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Amelioration by phytoadaptogene of effects of balneofactors of Truskavets' Spa on patients with post-radiation encephalopathy

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Abstract

Background. We have previously explored effects of Ukrainian phytocomposition "Balm Truskavets'" on parameters of neuro-endocrine-immune complex and biophotonics in humans with maladaptation. It is known that in patients with post-radiation encephalopathy the reaction to some stimuli is significantly changed, therefore it needs correction. The purpose of this study is to test the ability of this phytocomposition to amelioration the effects of standard balneotherapeutic complex in patients with post-radiation encephalopathy. **Material and methods.** The research was carried out through a retrospective analysis of the database of the Truskavetsian Scientific School of Balneology, which remained unpublished. The object of observation in 1997 were 19 men and 3 women with urate urolithiasis and chronic pyelonephritis who were exposed to pathogenic factors of the accident at the Chornobylian nuclear power plant during the liquidation of its consequences in 1986-87. The survey was conducted twice: on admission and after two weeks of rehabilitation in sanatorium "Perlyna Prykarpattya" (Truskavets' Spa). 11 patients received standard balneotherapy while the other 11 patients additionally received the phytocomposition "Balm Truskavets'". According to the protocol, blood pressure, routine hematological and biochemical blood parameters were determined. In addition, physical working capacity (PWC_{150}) as well as EEG, heart rate variability (HRV) and immunity parameters were determined. **Results**. Standard balneotherapy increases the decreased level of T-helper lymphocytes, but further decreases the level of B-lymphocytes, glomerular filtration rate and PWC_{150}, in combination with increased normal levels of blood creatinine and urea, as well as decreased levels of diastolic BP and heart rate. This is accompanied by a further increase in the sympathetic tone and the leveling of the increased of ULF band HRV as marker of level in the plasma of catecholamines and glucocorticoids. Additional use of phytocomposition limits the adverse effects of standard balneotherapy by modulating EEG and HRV parameters. **Conclusion**. Phytocomposition "Balm Truskavets'" by modulating the parameters of the nervous system limits the adverse effects of standard balneotherapy at the Truskavets' Spa in patients with post-radiation encephalopathy.

Keywords: Phytocomposition "Balm Truskavets'"; Truskavets' Spa; post-radiation encephalopathy; changes in parameters of body.

INTRODUCTION

Many years of experimental and clinical research of the Truskavetsian Scientific School of Balneology have demonstrated the adaptogenic properties of the main therapeutic factor of the spa, Naftussya bioactive water, as well as ozokerite and mineral baths, which together make up a standard balneotherapeutic complex [10][21][28][29].

However, in contrast to the beneficial effect of the latter on stress resistance and the neuro-endocrine-immune complex, the effect on the physical performance of both rats and resort patients is ambiguous [10][15][16][21][35][36][37][42], which prompted the additional use of aerobic training [37][40][41] and/or phytoadaptogens, both well-known (ginseng, Bittner's balsam), and the Ukrainian phytocomposition "Balm Kryms'kyi" [10][11][15][16], the adaptogenic properties of which first discovered by representatives of the Truskavetsian Scientific School of Balneology [1][11][25].

We have previously explored effects of phytocomposition "Balm Truskavets'", which is analogous to the "Balm Kryms'kyi", on parameters of neuro-endocrine-immune complex and biophotonics in humans with maladaptation [6][7][9][32].

It is known that in patients with post-radiation encephalopathy the reaction to some stimuli is significantly changed [1][21][31], therefore it needs correction.

The purpose of this study is to test the ability of this phytocomposition to amelioration the effects of standard balneotherapeutic complex in patients with post-radiation encephalopathy.

MATERIAL AND RESEARCH METHODS

The research was carried out through a retrospective analysis of the database of the Truskavetsian Scientific School of Balneology, which remained unpublished.

Participants. The object of observation in 1997 were 19 men (age 26÷61 years) and 3 women (38, 40 and 47 years) with urate urolithiasis and chronic pyelonephritis who were exposed to pathogenic factors of the accident at the Chornobylian nuclear power plant during the liquidation of its consequences in 1986-87. According to the documents, the total effective radiation dose was 10÷25 cGy, which is most typical for this contingent [1][31]. The survey was conducted twice: on admission and after two weeks of rehabilitation in sanatorium "Perlyna Prykarpattya" of the Ministry of Internal Affairs (Truskavets' Spa). 11 patients received standard balneotherapy: bioactive Naftussya water by 3 mL/kg for 1 hour before meals three times a day; baths with mineral water (Cl^--SO_4^{2-}-Na^+-Mg^{2+} containing salt concentration 25 g/L; t^0 36-37^{0}C during 8-10 min); application of Ozokerite on the lumbar region (t^0 45^{0}C, exposure 30 min, every other day, 5 procedures); therapeutic physical exercises (motion mode II). The other 11 patients additionally received the Ukrainian phytocomposition "Balm Truskavets'" (5 ml, pre-diluted in 45 ml of boiled tap water, half an hour before meals three times a day). Balm produced by private research-production enterprise "Ukrainian Balms" (Mykolayïv, Ukraine).

