



Clinical Assessment of the use of Sublimated Mare's Milk in Complex Therapy of Mild and Moderate Psoriasis

Togzhan Algazina¹, Alexandr Gulyayev², Alma Aimoldina¹, Almagul Kushugulova², Bakytgul Yermekbayeva^{3*}

¹Non-Profit Joint-Stock Company "Medical University of Astana".

²Nazarbayev University "National Laboratory Astana".

³Corporate Fund "University Medical Center".

*Corresponding Author: Bakytgul Yermekbayeva

Abstract

The article discusses the therapeutic effect of mare's milk in complex treatment in patients with psoriasis. Research objective: Clinical assessment of the use of sublimated mare's milk in complex therapy of mild and moderate psoriasis. Materials and methods: 20 patients in main group with mild and moderate psoriasis took part in the study - control, who during 12 weeks of standard therapy took sublimated mare's milk and 20 comparison group patients on standard therapy. In the study participants in main group, the severity index of psoriasis course and spread (PASI) was calculated at 0 and 12 weeks. Results: A statistically significant decrease in the PASI index was found: after 6 weeks by 68%, with treatment within 12 weeks - by 88% ($p = 0.0003$) in the main group compared with the comparison group. Conclusions: in patients with psoriasis, it is necessary to include sublimated mare's milk in the complex treatment to increase the effectiveness of therapy and lengthen the period of remission.

Keywords: *Psoriasis, PASI index, Sublimated mare's milk.*

Introduction

Psoriasis is one of the most common dermatoses, the frequency of which varies widely in different countries [1]. According to the world health organization, the prevalence of psoriasis in the world is about 2%. However, according to a number of studies, in developed countries, the indicator is much higher and can vary from 4.6 to 7% [2].

In the United States, the prevalence of psoriasis is from 0.5 to 1.5%, in Russia – 1-2%. According to official statistics in the Republic of Kazakhstan, psoriasis takes the third place in the structure of dermatoses, giving the lead to eczema, allergic skin diseases associated with this disease and mycoses. Moreover, the majority of patients with a diagnosis established for the first time in their life are people aged 16 to 30 years. Psoriasis is an important medical and social problem due to the chronic recurrent nature of the disease, high comorbidity with other diseases, insufficient effectiveness of therapy,

development of musculoskeletal injury and possible subsequent disability, which significantly reduces the quality of life of patients with psoriasis [3, 4]. The problem is exacerbated by the fact that today the vast majority of patients (up to 78%) are not satisfied with the level of treatment of psoriasis, which is due to intolerance and high cost of medicines, and in some cases - insufficient effectiveness [5].

Currently, the search for the causes and mechanisms of the disease is continuing in order to develop more effective methods of its treatment and prevention. In this connection, the use of sublimated mare milk is of great interest, which activity has been proven in relation to the correction of the composition of the intestinal microbiome associated with the serum fraction of mare's milk. Mare's milk contains about 40 biological components necessary for the human body: amino acids, fats, enzymes (lysozyme, amylase),

microelements (calcium, sodium, potassium, phosphorus, iron, magnesium, copper, iodine, sulfur, cobalt, zinc, bromine) and vitamins (A, C, B1, B2, B6, B12, E, H, PP, beta-carotene, folic acid...) in optimally balanced proportions [6]. Sublimated mare's milk is characterized by a large amount of lactose (72.80 g / l, 0.03 s) and a reduced fat content (6.40 g / l; 0.4 s.d.), as well as proteins (caseins) (15.52 g / l, 0.11 s), especially caseins (13.4 g / l, 0.04 s) [7].

Mare's milk by its composition belongs to the albumin group. At the same time, milk of other pets (except donkeys) belongs to casein group. Albumin and casein are types of proteins that give milk a characteristic white color [8]. Albumin, like the main globulin of maternal milk, is a finely divided (whey) protein and is easier to digest. Mare's milk also contains about 50% casein and about 39% whey protein, while cow's milk contains about 80% casein. [9].

