THE PHENOMENON OF SILYBUM MARIANUM

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The article presents the results of study of composition, properties, biological activity Silybum marianum. It is shown that the unique components of the plant possess wide range of biological effects. On the basis of the conducted researches we developed drugs Natursil and Silystrong, biologically active supplements to food, with well-expressed membrane-protective, antioxidant, reparative, immunomodulatory, cardiotonic, choleretic, hepatoprotective properties. This leads to the use of drugs in different branches of medicine: gastroenterology, surgery, obstetrics and gynecology, pulmonology, cardiology, otolaryngology, dentistry. With the use of experimental models at different levels of structural-functional organization, the molecular mechanisms of action and biologically active substances of milk thistle were studied. We installed their activating effect on enzymes of glycolysis, including revitalizing effect under conditions of oxidative stress, studied neuron activating properties of drugs. The ability of silystrong to affect protein-protein interaction allows the use of the drug as a metabolic probe. Shows the different responses of group-specific antigens of the system AB0 to the introduction of Silystrong, demonstrating the specificity of individual response to the action of biologically active substances, drugs, xenobiotics, toxicants, due to the peculiarities interprotein relationships. The obtained results allow to recommend drugs from Silybum marianum as tools for targeted correction of metabolism, ecoprotection with broad spectrum.

Keywords: Silybum marianum, biologically active substances, ecoprotector, natursil, silystrong, metabolic processes, glycolytic enzymes, protein-protein interaction, the ABO blood group antigens

Public health has been the most important biosocial problem for years. Human existence in a technologically transformed environment leads inevitably to environmentally induced changes, which are the metabolic substrates for the multifactorial diseases. In the current situation, the maintenance of the dynamic constancy of the environment and the balance of interspecies relationships are essential as a foundation for successful interactions in the global ecosystem. This approach considers the objects of animate and inanimate nature as carriers of biologically active substances accumulated in various species. The optimal source of these compounds are plants, as they are capable for self-reliance, preservation of species, synthesis of biopolymers, aliphatic and polycyclic substances with complex structure and different regulatory properties [1, 2, 3, 4]. These natural compounds are similar to the human being, as they ingested to the organism historically via food chains and participated in metabolism.

We studied milk thistle (Silybum marianum), planted in Samara region as a carrier of biologically active substances. The idea of our study was preceded with a large research of exchange processes in norm and pathology by professor F. N. Gilmiyarova. For the first time from human and animal tissues glycolytic enzymes were isolated, purified to a homogeneous state, and their structural and functional properties were studied in physiological conditions, atherosclerosis, alcohol intoxication. We installed the molecular level of alteration under these pathological conditions and revealed the specific parts of pathogenesis [5–14]. Enzyme drugs of fructose-bisphosphate aldolase (EC 4.1.2.13), glyceraldehyde-3-phosphate dehydrogenase (EC 1.2.1.12), glycerol-3-phosphate dehydrogenase (EC 1.1.1.8) were obtained by F.N. Gilmiyarova, V.M. Radomskaya, L.N. Vinogradova using the original technology, normalized and proposed for performing analytical studies and enzyme diagnostics. Asolation and purification enzyme methods are protected by copyright certificates and patents [15–17].

We also studied the influence of exogenous dehydrogenases on the integral metabolism. Malate dehydrogenase (EC 1.1.1.37) and lactate dehydrogenase (EC 1.1.1.27), marked with tritium were used as molecular probes. For the first time penetration into the brain, the liver, the heart, kidneys and other organs were discovered by analyzing the distribution of enzymes in the organs and tissues, evaluation of the dynamics of distribution and excretion. All of these opens up a lot of prospects for the development of new enzyme therapy areas [18–20].

Quite a large branch of research focused on valeological direction. We studied the state of metabolism in ecologically unfavorable regions and elucidated the biochemical deterioration mechanisms of public health. Furthermore, we identificated targets for target metabolism correction [21–29]. Searching the essential factors with curative properties had become one of the scientific biochemistry school branches in Samara.