Procedure / Test protocol / Skill test trial / Measure / Instruments.

According to the protocol, routine hematological (hemoglobin, erythrocytes, reticulocytes, hematocrit, erythrocyte sedimentation rate) and biochemical blood parameters: albumins, alpha-1, alpha-2, beta- and gamma-globulins, urea, uric acid, creatinine, glucose, sialic acids, alkaline phosphatase, pseudocholinesterase, amylase, alanine and aspartic transaminases, medium-weight molecules, lipids in general, high-, low-, and very-low-density lipoprotein cholesterol, diene conjugates, malondialdehyde, catalase, and erythrocyte superoxide dismutase were determined. The analyzes were carried out according to the instructions. The

analyzers “Pointe-180” ("Scientific", USA) and “Reflotron” (Boehringer Mannheim, BRD) were used with appropriate sets.

For estimation of physical working capacity (PWC) a bicycle ergometer “Tunturi” (Finland) was used. The power of the first load was 0,5 W/kg at a pedaling frequency of 60-75 rpm. The power of the second load (after 3 min), according to the recommendations for a gentle version of the PWC test, taking into account the age of the subjects [2], was selected so that the heart rate (HR) at the end of the load was close to that calculated by the formula: HR = (220 - Age)•0,87. Calculated submaximal PWC_{150} with the mechanical power in Watt per kilogram body weight (W/kg) as indicator of cardiorespiratory fitness.

Systolic and diastolic blood pressure as well as heart rate was measured by tonometer “Omron M4-I” (Netherlands) in a sitting position. Then recorded electrocardiogram in II lead to assess the parameters of heart rate variability (HRV) (software and hardware complex "CardioLab+HRV" produced by "KhAI-MEDICA", Kharkiv, Ukraine). For further analysis the following parameters HRV were selected. Temporal parameters (Time Domain Methods): the standart deviation of all NN intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), the percent of interval differences of successive NN intervals greater than 50 msec (pNN_{50}). Spectral parameters (Frequency Domain Methods): absolute ($msec^2$) and relative (%) power spectral density (PSD) bands of HRV: high-frequency (HF, range 0,4÷0,15 Hz), low-frequency (LF, range 0,15÷0,04 Hz), very low-frequency (VLF, range 0,04÷0,015 Hz) and ultralow-frequency (ULF, range 0,015÷0,003 Hz) [14].

EEG recorded at rest during 25 sec a hardware-software complex “NeuroCom Standard” (KhAI Medica, Kharkiv, Ukraine) monopolar in 16 loci (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2) by 10-20 international system, with the reference electrodes A and Ref on the earlobes. Among the options considered the average EEG amplitude (μV), average frequency (Hz), frequency deviation (Hz), index (%), absolute ($\mu V^2/Hz$) and relative (%) PSD of basic rhythms: β (35÷13 Hz), α (13÷8 Hz), θ (8÷4 Hz) and δ (4÷0,5 Hz) in all loci, according to the instructions of the device.

In addition, calculated for HRV and each locus of EEG the Entropy (h) of normalized PSD using Popovych’s IL [13] formulas based on classic Shannon’s CE formula:

$$hEEG = -[PSD\alpha \bullet \log_2 PSD\alpha + PSD\beta \bullet \log_2 PSD\beta + PSD\theta \bullet \log_2 PSD\theta + PSD\delta \bullet \log_2 PSD\delta]/\log_2 4;$$

$$hHRV = -[PSDHF \bullet \log_2 PSDHF + PSDLF \bullet \log_2 PSDLF + PSDVLF \bullet \log_2 PSDVLF + PSDULF \bullet \log_2 PSDULF]/\log_2 4.$$

The parameters of immunity were determined as described in the manual [27]. Determined the relative content of the population of T-lymphocytes in a test of spontaneous rosette formation with erythrocytes of sheep, their theophylline-resistant and theophylline-sensitive subpopulations (by the test of sensitivity of rosette formation to theophylline), B-lymphocytes by the test of complementary rosette formation with erythrocytes of sheep.

The reference values are taken from the database of the Truskavetsian Scientific School of Balneology.

Data collection and analysis / Statistical analysis.

Statistical processing performed using a software package “Microsoft Excell” and “Statistica 6.4 StatSoft Inc”.

RESULTS AND DISCUSSION

Previously, statistically significant deviation from the norm of 18 EEG parameters (increase in 8 and decrease in 10) have been revealed in this cohort of patients, which were not affected by balneotherapy and were interpreted as a manifestation of post-radiation encephalopathy. Such an EEG state was accompanied by a pronounced sympathotonic shift of the autonomic balance [38].

In this study, it was found that autonomic dysfunction, as well as some normal (but not abnormal) EEG parameters were sensitive to balneofactors, but the severity and even the directionality of nervous system reactions differed in patients who received standard balneotherapy or balneotherapy supplemented with Balm. This also applies to a number of other registered parameters.

