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Diabetes Mellitus Type 2: A New Sour-Milk Product for Prevention and Treatment

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Abstract— *Based on camel milk, a new multicomponent, specialized fermented dairy bio-product "Inulakt-Fito" was developed for the prevention and treatment of type 2 diabetes mellitus. Its expressed hypoglycemic, antioxidant effect was established in experimental alloxan diabetes.*

Keywords— sour-milk bioproduct, diabetes mellitus, antioxidant protection.

I. INTRODUCTION

Disease of diabetes is one of the most serious in modern endocrinology. According to ethnoecological research, type 2 diabetes mellitus at the early stages can be cured completely with the help of phytotherapeutic drugs (Ashcroft F.M. and Rorsman P., 2004, Abdel-Zaher A.O. et al., 2005, Andrade-Cetto A. et al., 2005, Eidi A. et al., 2006). Now several hundred food and medicinal plants are known that can reduce blood glucose levels (Esmaeili M.A. and Yazdanparast R., 2004, Arambewela L.S. et al., 2005, El-Demerdash F.M. et al., 2005). However, the mechanism of the sugar-reducing effect of medicinal plants has not yet been elucidated (Johnson L. et al., 2006). One of the reasons for the complexity of managing patients with diabetes mellitus is the unsatisfactory correction of high glucose in the blood with exogenous insulin and other antidiabetic drugs, which requires finding additional ways to optimize the level of glycemia (Knowler W.C. et al., 2002, Ashcroft F.M. and Rorsman P., 2004, Wild S. et al., 2006). For this purpose, not only medicines are often used, but also various natural compounds for which the effect on carbohydrate metabolism is shown. The huge variety of plant material, the need to take into account its complex effects, the individual approach to the state of health of a diabetic person, the presence of possible contraindications or complications - all this requires careful testing first in model experiments. So, it is extremely important to search for and preclinical trials of plant material with subsequent clinical studies to create valid recommendations for the pharmacological industry.

In sour-milk products, many of the nutrients of milk become more accessible: so proteolytic enzymes of milk microflora, partially break down proteins, which increases the completeness and speed of their assimilation (Mal G. et al., 2007, Shabo Y. et al., 2008, Abbas S, et al., 2013). Whey milk proteins of camel milk are considered biologically active substances and some of them possess anti-carcinogenic, antioxidant and immunostimulating properties (Al Haj O.A. et al.,2010, Yadav A. K. et al., 2015).

The most promising direction for inclusion in the diet of sweeteners as a substitute for sugar is the use of the products of processing stevia plants (*Stevia Rebaudiana Bertoni*), a natural sweetener of non-carbohydrate nature, possessing unique therapeutic and prophylactic and improving properties.

On the basis of the foregoing, to date, relevant are: research, development and creation of a new sour-milk biopreparation, in combination with medicinal extracts, which in the future is a unique therapeutic and prophylactic biopreparation that have no analogues in the world's dairy and pharmaceutical industries.

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II. MATERIAL AND METHODS

The experiment was performed on sexually mature rats weighing 180-210 g. of both sexes, grown in a vivarium with a standard diet at the Scientific Research Institute of Fundamental and Applied Medicine named after B. Atchabarov of the Kazakh National Medical University named after S.D. Asfendiyarov. Control animals were grown under the usual diet regime, without the administration of alloxan. The maintenance, care of animals and deducing of them from experiment were carried out according to (Frode T.S. and Medeiros Y.S., 2008).

Induction of diabetes in the animals studied was caused by intraperitoneal injection of a 5% solution of alloxan monohydrate (AL) at a rate of 100 mg / kg of the animal's weight in a 0.9% solution of NaCl (Methodical recommendations, 1986). All laboratory animals were

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previously starved for 24 hours, while access to water was not restricted. The Inulakt-Fito sour milk product was injected intragastrically at the experimental therapeutic dose of 1000 mg / kg once a day throughout the experiment. The indices of the group of animals receiving the Inulakt-Fito bio-product were compared to the group of animals treated with metformin at a dose of 500 mg / kg. The studies were performed 7, 14 and 28 days after the start of alloxan administration. The level of glucose in the blood was determined by the Bionime Rightest GM300. Also in the blood serum standard biochemical methods were used to study lipid and nitrogen metabolism using a set of Lahema reagents (Czech Republic). Catalase activity was determined according to a previously reported method(Abei H., 1974, Qujeq D. and Rezvani T., 2007.), the content of malonic dialdehyde in blood serum - according to the method (Kuntz E. and Kuntz H.D., 2006)

The statistical processing of the results was carried out using the computer program SPSS (Statistical Package for the Social Sciences).

