size of the reaction products formed. It is noteworthy that only RT-class enzymes can synthesize high-molecular polyisoprene ([41, 42, 86]. For cloning CPT *T. kok-saghyz* used degenerate primers corresponding to conservative sites of *H. brasiliensis* HRT1 and HRT2 [87], *Arabidobsis thaliana* ACPT [88] and *S. cerevisiae* Rer2 [89] enzyme sequences. RT-PCR (reverse transcription polymerase chain reaction) analysis performed using total latex RNA (milky juice rubber-bearing plants) as a matrix, led to the identification of three cDNAs encoding structurally related CPT1-3 [90]. It is extremely important to note the fact that the intracellular concentration of CPT regulates the biosynthesis of natural rubber in cells *T. brevicorniculatum* is the closest relative of *T. kok-saghyz*. For a more complete understanding of the role of CPT1-3 in latex, transgenic plants of *T. brevicorniculatum* were obtained in which the expression of all three CPT genes was suppressed using the RNA interference method (RNAi) [91]. Transgenic lines demonstrated almost complete suppression of NK biosynthesis. It is noteworthy that transgenic plants were morphologically indistinguishable from wild-type plants.

Proteins functionally related to CPT have been identified relatively recently. One of them is SRPP, an acidic protein (pI 4.8) found in H. brasiliensis latex with a molecular weight of 23 kDa [92)]. The important role of SRPP in the biosynthesis of natural rubber has been reported [42]. Comparative analysis of *T. kok-saghyz* EST sequences using the known SRPP sequence from *H. brasiliensis* led to the identification of five cDNAs encoding potential SRPP1-5 ([90]. Studying the proteome *T. kok-saghyz* showed that three of these proteins (TkSRPP3, TkSRPP4 and TkSRPP5) are associated with rubber particles [93]. The main isoform associated with rubber particles, TkSRPP3, was studied in more detail. To characterize the functional role of SRPP in NK biosynthesis, the TkSRPP3 protein gene was overexpressed in the transgenic *T. kok-saghyz*. Real-time RT-PCR analysis showed that the number of transcripts of the TkSRPP3 gene in transgenic lines was increased (by more than 2 times). The Western blot also confirmed an increase in the level of TkSRPP3 in overexpressing transgenic lines. Measurement of the NR content in these lines demonstrated its increase (for example, by 30%) compared to the control. The molecular weight of natural rubber in the overexpressing lines practically did not differ from that in the control line and varied in the range of 1.0-1,2×10^6 Da [95]. Phenotypically transgenic plants did not differ from wild-type plants. To study the role of SRPP in NK biosynthesis, the expression of the TkSRPP3 gene in *T. kok-saghyz* was suppressed by RNA interference (RNAi). Several transgenic lines were obtained in which the mRNA level of the TkSRPP3 protein was significantly lower than in the control line. Western blot showed that the accumulation of TkSRPP3 protein in these lines was also reduced (by 60%). The molecular weight of the rubber in transgenic lines was also significantly lower than in the control [93]. Thus, the suppression of the expression of the TkSRPP3 gene in *T. kok-saghyz* cells significantly affects the amount of synthesized NR and its molecular weight.