And now in more detail. At the first stage of the analysis, only those parameters that were significantly changed in at least one group of patients were selected. Then, according to the algorithm of the Truskavetsian Scientific School of Balneology, the actual values were normalized, that is, recalculated into Z-scores. The effects of standard balneotherapy were assessed by the difference between final and initial Z-scores. The difference between the Z-scores after the combined (ST+B) and standard (ST) balneotherapy makes it possible to evaluate the partial (per se) effects of the Balm (B) (please see Table 16). Finally, 6 clusters were formed from 22 parameters (Fig. 1).

The first cluster reflects the enhancing effect of ST on normal heart rate and already increased sympathetic tone. This is consistent with the data of a previous clinical study [28] and an experiment on rats [34]. Additional use of the Balm reduces sympathetic tone to normal, and HR to the lower normal range, i.e. the phytocomposition has a sympathoinhibitory/vagotonic effect.

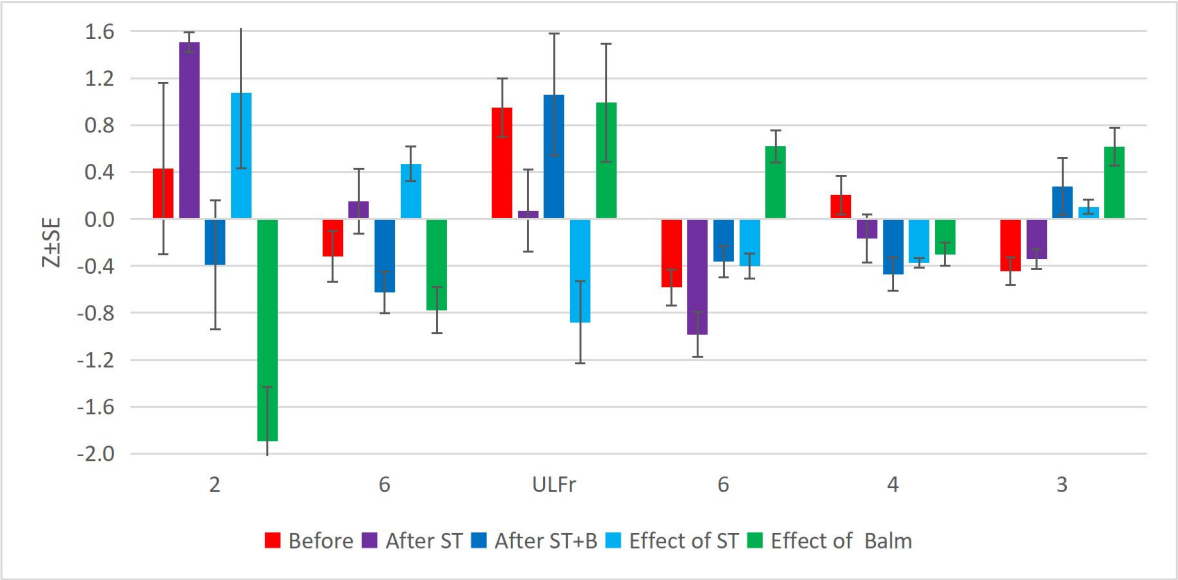


Fig. 1. Clusters of normalized parameters before and after standard (ST) and combined (ST+B) balneotherapy; the effects of standard balneotherapy and Balm were also calculated. Below is the number of parameters combined into a cluster

The second cluster reflects the normalizing effect of ST on reduced blood pressure diastolic (but not systolic), which is probably related to its sympathomimetic effect. Naturally, the Balm limits this effect of ST. However, Balm reduces the normal level of Entropy of PSD in both right temporal loci, while ST does not affect these EEG parameters. On the other hand, ST reduces the degree of reduction in the level of T-helper lymphocytes, while the Balm does not affect this parameter of immunity. It turned out quite unexpectedly that after ST, the normal level of urea increases and the upper limit level of creatinine increases even more. This is combined with a deepening of the lower boundary level of glomerular filtration rate (fourth cluster). Additional use of the Balm normalizes the creatinine level, lowers the urea level to the lower normal range and limits the decrease in glomerular filtration rate.

The third cluster contains only one parameter, the increased level of which is completely normalized due to ST, while the Balm completely counteracts this effect. It is speculated that

ULF band HRV associated with oscillation blood level of norepinephrine (0,002 Hz) as well as 17-OCS (0,0019 Hz) [cit. by: 22]. This assumption is consistent with literature data that such a cohort of patients had elevated plasma levels of both catecholamines and glucocorticoids [21], as well as with the previously registered dramatically increased Baevsky stress index in these patients: 688±134 units versus reference level 132±11 units [38].

Such hypothetical changes in ergotropic hormones are accompanied by a further decrease in the lower limit level of PWC_{150}, which is reversed by phytoadaptogen. This is in excellent agreement with the data of our experiment on rats. It was found that the weekly use of Naftyssya bioactive water reduces the duration of swimming of rats to exhaustion by 30% compared to the daily water control; addition of Balm to Naftyssya softens its negative actotropic effect by up to -9%, and adding Balm to daily water prolongs the maximum duration of swimming compared to the control by 11%; a positive correlation of the swimming test with 17-KS excretion was revealed, but a negative correlation with mineralocorticoid activity [8].

Changes in PWC_{150} are accompanied by unidirectional changes in other parameters combined in the fourth (and also sixth) cluster, instead, by opposite changes in some other parameters. Let's dwell on these connections in more detail.