Milk thistle (Silybum marianum, cardus marianus) is an annual or biennial plant of the Asteraceae family, achenes are used as a medical raw. The author's collective studied chemical composition of achenes in detailed. Due to variety of methods, such as gas-liquid chromatography, high-performance liquid chromatography, emission analysis, ultraviolet and infrared spectroscopy, spectrophotometry, NMR we determined the composition of milk thistle seeds: proteins (17–18 %), lipids (10–11 %), including saturated and unsaturated fatty acids, tocopherols (17–18 mg %), carotenoids (1,6 mg %), flavolignans (2–3 % of dry weight), carbohydrates (2,0 %), trace minerals [30]. The lipophilic fractions composition of the Silybum marianum fruits (milk Thistle oil) is diverse, it contains a complex of biologically active substances [31] (Table 1).

Unique composition of studied fruits are allowed to presume that the fraction remaining after the primary processing of raw materials may contain substances with remarkable biological properties. Using this non-waste technology, we obtained Natursil drug (thistle oil) from the fruit by pressing and Silistrong drug (water-alcoholic extract) from the grist; both of them are food supplements.

Mass production of drugs was preceded by the series of experimental studies based at Samara State Medical University, as well as in cooperation with Russian leading specialized research centers: the laboratory of drug toxicology, institute of experimental cardiology of Russian cardiological center, research institute of nutrition (Russian Academy of Sciences), research institute of Emergency care named after N.V. Sklifosovsky, institute of surgery named after A.V. Vishnevsky, interregional center of thermal injuries and plastic surgery, Samara Military Medical Institute, chair of biochemistry of Bashkir state medical University.

During the preclinical phase general and specific pharmacological activity, pharmacokinetics, acute and chronic toxicity, local irritating, immune, allergenic action, the possibility of carcinogenic, mutagenic properties were defined. Laboratory experiments on various species showed that milk thistle drugs did not possess local irritant, skin-resorbing, sensitizing effects. Toxicity study revealed the low drugs toxicity even at the maximum possible doses (200–250 times greater than recommended for human highest daily therapeutic dose). The absence of the studied drugs mutagenic

Table 1

Physical and chemical composition of milk thistle oil

Category	Charasteristics
Color	From light yellow to yellowish brown
Physical condition	Oily liquid
Density	0,910–0,930
The refractive index	1,457–1,480
Acid number	≤ 5,0
Saponification value	180–205
Iodine number	65–90
The fatty acid composition, %	
Saturated:	
– palmitic (16:0)	10,8 ± 2,3
– stearic (18:0)	3,61 ± 0,84
Unsaturated:	
– oleic (18:1)	22,1 ± 5,37
– linoleic (18:2)	60,8 ± 9,16
– linolenic (18:3)	1,32 ± 0,38
Tocopherols, mg %:	
– α-Tocopherols	35,4
β- and γ-Tocopherols	16,8
Carotenoids, mg % (lutein and zeaxanthin)	4,9
Flavolignans (silymarin), mg %	≥ 25

and DNA-damaging effects, potential carcinogenic risk was discovered. In addition, milk thistle preparations had no negative effects on the reproductive function, no embryo toxicity and teratogenicity were found.

Completing this block of studies, we moved to clinical trials. Initially Natursil was declared as anti-ulcer agent (patent № 2051686 from 10.01.1996). Its ability to accelerate epithelialization, reparation and regeneration of skin defects of different origin was established during the pre-clinical stage. However, in clinical studies it was shown that milk thistle drugs had not only anti-inflammatory and wound-healing effect, but also membrane-protective, immunomodulatory, cardiotonic, choleretic, antioxidant, hepatoprotective properties, they increased tolerance to physical and mental stress. Based on these results we registered drugs Silistrong (Pharmacopoeia article 42-0211-0703-01) and Natursil (Pharmacopoeia article 42-3889-99). They were included in the State register of medicines of the Russian Federation. We obtained 14 patents for invention, for 24 PhDs and 14 doctorates of science it was the basis of their researches.

The result of the scientific research was the creation of scientific and methodological basis for the nutritional supplements Natursil and Silistrong production. Technological complex in the ecologically clean region of Ulyanovsk was built on the basis of Sengileevskiy grain enterprises for growing plants, raw materials processing and obtaining biologically active substances from milk thistle. These nutritional supplements are available in pharmacies and can be used not only for ecological protection. The milk thistle clinical effects variety determined a wide scope for using it in different branches of medicine (Table 2).