The mineral composition of sublimated mare's milk is very close to maternal milk [10]. Sublimated mare's milk contains amino acids that are important for our body, such as tryptophan, tyrosine and casein. The fat found in sublimated mare's milk is the best animal fat in nature. Due to the specific highly dispersed structure, it is emulsified as quickly as possible (split) and absorbed. A large percentage of all fats consist of polyunsaturated fatty acids omega-3 and 6 [9, 10].

Upon digestion, sublimated mare's milk proteins release bioactive peptides with many different properties. These include blood pressure regulators, antimicrobial and anti-inflammatory peptides [11, 12]. Research objective- to evaluate clinical effect of sublimated mare milk in complex treatment of patients with mild and moderate psoriasis.

Materials and Methods

This research was carried out as part of a scientific project Individual registration number No. AP05135585 "Development of auxiliary methods of psoriasis therapy depending on the structure of the microbiome" of the Science Committee of the

Ministry of Science and Education of the Republic of Kazakhstan; registration on the website ClinicalTrials.gov, NCT03594877.

Permission for conduction of this research was obtained from the local ethics committee. The study included 40 patients with mild and moderate psoriasis in the progressive stage, whose average age was 34.95±4.11 years. All patients were divided into 2 groups: group 1 (main) consisted of 20 patients who received comprehensive treatment, including sublimated mare milk; the 2nd group (comparison group) of 20 people received standard therapy.

Sublimated mare's milk for research was obtained from Eurasia Invest Ltd (Karaganda, Kazakhstan), which produces the product under laboratory control at all stages of production: sublimation is carried out at a temperature of - 50°C degrees immediately after milking the mares, then it is dried at a temperature of + 30°C degrees and packaged in sterile jars - thanks to this, all the useful components of fresh natural mare's milk are preserved. Product tested in Hong Kong by Faitheul Wise International Limited No. Hkgfd 1900484300 dated July 17, 2019.

As part of the study after the initial examination all patients with psoriasis received standard treatment for mild to moderate severity of the disease for 14-21 days according to the clinical Protocol of the Republic of Kazakhstan: desensitizing, antihistamines, local corticosteroids of medium and strong action, zinc pyrithione, calcioptriol, emollients, salicylic ointment and Ultraviolet irradiation. 20 patients of the main group received sublimated mare's milk for 60 grams per day for 12 weeks.

This dose was used according to calculations described in A. Zhangabylov 's monograph [13]. The effectiveness of treatment was judged by the dynamics of the psoriasis area severity index (PASI index) at the 6th and 12th weeks of treatment. The obtained PASI values were interpreted using the gradation shown in Table 1.

Table 1: Gradations of the PASI index value

Graduation, points	Severity of psoriasis
0-10	mild course
11-30	moderate severity of the process

Moreover, patients were monitored out-patient for 6 months after treatment. Statistical processing of the material was carried out using non-parametric statistics methods. Validity of the identified differences between groups was evaluated by the Mann-Whitney criterion, the differences were considered to be valid at $p < 0.05$. The relationship between the studied parameters was evaluated using Spearman's rank correlation coefficient. Statistical processing was performed using the STATISTICA 6.0 program.

Results

As part of our study, in order to study the composition of the subjects, we conducted a clinical examination of group 1 patients with psoriasis (n=20) of mild and moderate severity. In order to analyze in more detail, the factors associated with the development

of psoriasis in the main group, we additionally studied a number of anamnestic and clinical-morphological data: the presence of burdened heredity for psoriasis, the manifestation and duration of the disease, the clinical form of psoriasis.

As a result of the analysis of anamnesis data in patients with psoriasis, it was found that the majority of them (13 patients) do not confirm the burden of family history for this disease, which is consistent with the data of world studies [14]. In the rest of the patients, the inheritance of psoriasis was as follows: in 4 cases the family psoriatic history is observed by paternal line, in 2 people - by maternal line and, finally, in 1 patient the transmission of psoriatic genes was observed from both father and mother. Summary data on the family history of patients with psoriasis are graphically presented in Figure 1.