Among the EEG parameters, a significant negative correlation of changes in PWC_{150} and PSD Fp2-θ (Fig. 2), F8-θ (r=-0,50), T5-θ (r=-0,28), Entropy of PSD in T6 locus (r=-0,50), instead, a positive correlation with changes in PSD O1-δ (Fig. 3) and O2-δ (r=0,40).

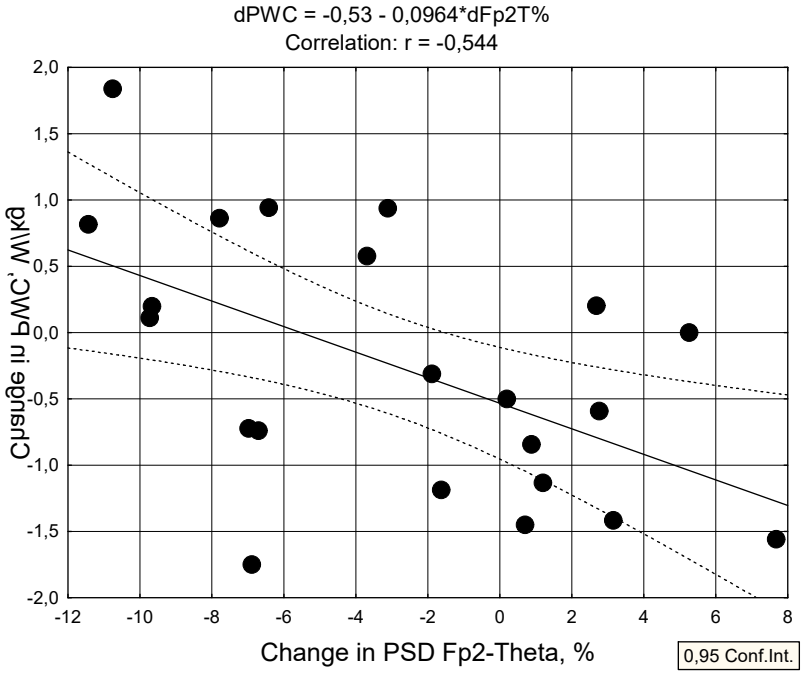


Fig. 2. Scatterplot of correlation between the changes in PSD of theta-rhythm in Fp2 locus (X-line) and PWC_{150} (Y-line)

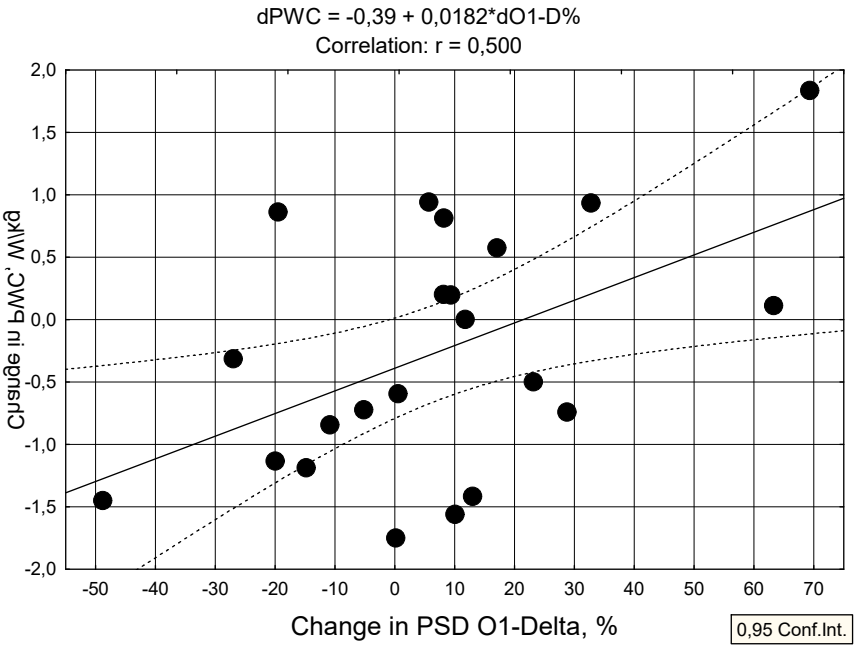
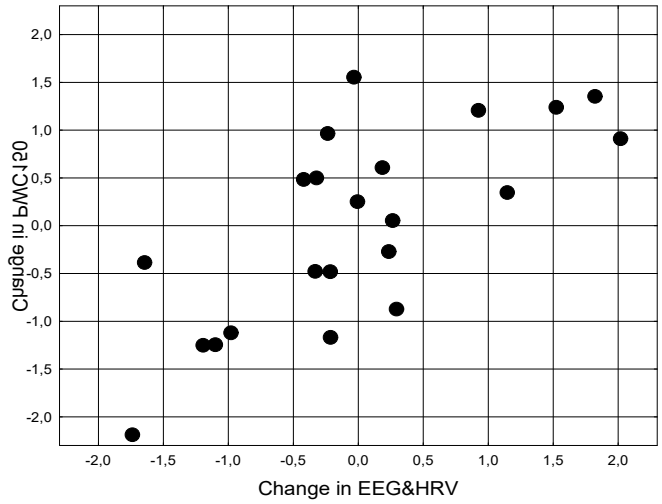


Fig. 3. Scatterplot of correlation between the changes in PSD of delta-rhythm in O1 locus (X-line) and PWC_{150} (Y-line)

It is interesting that when building a regression model by stepwise exclusion until reaching the maximum value of Adjusted R^2, some parameters were left out of the model, instead, the ULF band was included in it despite the insignificant relationship (Table 1). Taken together, changes in the three parameters of the nervous system determine changes in PWC_{150} by 51,5% (Fig. 4).