The CPT family includes not only enzymes responsible for NR biosynthesis, but also other CPT capable of synthesizing polyisophene chains with a maximum length of up to 50 monomers [94, 95]. In eukaryotes, these enzymes synthesize dolichol, which is necessary for glycosylation of proteins, and other polyisoprenoids that perform various functions, including adaptation to stress [96, 97]. In humans, CPT, responsible for the biosynthesis of dolichol containing 22 isoprene units, interacts with Nogo-B receptor protein (NgBR). This protein stabilizes the enzyme through direct protein-protein interactions. It is also necessary for the enzymatic activity of CPT [98, 99]. Studying whether proteins related to NgBR can stabilize cis-prenyltransferases responsible for the biosynthesis of NR, which are part of the transferase complex on the surface of rubber particles, such a protein was found in *T. brevi-tacorniculatum* cells. It contains three conservative sites (motifs I, II and III), which are characteristic of NgBR plants and mammals. Based on the assumed functional analogy with NgBR, the authors named this protein a cis-prenyltransferase activator (TbRTA) [100]. RT-PCR analysis showed that the concentration of mRNA encoding TbRTA in latex is much higher than in plant tissues. This correlates with the expression level of the CPT1-3 gene and suggests that TbRTA is involved in NR biosynthesis. To study the role of TbRTA in this process, the expression of the TbRTA gene in *T. brevicorniculatum* cells was suppressed using RTA-RNAi. The obtained transgenic lines showed pronounced inhibition [100]. It is noteworthy that the suppression of the expression of the TbRTA gene did not affect the growth and development of transgenic plants, they were indistinguishable from wild-type control plants. The effect of TbRTA gene expression pressure on NR synthesis was also studied. In wild-type plants, latex formed a foam-like upper layer containing rubber particles after centrifugation, while in transgenic plants the upper layer was absent. The absence of NR in transgenic lines was confirmed by ^{1}H-NMR analysis [100]. To find out whether the absence of natural rubber in transgenic plants is associated with the inhibition of TbCPT1-3 gene expression or there is a posttranslational loss of TbCPT1-3 proteins, RT-PCR analysis and Western blot were performed. It was shown that the mRNA levels of TbCPT1-3 genes are approximately the same in transgenic RNAi lines and a wild-type control plant, however, Western blot did not detect TbCPT1-3 proteins in transgenic lines. These results suggest that TbRTA is necessary to maintain the active formation of TbCPT1-3 as part of the transferase complex on the membrane of rubber particles and explain the absence of polyisoprene in TbRTA-RNAi transgenic lines. Thus, TbRTA not only activates TbCPT1-3, but also protects transferases from degradation. Moreover, because TbCPT1-3 do not have a transmembrane domain, TbRTA may play an important role in the localization of transferases on the surface of rubber particles (100). Thus, TbRTA is a key component of the transferase complex.

The technology of obtaining NR from *T. kok-saghyz* biomass is described [77, 79]. It is constantly being modernized and improved, however, for new rubber-bearing crops to become economically competitive, effective complex processing of by-products from leaves and residues of root biomass after isolation of rubber, resins and inulin is also necessary [80].

Advantages and disadvantages of natural rubber from T. kok-saghyz. Laboratory studies of the physical and chemical properties of NR from *T. kok-saghyz* have shown that this natural rubber has excellent quality and is in many ways like NR from *H. brasiliensis*. It is noteworthy that automobile tires made from this material are better in all characteristics than tires made from NR *P. argentatum* [6]. The high molecular weight (2.2×10^{6} Da) fully confirms this conclusion [13, 17, 101]. One of the potential problems associated with NR from Russian dandelion is the high protein content, which is even higher than in rubber from *H. brasiliensis* [11]. Consequently, people sensitive to NR from hevea may also be allergic to the polymer from *T. kok-saghyz* [37, 38], therefore, NR from kok-sagyz is preferable to use in areas not related to medicine, for example in the automotive industry.

Tau-sagyz (*Scorzonera tau-saghyz*). The perennial semi-shrub kozelets tau-sagyz (*Scorzonera tau-saghyz*) (Fig. 9) is certainly one of the most promising alternative sources of NR, to which, in our opinion, the scientific community pays insufficient attention. His homeland is the Karatau mountain range in Southern Kazakhstan. The content of NR in the roots of tau-sagyz changes with age. The roots of an annual plant usually contain 1-8% NR per dry mass. In 2-3-year-old plants, the content increases to 8-30%. Interestingly, when growing tau-sagyz under optimal conditions, the accumulation of NR in the roots can reach 40% of the dry weight. Unfortunately, the number of tau-sagyz in natural conditions critically decreased in the 1940s due to intensive harvesting. More than 12 million roots with a total dry weight of about 900 tons were used for the needs of the military industry. This was enough to produce about 300 tons of NR [102-104]. Currently, tau-sagyz is rarely found in nature, and the restoration of its natural habitats is very slow. Tau-sagyz is less competitive than other plants in the same habitats, and intensive development of adjacent territories leads to an even greater reduction in the number of this rare species. To restore it, technologies based on the use of microbiological preparations, in particular fungi that form arbuscular mycorrhizae, can be used.