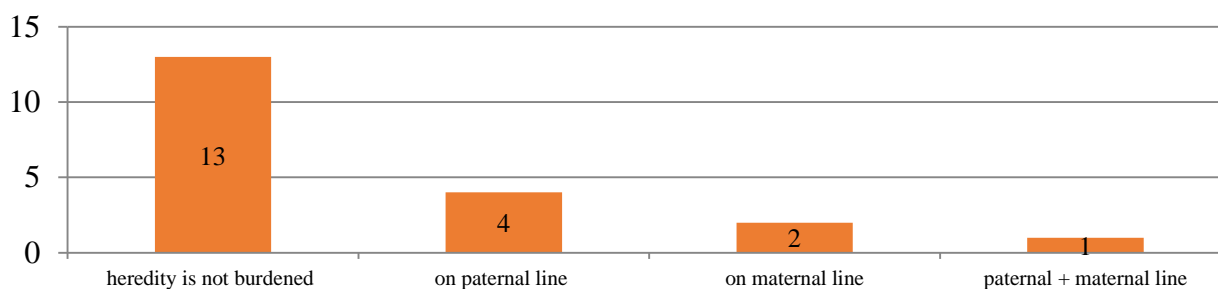


Figure 1: Graphical presentation of family history analysis results in patients with psoriasis

Regarding the length of psoriasis, it should be noted that no one newly diagnosed case of psoriasis was included in the study. The duration of the disease in the vast majority (80% - 16 people) exceeded 5 years, including

45.0% (9) of respondents, the duration of the disease varied from 5 to 10 years, in 35.0% (7) cases the first signs of psoriasis appeared more than 10 years ago, and in 20.0% the duration of the disease did not exceed 2 years (Figure 2).

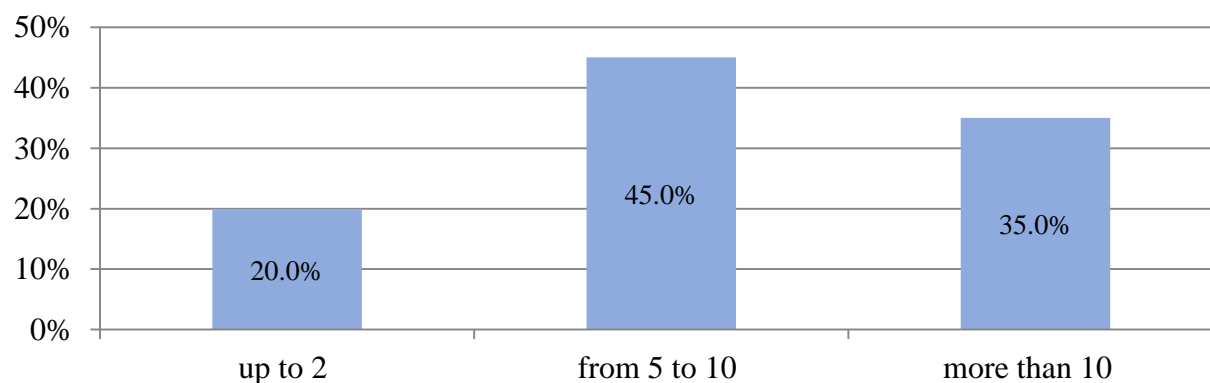


Figure 2: Graphical presentation of psoriasis disease duration analysis results

Observations of clinical forms of psoriasis revealed that the frequency of detection was led by the numular form of rashes (45.1%),

followed by large plaque (27.9%) and guttate (17.1%) forms, and the least frequent was the palmoplantar form (9.9%) (Figure 3).