III. RESULTS AND DISCUSSION

It is known that in the pathogenesis of diabetes mellitus one of the key links is the activation of processes of free radical oxidation: an imbalance occurs between pro-oxidants and antioxidants, leading to an excess of free radicals and the accumulation of products of free radical oxidation. The constant background of impaired prooxidant-antioxidant balance in the body in diabetes mellitus is one of the causes of death of pancreatic ß-cells and structural functional units of other organs, which causes the development of multiple organ dysfunction (Zhao Y.F. et al., 2005, Masiello, P., 2006). The mechanism of diabetic action of alloxan is also associated with its damaging effect through the formation of free radicals. In particular, it was shown that alloxane deposited in ß-cells due to its interaction with zinc generates the formation of O2-, OH-, H_2O_2. Formed free radicals and peroxide enter into a chain reaction of interaction with molecules of fatty acids of cell membranes, destroying them (Federiuk, I.F. et al., 2004) . The natural consequence of the decrease in the physiological action of insulin, due to its deficiency due to the destruction of a large number of β-cells of the pancreas, is hyperglycemia(*Table 1*).

Table.1: Influence of Inulakt-Fito on biochemical blood indices in alloxan diabetes in experimental rats

Indicators	**Groups of animals (n = 36)**			
	Intact	Control (Alloxan)	Experimental 1 (Alloxan + nulakt-Fito)	Experimental 2 (alloxan+ metformin)
7th day				
Glucose, mM / l	6,01 ± 0,33	9,63 ± 0,10	6,81 ± 0,58*	7,52 ± 0,09*
ALT, mE/ L	131,3 ±42,5	191,1±79 ,2	162,4±12 ,6 *	170,0±30,2 *
АСТ, мЕ/л	618,5 ±179, 0	1076,6±4 46,5	915,1±10 2,3*	936,6±93,2 *
Cholesterol, mM / l	0,63± 0,03	2,73±0,1 4	1,43±0,1 6*	1,45±0,06*
Urea, mM/ l	4,43± 0,07	12,63±1, 09	7,91±0,6 5*	6,92±0,68*
Creatinine, mmol / l	73,15 ± 1,22	173,27±9 ,50	129,02±5 ,20*	113,17±7,4 5*
14th day				
Glucose, mM / l	6,01 ± 0,33	12,40 ± 0,14	8,06 ± 0,08*	9,92 ± 0,09*
ALT, mE/ L	131,3 ±42,5	175,2±69 ,6	142,9±11 ,2*	154,7±29,3 *
АСТ, мЕ/л	618,5 ±179, 0	966,0±44 4,6	814,4±98 ,6*	852,3±86,1 *
Cholesterol, mM / l	0,63± 0,03	2,36±,25	1,38±0,1 1*	1,30±0,2*
Urea, mM/ l	4,43± 0,07	10,65±1, 7	5,42±0,7 *	4,53±0,36*
Creatinine, mmol / l	73,15 ± 1,22	149,35±7 ,60	86,36±4, 83*	92,6±5,3*
28th day				
Glucose, mM / l	6,48± 0,64	21,9 ± 0,22	9,85 ± 0,10*	13,9 ± 0,14*
ALT, mE/ L	131,3 ±42,5	171,3±10 0,3	132,8±9, 6*	143,8±22,9 *
АСТ, мЕ/л	618,5 ±179, 0	778,6±37 5,9	757,3±80 ,6*	770,1±92,3 *
Cholesterol, mM / l	0,63± 0,03	1,99± 0,67	1,13± 0,08*	1,15± 0,13*
Urea, mM/ l	4,43± 0,07	8,90± 0,53	3,18± 0,18*	3,56± 0,15*
Creatinine, mmol / l	73,15 ± 1,22	130,16± 8,50	77,60± 4,12*	83,80± 4,50*
NOTE - * Hereinafter, the difference is significant compared to the control group at P≤ 0.05				

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The administration of alloxan to rats is accompanied by a significant increase in the level of glucose in the blood, an increase in the cholesterol, creatinine and urea in the blood serum, which indicates a violation of carbohydrate and lipid metabolism, as well as a decrease in the functional state of the liver and kidneys.

Course introduction of rats with alloxan diabetes "Inulakt-Fito" was accompanied by normalization of carbohydrate metabolism. In particular, by the 7th day of observation, the blood glucose content under the effect of the tested bioproduct decreased by 41%, serum cholesterol concentration was reduced by 90%, urea by 59%, creatinine by 34%, alanine aminotransferase (ALT) - by 15%, aspartate aminotransferase (AST) - by 15%. By the 14th day of observation, the tendency towards normalization of biochemical parameters of blood persisted. Thus, the glucose level in the blood decreased compared to the parameters in the control by 23%. By the 28th day of observation, the blood glucose content under the action of the tested bioproduct was 41% lower than in the control group, and normalization of lipid and nitrogen metabolism was also observed in experimental diabetes mellitus in rats. The drug metformin also had a beneficial effect on the course of alloxan diabetes, but in a less pronounced degree than Inulakt-Fito.