Table 2

The fields of medicine and main clinical effects of Natursil

Field of medicine	Clinical effect	Way of use
Gastroenterology (Peptic and duodenal ulcer; acute and chronic liver diseases)	Recovering time reduction of mucous membrane natural morphological structure at the site of the ulcer, reduction of dyspepsia [33]	Per os (peptic ulcer), using endoscope (duodenal ulcer)
Surgery (Burn wounds different severity and localization)	Accelerated necrotic tissue rejection and epithelialization, formation of elastic scar tissue, healing of skin flap, epithelium activation in autological dermal transplantant, reduction of microbial contamination in burn surface [30, 34]	Application to the burnt surface
Obstetrics and gynecology: (Cervical erosion, post-natal complication)	Time reduction of inflammation with subsequent epithelialization of surface erosion, allows to avoid surgical treatment if recurrent and sluggish processes; metabolism normalization during gestation [30, 35]	Application, intravaginal tampons Per os 1/2 tea spoon 3 times per day from 32 to 34 gestation weeks
Pulmonology (Chronic bronchitis in acute stage)	Immunostimulating effect, enhancing antibacterial effect [36], reducing the time of nflammatory process resolution in the lungs [37]	Per os 1 tea spoon 2 times per day for 2 weeks
Cardiology (Cardiac ischemia)	Plastic process improvement in the cardiac muscle, antioxidant and membrane stabilizing effect in ischemia conditions [38, 39]	Per os 1 tea spoon 3 timed per day for 2 weeks
Otorhinolaryngology (Inflammatory diseases of the upper respiratory tract)	Anti-inflammatory effect on the mouth and nose mucous membranes [30]	Application
Stomatology (Inflammatory diseases of the oral cavity)	Anti-inflammatory, analgetic, regenerative effects in chronic generalized periodontitis, chronic apical periodontitis in the postoperative period [40–42]	Turunda into periodontal pockets, application
Dermatology and cosmetology	The improvement of the face skin, manifested by a decrease in dryness of the skin, fat normalization, decreasing the depth of wrinkles [43, 34, 44]	Application, masks

The desire to provide citizens of the ecologically unfavorable regions available methods of metabolic correction, which can be used routinely, prompted the authors to create the biologically active food supplements. Methods of administration milk thistle supplements in the composition of bakery and confectionery products, drinking water, soft drinks were developed:

– "Additive of ground seeds of milk Thistle", patent № 2053598 from 26.01.1996;

– "The composition of ingredients for the production of bread and bakery products", patent № 2099949 from 27.12.1997;

– "Mix butter biscuit", patent № 2099950 from 27.12.1997;

– "Composition for the preparation of aerated confectionery products with anabolic properties", patent № 2099960 from 27.12.1997;

– "Composition ingredients "Samaritan woman" for making non-alcoholic drinks", patent № 2113808 from 27.06.1998.

This approach allowed us to make food of average citizens more healthy adding antioxidant properties [45–47]. All supplements of milk thistle was registered in the Federal register of biologically active additives to food.

The success of using milk thistle drugs and food supplements for the prevention and treatment of various diseases, as well as the variety of clinical effects observed in different organs and systems, determined the further course of our research. We tried to study molecular mechanisms of action of the components of milk thistle at various levels of structural-functional organization by experiments in vitro, in vivo, ex vivo, in silico.