RESEARCH ARTICLE

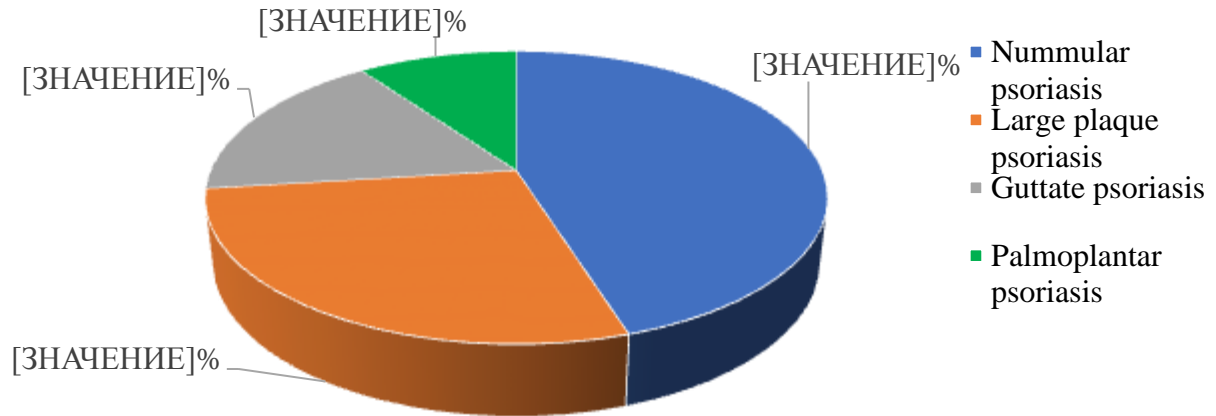


Figure 3: Graphical representation of the results of analysis of the frequency of various forms of psoriasis in patients of the main group

Note that these data are consistent with the distribution of frequency of occurrence of different forms of psoriasis in a similar age group described in literature [14]. When analyzing the severity index of psoriasis (PASI index), it was found that this indicator varied from 3.5 to 29.5 points and averaged 12.7 ± 6.73 points, which corresponds to the

moderate severity of the process. When distributing patients according to the severity of psoriasis, depending on the PASI score, a low score corresponding to the mild course was found in 35.0% (7) cases, and a median score corresponding to the moderate severity of psoriasis was found in 65.0% (13) patients, i.e. almost twice as often (Figure 4).

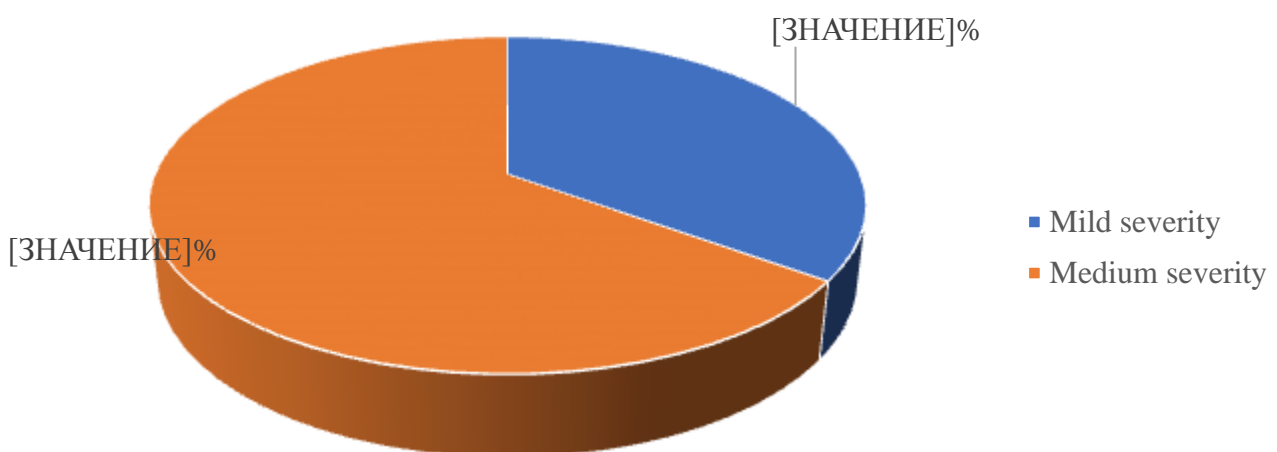


Figure 4: Graphical representation of PASI index distribution analysis results

The assessment of the effectiveness of including mare's milk in standard therapy for psoriasis was carried out taking into account the dynamics of the dermatological status at the 6th and 12th weeks of treatment: a

decrease in the PASI index by 68% and by 88% ($p = 0,0003$), respectively, in group 1 (Table 2). In the comparison group, these indicators were 55% and 73% ($p = 0.002$), respectively (Table 3).