Table 2 presents data characterizing the influence of Inulakt-Fito on the state of lipid peroxidation (LPO) indices and antioxidant protection in conditions of damage to the pancreas. As can be seen from *Table 2*, the introduction of this diabetogen has caused the development of "oxidative stress", characterized by an increase in the intensity of LPO, as evidenced by a significant increase in the level of malonic dialdehyde (MDA) and a decrease in the activity of antioxidant protection - there was a significant inhibition of catalase activity.

Thus, with alloxan diabetes in experimental rats on the 7th day in serum, the content of malonic dialdehyde is significantly increased 2.8 times, in the pancreas 56%. By the 14th day after the administration of alloxan, the content of lipid peroxidation products in blood of animals with alloxan diabetes increased, the content of malonic dialdehyde was 3.1 times, in the pancreas - by 78%. By 28 days with alloxan diabetes, respectively, quadrupled by 60% compared with the indices in animals of the intact group. Along with the activation of lipid peroxidation processes in alloxan diabetes in rats, the antioxidant defense of the organism decreases. In particular, reduced catalase activity of blood serum in animals of the control group by the 7th day of observation is 1.5 times, by the 14th day - by 1.7 times, by 28 days by 2.2 times. The application of Inulakt-Fito resulted in a significant improvement in the state of all the studied indicators. In particular, the MDA content in the blood serum decreased by 1.8 times in 7 days compared to the control. After 14 days, -58%, 28 days after the start of alloxan administration to rats in the blood serum, the MDA content was 72% higher than in the animals in the control group. The same regularity was noted in the evaluation of data on the content of lipid peroxidation products in the pancreas.

Table.2: Influence of Inulakt-Fito on LPO processes and blood catalase activity in alloxan diabetes in experimental rats

Indicators	**Groups of animals (n = 36)**			
	Intact	Control (Alloxan)	Experimental 1 (Alloxan + Inulakt-Fito)	Experimental 2 (alloxan + metformin)
7 th day				
MDA in serum, µM / ml min	2,35 ± 0,10	6,72 ± 0,33	4,52 ± 0,52*	5,72 ± 0,48*
MDA in the pancreas, nM / g	5,53 ± 0,60	8,62 ± 0,80	6,00 ± 0,60*	7,20 ± 0,20*
Catalase, mcd / l	21,32 ± 2,01	14,00 ± 1,32	18,2 ± 1,81*	16,52 ± 1,63*
14 th day				
MDA in serum, µM / ml min	3,27 ± 0,15	10,28 ± 0,11	3,95 ± 0,55*	4,92 ± 0,65*
MDA in the pancreas, nM / g	5,53 ± 0,60	9,85 ± 0,10	8,00 ± 0,80*	8,85 ± 0,90*
Catalase, mcd / l	21,32 ± 2,01	12,01 ± 0,80	18,62 ± 1,81*	15,41 ± 1,54*
28 th day				
MDA in serum, µM / ml min	3,85 ± 0,40	15,4 ± 0,16	4,86 ± 0,50*	7,47 ± 0,75*
MDA in the pancreas	5,55 ±	8,90 ± 0,90	6,02 ± 0,60*	7,80 ± 0,80*

, nM / g	0,60			
Catalase , mcd / l	2 1,35 ± 2,01	9,6 ± 0,85	17,08 ± 0,2*	13,2 ± 0,13*
NOTE - * Hereinafter, the difference is significant compared to the control group at P≤ 0.05				

When the animals were injected with Inulakt-Fito, the activity of blood catalase increased according to the observation periods by 35, 55 and 78%, as compared to the values in the control. The metformin comparison drug also inhibited lipid peroxidation processes, but to a lesser extent.

IV. CONCLUSION

As a result of studies on the basis of shubat (camel milk) in combination with 5 sugar-reducing medicinal extracts, a new multi-component, specialized fermented dairy bio-product "Inulakt-Fito" (conditional name) was designed for the prevention and treatment of type 2 diabetes mellitus. The pharmacotherapeutic effect of Inulakt-Fito on the parameters characterizing the course of experimental diabetes was established. This is due to its hypoglycemic and antioxidant properties and depends on the complex effects of its biologically active substances. The data obtained make it possible to consider the use of Inulakt-Fito in the complex treatment of type 2 diabetes.

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