Table 1. Regression Summary for change in PWC_{150}
R=0,718; R^2=0,515; Adjusted R^2=0,434; $F_{(3,2)}$=6,4; p=0,004; SE: 0,74 W/kg

N=22		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(18)}$	p-level
Change in Variables	r		Intercpt	-0,596	0,184	-3,24	0,005
Fp2-θ PSD, %	**-0,54**	-0,551	0,170	-0,098	0,030	-3,24	0,005
O2-δ PSD, %	**0,40**	0,359	0,168	0,016	0,008	2,13	0,047
ULF PSD, %	**0,19**	0,362	0,170	0,054	0,025	2,14	0,046



R=0,718; R^2=0,515; $\chi^2_{(3)}$=14; p=0,004; Λ Prime=0,485

Fig. 4. Scatterplot of canonical correlation between the changes in EEG&HRV parameters (X-line) and PWC_{150} (Y-line)

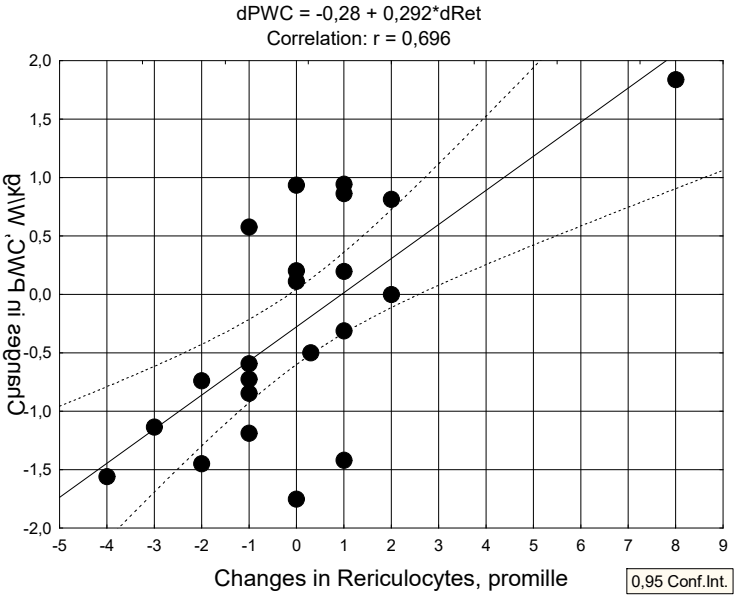


Fig. 5. Scatterplot of correlation between the changes in blood Reticulocytes level (X-line) and PWC_{150} (Y-line)

In addition, a strong positive correlation was found between changes in PWC_{150} and the content of reticulocytes in the blood (Fig. 5), but not erythrocytes (r=0,20) and hemoglobin (r=0,13), as well as malondialdehyde (r=0,28) and the level of glomerular filtration (r=0,25).

Instead, the correlation with changes in plasma urea is negative (Fig. 6).