RESEARCH ARTICLE

Table 2: PASI index disease dynamics in group 1 patients with mare's milk included in standard therapy

Course of the disease	Indicator	The first week	The sixth week	The twelfth week	p
Mild course	Erythema	5±0,23	2±0,23*	0	0,02
	Infiltration	4±0,15	1±0,14*	0	0,04
	Peeling	1±0,16	0	0	0,07
	Overall PASI index dynamics	10±0,62	3,52±0,7*	0	0,01
Moderate course	Erythema	12±0,42	7±0,21*	3,05±0,5*	0,03
	Infiltration	9±0,31	4±0,15*	0	0,02
	Peeling	8±0,12	1±0,17*	0	0,01
	Overall PASI index dynamics	29,51±0,7	12,5±0,7*	3,05±0,5*	0,04

Table 3: Dynamics of the disease course according to the PASI index in group 2 patients who received standard therapy

Course of the disease	Indicator	The first week	The sixth week	The twelfth week	p
		Group 2	Group 2	Group 2	
Mild course	Erythema	4±0,17	1,9±0,31	1,2±0,3	0,07
	Infiltration	4±0,1	2,0±0,1	1,1±0,15	0,05
	Peeling	1±0,12	0,6±0,02	0,4±0,2	0,17
	Overall PASI index dynamics	10±0,39	4,5±0,8	2,7±0,4*	0,03
Moderate course	Erythema	12±0,35	5,4±0,21	3,3±0,28	0,06
	Infiltration	9±0,37	4,0±0,1	2,4±0,41	0,08
	Peeling	8±0,11	3,6±0,19	2,1±0,1	0,06
	Overall PASI index dynamics	29 ±0,83	13,1±,05	7,8 ±0,65*	0,03

In general, the decrease in the total PASI index against the background of complex therapy using sublimated baby milk at mild severity of psoriasis ranged from 10 ± 0.62 to 0, with moderate severity ranging from 29, 51 ± 0.7 to 3, 05 ± 0.5. Significantly decreased the severity of the individual

components of the psoriatic process (erythema, infiltration and peeling). The comparison group also showed positive dynamics: a decrease in the overall PASI index from 10 ± 0.39 to 2.7 ± 0.4 for mild cases, and from 29 ± 0.83 to 7.8 ± 0.65 for moderate psoriasis (Figure 5).