As we mentioned before, there was a large group (12 compounds) of flavolignans in the composition of milk thistle among substances with valuable biological properties. Flavolignans were up to 70–90 % of the total flavonoids amount presented with silybin and its isomers – isosilybin, dehydrosilybin, silychristin, silychristin, digidroergochristyn, silidianin [48–50]. Considering the effects of milk thistle and possible mechanisms of their realization at the molecular level, we applied to the basic postulate of A.M. Butlerov theory: the properties of substances are determined by their chemical structure. This problem was solved by using computer aided Prediction of Activity Spectra for Substances (PASS C&T) and "Pharma Expert", developed by the staff of the structural and functional drugs design Laboratory of the research Institute of Biomedical chemistry named after V.N. Orechovich – full member of the Russian Academy of medical Sciences Professor V.V. Poroikov, PhD A. Filimonov. Prediction of pharmacological activity, biological effects of substances and possible mechanisms of their realization are based on the analysis of their chemical structure. Spectrum of biological activity is described qualitatively: estimated probability of presence (Pa) and the lack of each type of activity (Pi) having values from 0 to 1. Since in our case we investigated molecules with known structure, the optimal value of the presence activities probability was considered more than 0,5. The use of the computer program allowed us to identify 154 the possible effects of milk thistle flavolignans, including a number of new properties along with established in the experimental studies [52]. The probability to possess antitoxic, hepatoprotective, antiviral, antioxidant, antineoplastic, anti-apoptotic, fibrinolytic effects and to regulate the metabolism of lipids and nucleotides were shown.

We found meaningful to compare the spectra of biological activity of each isomer of silybin. Different isomers had different spectre of activity which is probably due to the peculiarities of the chemical structure. Hence, silybin and isosilybin, being identical in chemical structure, differing only slightly in the spatial configuration of remnant of conifery alcohol, have identical effects and numerical values of the effects presence probabilities. These isomers have antioxidant (Pa 0,688), fibrinolytic (Pa 0,666), antiherpetic (Pa 0,655) activity, as well as the ability to inhibit lipid peroxidation (Pa 0,586). Dehydrosilybin involved in the strengthening of vascular walls (0,629 Pa), moreover, it is an agonist of apoptosis (Pa 0,792) and regulator of the nucleotides metabolism(Pa 0,535).

Silychristin, being the most reactive object, shows the highest ability to stabilize the cell membranes (Pa 0,952), has antitoxic and hepatoprotective effects (Pa 0,904 and 0,816). Isosilybin (silychristin isomer) acts as a "free radicals trap" (Pa 0,762). Silydianin has the strong antitumor effect (Pa 0,782). It is highly noteworthy, that no mutagenicity, teratogenicity, carcinogenicity, cardiotoxicity was revealed during our study.

Paying attention to the wide range of possible milk thistle lignan flavonoids biological effects, we may conclude that the mechanisms of their realization is regulation of the cell metabolism key enzymes activity. We used polisubstrate multienzyme system of muscle tissue homogenate and lysate of erythrocytes as an experimental model. Studying the influence of silystrong, as well as silymarin and ethanol on the activity of glyceraldehyde 3-phosphate dehydroganase (EC 1.2.1.12), glycerol phosphate dehydrogenase (EC 1.1.1.8) and lactate dehydrogenase (EC 1.1.1.27) we discovered that, silystrong caused significant rate changes in the studied enzyme reactions; silymarin and ethanol showed less biological effects [51–53]. The activity of lactate dehydrogenase increased from 0,321 ± 0,006 to 0,623 ± 0,007 E/mg (+94,1 %, p < 0,001), glyceraldehyde 3-phosphate dehydroganase (+86,5 %, p < 0,001). The most important changes were observed in the reaction with glyceraldehyde-3-phosphate dehydrogenase. The rate of reaction catalyzed by this enzyme increased in 2 times (+110 %, p < 0,001). Adding erythrocytes in the lysate of the silymarin solution revealed no significant changes: the activity of glyceraldehyde 3-phosphate dehydrogenase increased (+8,9 %, p > 0,05), the reaction rate with lactate dehydrogenase stayed unchanged. However, the rate of the glycerol phosphate dehydrogenase reaction increased (+57,1 %, p < 0,01) compared to baseline. Incubation with ethanol resulted in an increasing activity of glyceraldehyde-3-phosphate dehydrogenase from 0,251 ± 0,003 to 0,440 ± 0,002 U/mg (+75,3 %, p < 0,001), glycerol phosphate dehydrogenase (+27,1 %, p < 0,05). The rate of the final stage of glycolysis increased in 1,6 times (+63,1 %, p < 0,01).