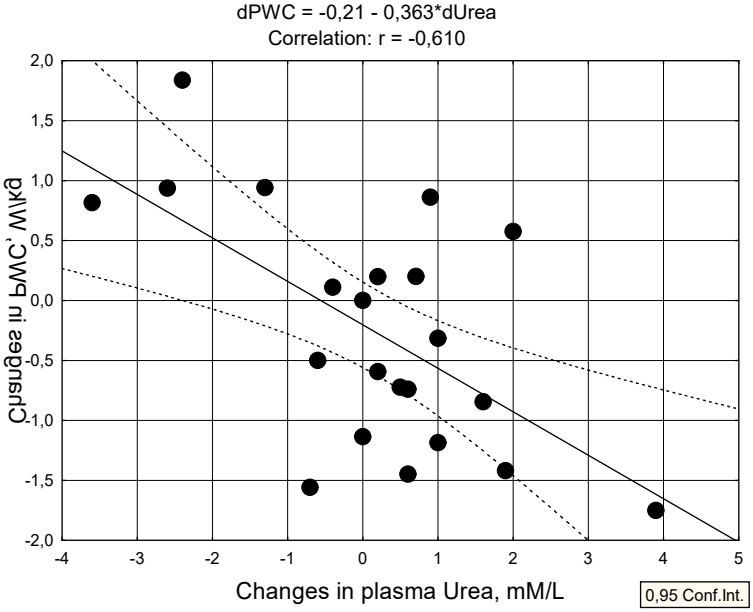


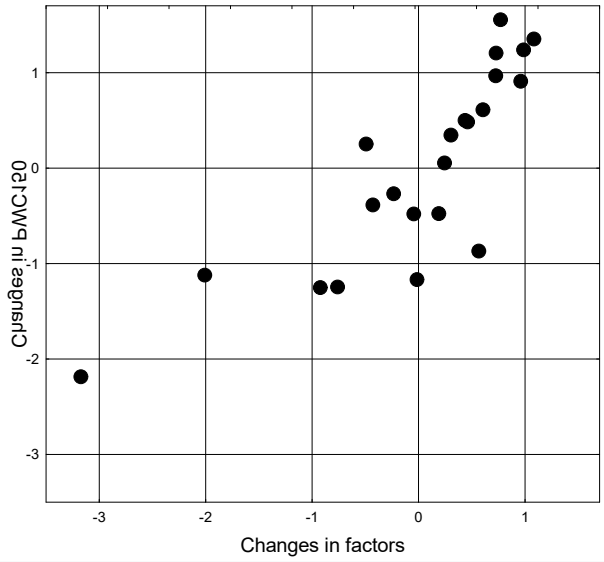
Fig. 6. Scatterplot of correlation between the changes in plasma Urea level (X-line) and PWC_{150} (Y-line)

Taken together, changes in these parameters determine changes in PWC_{150} by 67,8% (Table 2 and Fig. 7).

Table 2. Regression Summary for change in PWC_{150}

R=0,823; R^2=0,678; Adjusted R^2=0,624; $F_{(3,2)}$=12,6; p=0,0001; SE: 0,60 W/kg

N=22		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(18)}$	p-level
Change in Variables	r		Intercpt	-0,242	0,129	-1,87	0,078
Reticulocytes, ‰	**0,70**	0,634	0,153	0,266	0,064	4,13	0,001
Malondyaldehid, µM/L	**0,28**	-0,255	0,163	-0,007	0,004	-1,57	0,135
Urea, mM/L	**-0,61**	-0,505	0,154	-0,300	0,092	-3,27	0,004



R=0,823; R^2=0,678; $\chi^2_{(3)}$=21; p=0,0001; Λ Prime=0,322

Fig. 7. Scatterplot of canonical correlation between the changes in factors (X-line) and PWC_{150} (Y-line)

With regard to immunity parameters, an inverse relationship with the relative level of T-helper Lymphocytes (Fig. 8) was found, instead, a direct relationship with the level of B-Lymphocytes.

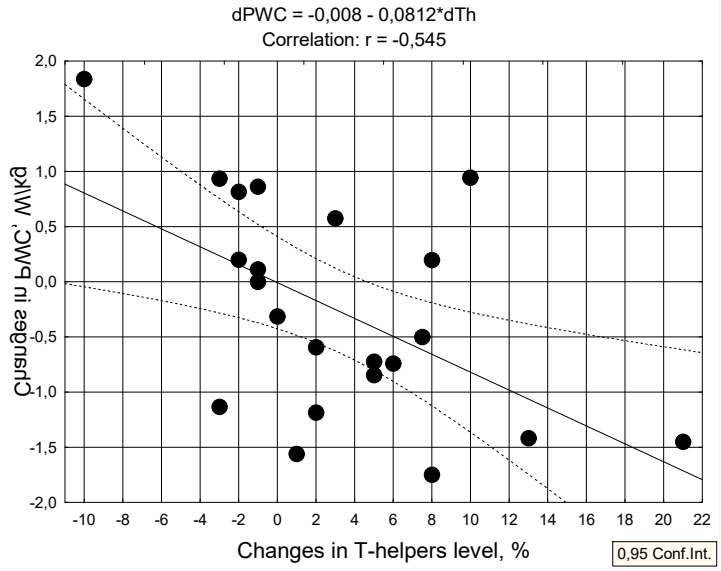
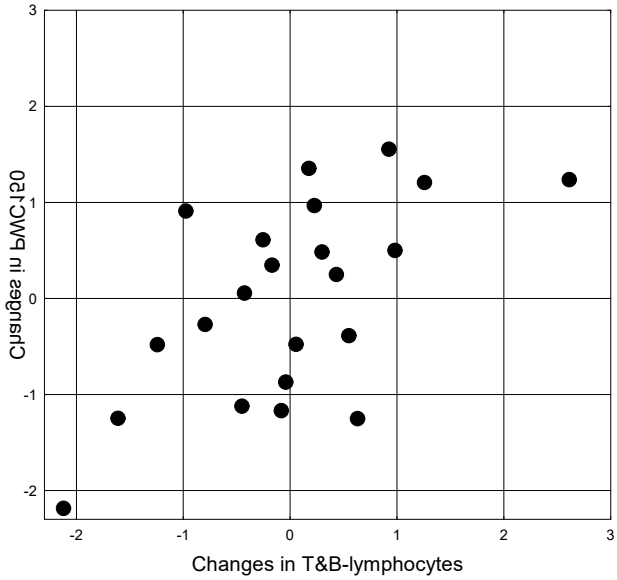


Fig. 8. Scatterplot of correlation between the changes in T-helper Lymphocytes level (X-line) and PWC_{150} (Y-line)

Taken together, changes in immune parameters determine changes in PWC_{150} by 36,7% (Table 3 and Fig. 9).