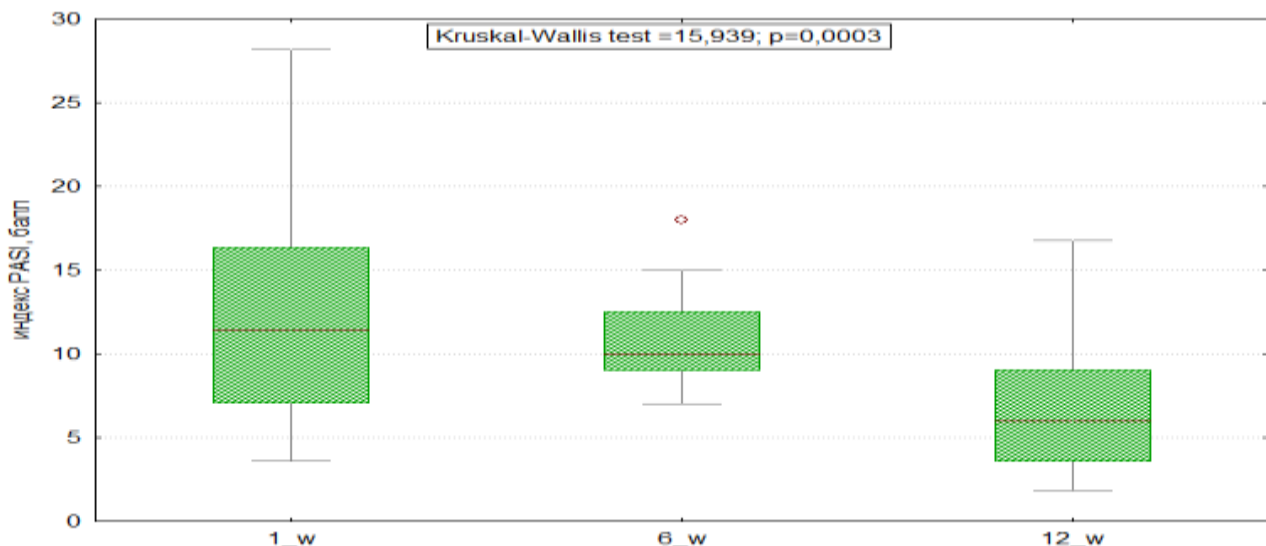


Figure 5: Graphical representation of the dynamics of the PASI index under the influence of complex therapy

The analysis showed that in patients with psoriasis in the 1st and 2nd groups, the therapeutic effect of different degree of expression was obtained as a result of treatment. However, it should be noted that in patients of the 1st group, the regression of rashes began at an earlier date, and the decrease in the PASI index (in the range of 68-88%) was higher compared with the 2nd group. This indicates the effectiveness of the complex therapy with the inclusion of a product based on mare's milk.

Discussion

Scientific evidence suggests the need for new treatments for psoriasis that combine high efficacy and safety. In this regard, it seems to us very promising to use sublimated mare's milk in the complex of therapy. Sublimated mare's milk is a valuable raw material and a very attractive product for solving the allergy to cow's milk, since sublimated mare's milk is highly similar to the properties, components and fractions of human breast milk. The distribution of di- and triglycerides is equally the same in mare's milk and in breast milk. Moreover, a similar ratio of whey proteins to casein can be a good argument for choosing this milk instead of milk from other animals as a diet for humans. The rich content of whey protein in mare's milk makes it more favorable for human nutrition due to the relatively higher supply of essential amino acids [15].

Since sublimated mare milk is a large source of easily assimilable calcium and contains vitamins, antioxidants, lactoferrin and lysozyme, which are important components of the diet, strict avoidance of its use is often associated with risk and can cause food imbalance, due to its proven immunomodulating effect, as well as probiotic capabilities.

Since koumiss has antibacterial activity, it has a bactericidal and bacteriostatic effect on a number of microorganisms. Obviously, the antibacterial properties of sublimated mare milk are provided by a high content of functional proteins such as lysozyme and lactoferrin. Lactoferrin has anticarcinogenic, antiviral, antibacterial, immunostimulating properties.

It should be noted that the content of lactoferrin in the mare's milk is intermediate between the lower values of cow's milk and high values of breast milk. In the latter, on the contrary, there is a lower lysozyme content than in mare's milk [16]. This also attracts attention in terms of the use of sublimated mare's milk in the treatment of psoriasis, given the autoimmune theory of its development.

It is generally recognized that milk is an optimized nutritional and signaling system for nutritional regulation during lactation. Milk plays an exceptional role at the beginning of mammalian life and performs its biological function by providing a kind of software in the form of exosomal microRNA that activates and supports the so - called "rapamycin complex"-mTORC1-dependent translation and other mTORC1-mediated anabolic effects during postnatal growth and postnatal metabolic programming [17].

The physiological and / or therapeutic potential of milk outside the neonatal period is a controversial, widely discussed problem related to the effect on the mTOR system and mediated on the immune system [18, 19]. The immunomodulatory properties of mare's milk are well documented. Under experimental conditions, it was found that the introduction of mare's milk led to an increase in the regulatory T-cell population (CD4 + Foxp3 +), decreased IL-4 mRNA levels and led to higher TLR-4 transcripts in all treatment groups; however, the levels of MCP-1, TNF- α , and TLR-2 did not change [20]. Some authors found an increase in the immune response and nonspecific resistance in a group of experimental animals fed a mare's milk diet [21].

Thus, the therapeutic shifts associated with the intake of sublimated mare's milk by psoriasis patients and expressed in a decrease in psoriatic activity and a decrease in the severity of the process described by us in this study, we tend to associate with the intervention of biologically active components of mare's milk in the autoimmune mechanisms of the pathogenesis of psoriasis. Naturally, further, more carefully planned clinical studies of this position are necessary.