We noticed similar patterns in the reactions with homogenate of muscle tissue (Table 3). The significant changes were observed in the reactions with the glyceraldehyde-3-phosphate dehydrogenase, the activity after the incubation with silystrong, silymarin and ethanol increased to 487,4; 190,4; 346,2 %, respectively (p < 0,001).

Considering high antioxidant activity of lignan flavonoids, we studied their effects on the glycolytic enzymes activity under the conditions of oxidative stress. In vitro experiments established the modifying effect of hydrogen peroxide on the studied dehydrogenases: complete disappearance of the of glyceraldehyde-3-phosphate dehydrogenase activity, inhibition of the lactate dehydrogenase (–53,5 %, p < 0,01) and glycerol phosphate dehydrogenase (–48,2 %, p < 0,01). Incubation of enzymes with silystrong observed the recovery of lactate dehydrogenase activity to 90,4 % (p < 0,01), glycerol phosphate dehydrogenase activity to 75,5 % (p < 0,01), glyceraldehyde-3-phosphate dehydrogenase to 12,0 % (p < 0,05). Pre-incubation with silistrong provided the protective effect, helped to enhance and maintain the activity of dehydrogenases. Thus, thistle flavolignans have a revitalizing effect on glycolytic enzymes that covers them from the damaging effects of oxidants. This is is one of the mechanisms of the silystrong activity [51–54].

The results of biological effects computer prediction and literature analysis showed that flavolignans possessed the neurotropic activity [55–58]. However, the specific mechanisms of this effect were not discovered during the study and deserves special attention, as it allows studying the effect of lignan flavonoids on the tissue and organ-specific level.

Table 3

The activity of glycolytic enzymes (U/mg) from the homogenate of muscle tissue after incubation with silystrong, silymarin and ethanol

	Control	Silystrong	Silymarin	Ethanol
Glyceraldehyde 3-phosphate				
Initial value	0,506 ± 0,049	0,492 ± 0,061	0,509 ± 0,038	0,511 ± 0,023
Incubation with drugs		2,89 ± 0,24***	1,48 ± 0,27***	2,28 ± 0,31***
Deviation, %		+ 487,4	+ 190,8	+ 346,2
Glycerol phosphate dehydrogenase				
Initial value	0,305 ± 0,026	0,311 ± 0,034	0,296 ± 0,026	0,298 ± 0,022
Incubation with drugs		0,521 ± 0,056	0,411 ± 0,033**	0,278 ± 0,022*
Deviation, %		+67,5	+38,8	–6,7
Lactate dehydrogenase				
Initial value	2,44 ± 0,26	2,32 ± 0,21	2,46 ± 0,28	2,39 ± 0,23
Incubation with drugs		3,28 ± 0,31***	3,07 ± 0,22**	2,69 ± 0,29*
Deviation, %		+41,4	+24,8	+12,6

N o t e s : * p > 0,5; ** p < 0,01; *** p < 0,001.

We studied the silystrong effects on the brain cells apoptosis and neurons pacemaker activity in the experiment with animals. The TUNEL-positive cells level was less than 2 % in the control group of animals. We registered 4 times increasing cells level in the group of animals with acute ischemia. The percentage of apoptotic cells to the total number increased from 3,4 ± 0,46 % after 24 hours after the start of the experiment to 8,1 ± 0,73 % on the 7th days after surgery. We registered the lower level of apoptosis in the group of animals with ischemia giving the silitrong to the animals. The number of TUNEL-positive cells remained stable, not exceeding the limit throughout the experiment (Table 4) [20, 59].

In our opinion, flavolignans may act as a source of protons, which are essential for the normal functioning of the mitochondria respiratory chain and the processes of energy saving. Hence, these allow them to maintain the apoptosis at the physiological level.

The results of the study indicated the possibility of silystrong to influence various biochemical and physiological processes, into the nerve cell in particular. Next, we tried to discover the mechanisms of silystrong effect on the group neurons activity and to clarify the role of the drug in the electrophysiological processes of interaction. The task was solved with simulation of neuronal centers activities in vitro. We investigated spontaneous electrical activity with pontobulbospinal and bulbospinal preparations of newborn rats perfused with artificial CSF with the addition of silistrong. It was established that the introduction of milk thistle hydroalcoholic to the bulbospinal preparation caused the increasing pacemaker activity of the respiratory center [60]. Silystrong obviously affects the changes in action potential of the membrane receptors activating respiratory pacemaker due to the membranotropic properties and the ability to regulate the permeability of cell membranes.