Table 3. Regression Summary for change in PWC_{150}
R=0,606; R^2=0,367; Adjusted R^2=0,300; $F_{(2,2)}$=5,5; p=0,013; SE: 0,82 W/kg

N=22		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(19)}$	p-level
Change in Variables	r		Intercpt	-0,012	0,195	-0,06	0,952
T-helper Lymphocytes, %	**-0,65**	-0,507	0,184	-0,075	0,027	-2,75	0,013
B-Lymphocytes, %	**0,34**	0,267	0,184	0,046	0,032	1,44	0,165



R=0,606; R^2=0,367; $\chi^2_{(2)}$=8,7; p=0,013; Λ Prime=0,633
Fig. 9. Scatterplot of canonical correlation between the changes in immune parameters (X-line) and PWC_{150} (Y-line)

Finally, a strong negative correlation of changes in PWC_{150} and diastolic (but non systolic) blood pressure was found (Fig. 10).

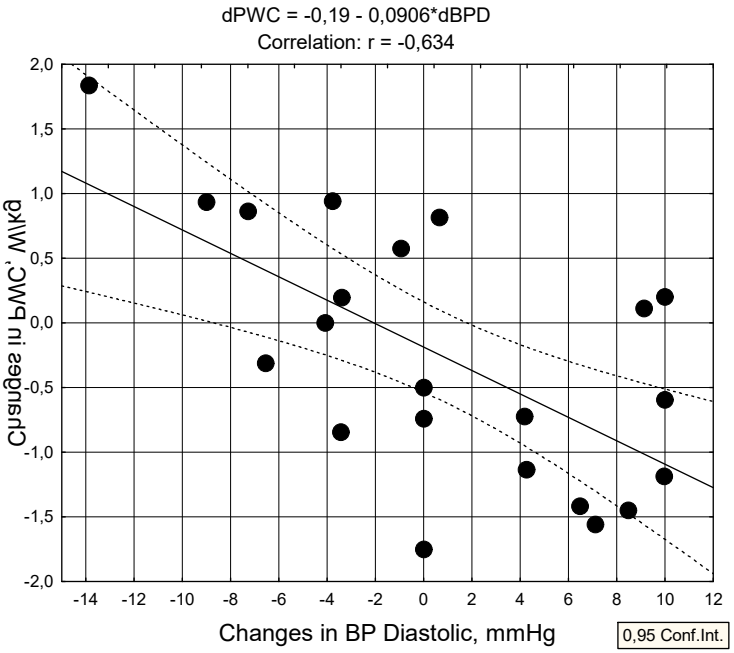


Fig. 10. Scatterplot of correlation between the changes in Blood Pressure Diastolic level (X-line) and PWC_{150} (Y-line)

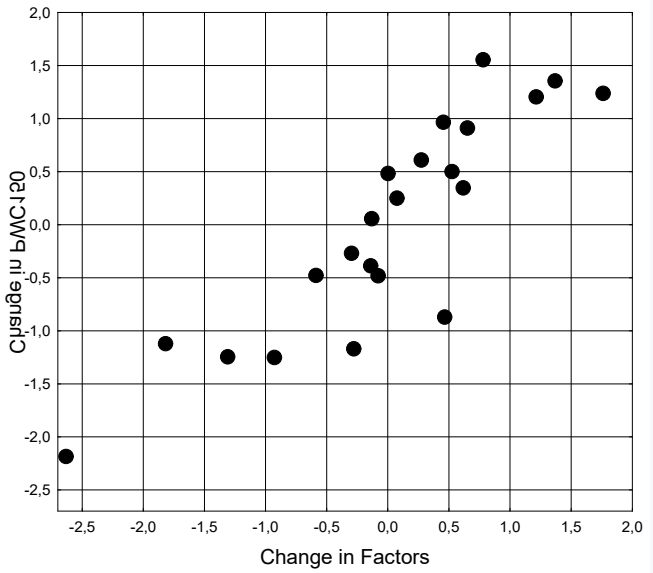
However, despite the significant correlation coefficient, the last parameter was outside the integral regression model (Table 4).

Table 4. Regression Summary for change in PWC_{150}
R=0,880; R^2=0,774; Adjusted R^2=0,683; $F_{(6,2)}$=8,6; p=0,0004; SE: 0,55 W/kg

N=22		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(15)}$	p-level
Change in Variables	r		Intercpt	-0,280	0,152	-1,84	0,085
Reticulocytes, ‰	**0,70**	0,248	0,167	0,104	0,070	1,49	0,158
B-Lymphocytes, %	**0,34**	0,190	0,145	0,033	0,025	1,31	0,211
ULF PSD, %	**0,19**	0,162	0,133	0,024	0,020	1,22	0,241
T-helper Lymphocytes, %	**-0,65**	-0,242	0,143	-0,036	0,021	-1,70	0,111
Urea, mM/L	**-0,61**	-0,269	0,143	-0,160	0,085	-1,88	0,080
Fp2-θ PSD, %	**-0,54**	-0,385	0,157	-0,068	0,028	-2,45	0,027

Judging by the coefficient R^2, changes in PWC_{150} are determined by changes in the parameters included in the regression model by 77,4% (Fig. 11).