Quite a little is known about the therapeutic phenomenon of mare's milk, and the evidence is sporadic. The biological significance of the mare's milk processing product-koumiss - has been studied much more. Thus, in the works of Kazakh scientist Akhmetova N. M. (2007), it was shown that the use of natural koumiss (fermented milk drink from Mare's milk) has an immunocorrective effect in the form of normalization of subpopulation imbalance of T-lymphocytes with a significant increase in CD3, CD4, immunoregulatory index, and a decrease in CD8. Scientists from in their studies, they revealed the dynamics of immunological parameters against the background of koumiss treatment, – it turned out that the drink helps to normalize the level of immunoglobulins, circulating immune cells, stabilize the cytokine status, which indicates its immunomodulatory properties.

The immunomodulating, anti-inflammatory and antioxidant effects of koumiss have been demonstrated in a number of other works [22, 23]. Furthermore, *Lactobacillus casei* microorganisms were isolated by Chinese scientists from koumiss. Experiments conducted in vivo showed that lactobacilli administered orally to mice increased immunity by increasing the production of immunoglobulin (IgA), interleukin-2 (IL-2), and u-interferon (IFN- γ) in the blood serum and induced intestinal fluid of mice [25, 25].

Moreover, koumiss lactobacillus and in vitro experiments showed immunomodulatory effects. Thus, it was shown that *Lactobacillus casei* affected the expression of cytokines and toll-like receptors (TLR) in macrophages. It was also proved that live lactobacilli promote

the production of nitric oxide (NO), tumor necrosis factor (TNF- α), interleukin-6 (IL-6) [26].

Currently sublimated mare's milk serves as the basis for the production of functional, specialized food products with immunomodulating properties, for example, by sublimation of mare's milk, dry powder is made that retains 99.9% of the beneficial properties. There is information about the beneficial properties of food products based on mare's milk, manifested by a pronounced corrective effect on the immune system (an increase in the CD4 + / CD8 + index, a decrease in high B-cell values) [26]. Thereby, qualities revealed during the experiment make sublimated mare milk attractive for use in the complex treatment of psoriasis.

Conclusion

Complex therapy of psoriasis with the inclusion of sublimated mare's milk, which has a prebiotic immunomodulating effect, to the standard therapy of psoriasis, helps to achieve an earlier and more stable resolution of skin manifestations of the disease. In patients receiving mild to moderate psoriasis of sublimated mare's milk at a dose of 60 g / day for 12 weeks, a clinical effect was achieved.

There was a significant decrease in the severity of certain components of the psoriatic process-erythema, infiltration and peeling. We assume, that the addition of sublimated mare milk to standard therapy for psoriasis patients increases the clinical effectiveness of treatment.

References

- 1 Butov Yu.S., Mordovtseva V.V., Vasenova V.Yu., Shmakova A.S. Psoriasis. In the book: edited by Butov Yu.S., Skripkin Yu.K., Ivanov O.L. Dermatovenerology: national leadership. Moscow; 2013.p. 487-497.
- 2 Psoriasis http://apps.who.int/gb/ebwha/pdf_files/EB133/B133_5-ru.pdf. February 21,2019
- 3 Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol.* 2006; 55(5):829-35
- 4 Jankovic S, Raznatovic M, Marinkovic J, Maksimović N, Janković J, Djikanović B. Relevance of psychosomatic factors in psoriasis: a case-control study. *Acta Derm Venereol.* 2009; 89:364-368.
- 5 Ellis C.N, Krueger G.G. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N. Engl. J. Med.* 2001; 345:248-255.