This researches revealed the mechanisms of silystrong neurotropic action, which may explain the effectiveness in asthenic syndrome [61], it can be used as a reserved drug on the practice of disaster medicine and emergency situations (patent № 56880 from 05.04.2011 “lifeline”).

It should be noted that we used as a standard experimental model at each stage of the study, we have developed the methodology of the experiments that allowed us to assess the biological effects of the studied compounds. The success in proteomics, metabolomics, genomics, and progress in high-tech methods provided us a detailed study of the proteins structural organization. The key elements in the implementation of the functions of the body are protein-protein interactions, their alteration can lead to the chain of pathological conditions [62–66]. For the first time ss a model for studying protein-protein interactions, assessment of the dynamics in intact conditions and under the influence of biologically active substances we used the antigens and antibodies of the AB0 blood group system and the drug silystrong as abiological probe. This approach was chosen to detect group-specific features of intermolecular interactions of glycoproteins and erythrocytes, differing in chemical structure [67, 68], with natural and monoclonal antibodies. This determined not only the group AB0 blood group, but also the differences of individual response to various stimules.

It was shown that the primary target for silystrong was a glycoprotein A. The drug slowed down the recognition and interaction of the antigen with the antibody, prolonged the time of agglutination occurrence on 75,0 %. This effect was not revealed for the glycoprotein

Table 4

The percentage of TUNEL-positive cells in brain tissue of rats under the condition of acute ischemia with the introduction of silystrong (for 100 % accepted the total number of cells in the tissue sample)

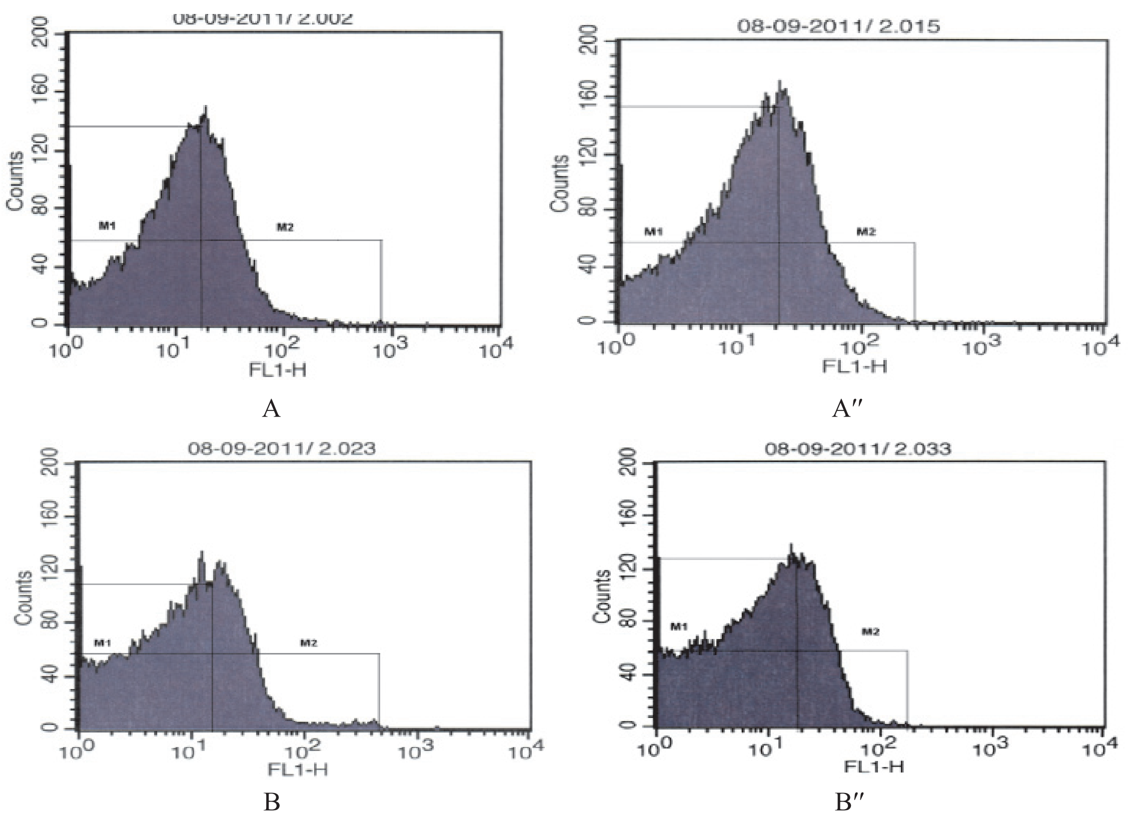
Animal groups	After 24 hours	After 48 hours	After 168 hours
Control	2,0 ± 0,087	1,9 ± 0,056	2,0 ± 0,088
Without silystrong	3,4 ± 0,46*	6,5 ± 0,51*	8,1 ± 0,73*
With silystrong	2,0 ± 0,053	1,0 ± 0,034	2,6 ± 0,081