Fig. 9. Tau-saghyz (*Scorzonera tau-saghyz* Lipsch. et Bosse): A — tau-saghyz plants in natural conditions; B — roots of tau-saghyz plants from places of natural growth; C — milky juice of tau-saghyz. Photos courtesy of K.K. Boguspaev (Kazakhstan)

Arbuscular mycorrhiza (endomycorrhiza) is a mutually beneficial symbiosis of microscopic fungi of the *Glomeromycota* department with higher vascular plants that significantly increases the viability of the host. Endomycorrhiza increases the availability of nutrients (in particular, phosphorus and nitrogen) for the host plant, increases the intensity of photosynthesis, which, in turn, leads to a significant accumulation of the root and aboveground mass of the mycorrhizal plant [105-107]. Mycorrhization of tau-sagyz seedlings using fungi of the genera *Claroideoglomus* and *Rhizophagus* [104] revealed structures in the roots (unsepted mycelium, vesicles and arbuscules) characteristic of fungi forming arbuscular mycorrhizae. The control samples lacked these structures. Plants treated with mycorrhizal fungus inoculum grew noticeably better than non-mycorrhizal ones [107)]. The average height and number of leaves in mycorrhizal plants were 1.5-2.0 times higher than in non-mycorrhizal plants. The conducted studies indicate that arbuscular mycorrhizae play an essential role in the life of tau-sagyz, and optimized biotechnologies for growing this rare and endangered species and promising rubber plant can be developed on their basis.

Summing up the discussion of the problem of natural rubber plants, we note that the interest in plants that can function as sources of various materials is due to many reasons. NC is not only one of the most important polymers used by mankind, but also a renewable polymer. Unfortunately, the source of this polymer, *H. brasiliensis*, is under the influence of negative biotic (SALB) [20, 21] and abiotic factors (economic development negatively affecting the natural habitat, and climate change). The development of alternative sources of NR is, of course, extremely important in the medium and long term, because it will not only ensure greater availability of this polymer, but also reduce the dependence of mankind on fossil fuels needed to produce synthetic analogues of NR. Rubber carriers can also be used to produce other important products, such as bioethanol from lignocellulose (*S. tau-saghyz, P. argentatum*) or inulin from *T. kok-saghyz.* The achievements of genomics, proteomics, metabolomics, and biotechnology will certainly help to make significant progress in understanding the processes of NR biosynthesis. This, in turn, will lead to the creation of new forms and genotypes of plants with a high rate of growth and development, the ability to super-synthesize NR, and will also allow the development of optimal technologies for their cultivation.

So, the ever-growing demand for natural rubber (NR) cannot be satisfied in the future at the expense of the rubber tree alone. Alternative crops are needed that can be grown on large areas in industrial volumes, and appropriate technologies for processing and obtaining final products. The economic feasibility of introducing new NR producing crops depends not only on increasing the productivity of the plant, but also on the complex processing of the entire plant to obtain additional products. The introduction of any new culture is an extremely difficult task. In the case of rubber carriers, simultaneous coordinated expansion of agricultural areas and processing capacities is required. In the long term, rubber from alternative crops, especially its thermostable derivatives such as epoxidized rubber, can supplement the market share currently occupied by various synthetic rubbers, with a significant reduction in the carbon footprint.

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