- 6 Kushugulova A, Kozhakhmetov S, Sattybayeva R, Nurgozhina A, Ziyat A, Yadav H et al. mare's milk as a prospective functional product. *Functional Foods in Health and Disease* 2018; 8(11):537-543.
- 7 Zharykbasova K. S, Smirnova I.A., Tazabaeva E.S. and others. Improving the immunomodulating properties of koumiss with the use of plant extract from *Eminium regela*. *Technique and technology of food production* 2017; 47 (4): 106-109.
- 8 Fotschki J, Szyc AM, Laparra JM, Markiewicz LH, Wróblewska B. Immunomodulating properties of horse milk administered to mice sensitized to cow milk. *American Dairy Science Association* 2016; 99(12): 9395-9404.
- 9 Csapó J, Csapó-Kiss Z, Stefler J, Martin TG, Némethy S. Influence of Mastitis on D-Amino Acid Content of Milk. *Journal of Dairy Science* 1995; 78(11): 2375-2381.
- 10 Malacarne M, Martuzzi F, Summer A, Mariani P. Protein and fat composition of mare's milk: some nutritional remarks with reference to human and cow's milk. *International Dairy Journal*, 2002; 12:869-877.
- 11 Haddad Y, Vallerand D, Brault A Haddad PS. Antioxidant and hepatoprotective effects of silibinin in a rat model of nonalcoholic steatohepatitis. *Evidence-based complementary and alternative medicine*. Oxford University Press 2011; 35: 8-115.
- 12 Uniacke-Lowe T, Huppertz T, Patrick FF. Equine milk proteins: Chemistry, structure and nutritional significance. *International Dairy Journal* 2010; 20(9):609-629.
- 13 Zhangabylov A.K. not fermented mare's milk- healing properties. *Almaty: Dyke-Press; 2015.* Campalani E, Barker JN. *The Clinical Genetics of Psoriasis*. *Current Genomics* 2005; 6:51-60.
- 14 Paula C. Pereira Milk nutritional composition and its role in human health. *Nutrition* 2014; 30:619-627.
- 15 Salimei E, Fantuz F. Review: Equid milk for human consumption. *Int Dairy J*. 2012; 24:130-142.
- 16 Melnik BC, John SM, Schmitz G. Milk is not just food but most likely a genetic transfection system activating mTORC1 signaling for postnatal growth. *Nutr J*. 2013; 12(1):103.
- 17 Laplante M, Sabatini DM. mTOR signaling in growth control and disease. *Cell* 2012; 149(2): 274-93.
- 18 Bodo C. Melnik Milk – A Nutrient System of Mammalian Evolution Promoting mTORC1-Dependent Translation. *Int J Mol Sci*. 2015; 16(8):17048-17087.
- 19 Fotschki J, Szyc AM, Laparra JM, Markiewicz LH, Wróblewska B. Immunomodulating properties of horse milk administered to mice sensitized to cow milk. *Journal of Dairy Science* 2016; 99(12):9395-9404.
- 20 Valiev AG, Valieva TA, Valeeva GR, Speranskii VV, Levachev MM. The Effect of the Essential Fatty Acids in Mare's Milk on the Function of the Immune System and of Nonspecific Resistance in Rats. *Vopr Pitan* 1999; 68(3):3-6.
- 21 Gilmutdinova L.T., Gilmutdinov A.R., Kudayarova R.R. etc. Immunomodulating effects of koumiss treatment in the sanatorium rehabilitation of patients operated on for cholelithiasis. *Pacific Medical Journal* 2009; 3: 118-120.
- 22 Gilmutdinova L.T., Khabibrakhmanov M. M., Akhmadullin R.V. Rehabilitation and comprehensive treatment of patients in the koumiss medical sanatorium "Yumatovo". Ufa city, Humanitarian University of Trade Unions, Ufa Printing Plant; 2004.
- 23 Gilmutdinov A.R. The use of koumiss in the sanatorium rehabilitation of patients operated on for peptic ulcer. *Bulletin of Restorative Medicine* 2007; 1: 45-47.
- 24 Zhang HP, Menghebilige, Wang JG, Sun TS, Xu J, Wang LP et al. Assessment of potential probiotic properties of *Lactobacillus casei* Zhang strain isolated from traditionally home-made koumiss in Inner Mongolia of China. *China Dairy Industry* 2006; 34: 4-10.
- 25 Ya T, Zhang Q, Chu F, Merritt J, Bilige M, Sun T et al. Immunological evaluation of *Lactobacillus casei* Zhang: a newly isolated strain from koumiss in Inner Mongolia, China. *BMC Immunol*. 2008; 9:68-76.