Note: * P < 0,01.

B. Monoclonal anti-A and anti-B antibodies were modified by silistrong, which increased the protein-protein interaction with the respective antigens. In the experiment with natural antibodies revealed a reduced capacity for agglutination anti-B antibodies in 70 %, indicating a high sensitivity of the antigen-antibody system for A(II) blood group. The agglutinating capacity of anti-A-antibodies decreased by 16,0 %, indicating a smaller reaction to external stimules the antigen-antibody system of B (III) blood group. The results revealed the molecular basis of interaction with various pathogens, toxicants, leading to high morbidity for A(II) blood groups in comparison with B(III) blood group [69–71].

Visualization of antigen-antibody complexes using flow-cytometry and confocal laser scanning microscopy with labelled monoclonal antibodies discovered the differences in A and B antigens. Silystrong caused increasing the number of antigen-antibody complexes formed by glycoprotein and A monoclonal anti-A-antibody, the number of antigen-antibody complexes with the glycoprotein B remained stable (Figure).

The obtained results allowed to higlight both theoretical and practical importance in various areas of scientific research. Firstly, silyistrong can modify protein-protein interactions, hence, it can be a metabolic probe for studying these interactions. Secondly, we developed the molecular model of antigen-antibody interaction which can be used in testing a wide range of substances with biological and pharmacological activity ("Way of effect assessing of biologically active substances on antigen-antibody interaction" [72]. Thirdly, the differences in reactions with glycoproteins A and B to external stimules revealed a necesserity of population screening for the blood group affiliation, focusing on the people with A (II) blood group, as they form high-risk groups and are needed to perform personalized prevention. We developed the model rendered a qualitative and



Visualization of the antigen-antibody interaction using flow-cytometry:
Glycoprotein A – antibody complex (control); A′. Glycoprotein
A – antibody Complex (silystrong incubation); B. Glycoprotein B – antibody complex (control);
B′ – Glycoprotein B – antibody complex (silystrong incubation)

quantitative assessment of protein-protein interaction, it is a target for the intermolecular interaction, determining the characteristics of the individual response to the action of biologically active substances, drugs, various xenobiotics, toxicants.

Thus, as a result of this research studyng the composition and properties of milk thistle carried out by our team, as well as experimental and clinical substantiation of drugs using created on its basis and the molecular mechanisms of the biological activity implementation of Natursil and Silystrong components in various levels of structural and functional organization, we can recommended them as drugs for targeted metabolic correction and as ecoprotectors with wide spectrum of activities, maintaining a good quality health level.

P.S. Looking trought this article, turning back 20 years ago, when the idea and the ways of its realization only arose, when we were making the first steps to understanding the phenomenon of milk thistle – only now you feel how much has been done and how much still can be done. The desire to reveal the pages of the secrets of nature, carefully planned experiments, daily painstaking work of scientists allowed to touch the truth, to keep the accumulated time of knowledge, to see the unknown, to understand the essence. All the amazing is very close, all the the interesting is ahead…

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