Since PWC is calculated based on HR response to exercise, its relationship with HRV&EEG parameters is quite natural [33]. It is also possible to understand the physiological mechanism of the direct connection between PWC_{150} and the content of reticulocytes in the blood, even in the absence of connections with the content of erythrocytes and hemoglobin. Instead, the physiological mechanisms of direct connections between PWC and the content of immunocytes and metabolites in the blood seem to be problematic. Given the well-known functional relationships between HRV&EEG parameters and immunity [12][13][23][30], it was appropriate to analyze them in this cohort.



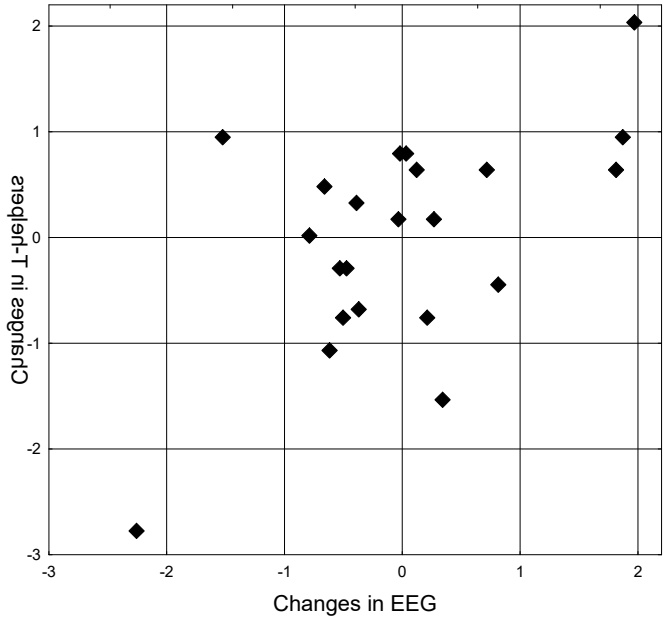
R=0,880; R^2=0,774; $\chi^2_{(6)}$=25; p=0,0003; Λ Prime=0,226
Fig. 11. Scatterplot of canonical correlation between the changes in factors (X-line) and PWC_{150} (Y-line)

It was found that changes in the levels of both T-helper (Table 5 and Fig. 12) and B-Lymphocytes (Table 6 and Fig. 13) as well as reticulocytes close to them in terms of genesis (Table 7 and Fig. 14) are determined by changes in neural parameters, that is, their connections with PWC_{150} are formal (mathematical), but not causal.

Table 5. Regression Summary for change in T-helpers

R=0,564; R^2=0,318; Adjusted R^2=0,247; $F_{(2,2)}$=4,4; p=0,026; SE: 5,7%

N=22		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(19)}$	p-level
Change in Variables	r		Intercpt	4,937	1,366	3,61	0,002
F8-θ PSD, %	**0,50**	0,383	0,206	0,392	0,211	1,86	0,079
O2-δ PSD, %	**-0,44**	-0,290	0,206	-0,088	0,062	-1,41	0,176



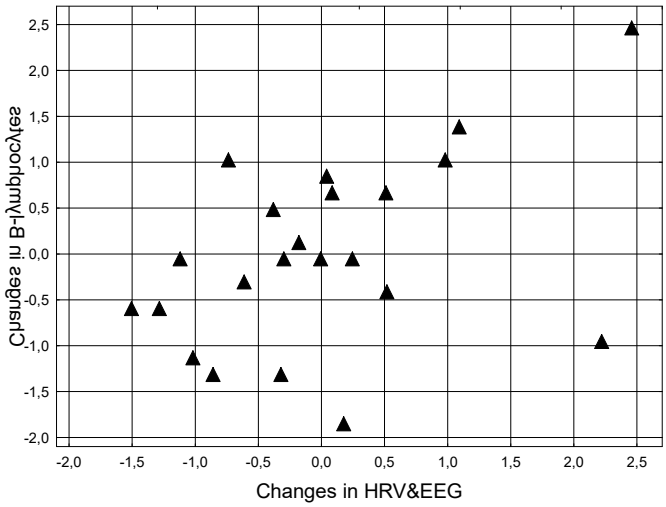
R=0,564; R^2=0,318; $\chi^2_{(2)}$=7,3; p=0,026; Λ Prime=0,682

Fig. 12. Scatterplot of canonical correlation between the changes in EEG (X-line) and T-helpers (Y-line)

Table 6. Regression Summary for change in B-lymphocytes

R=0,455; R^2=0,207; Adjusted R^2=0,123; $F_{(2,2)}$=2,5; p=0,111; SE: 5,3%

N=22		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(19)}$	p-level
Change in Variables	r		Intercpt	0,496	1,192	0,42	0,682
ULF PSD, %	**0,33**	0,404	0,210	0,351	0,183	1,92	0,070
T6 PSD Entropy	**0,23**	0,323	0,210	7,746	5,040	1,54	0,141

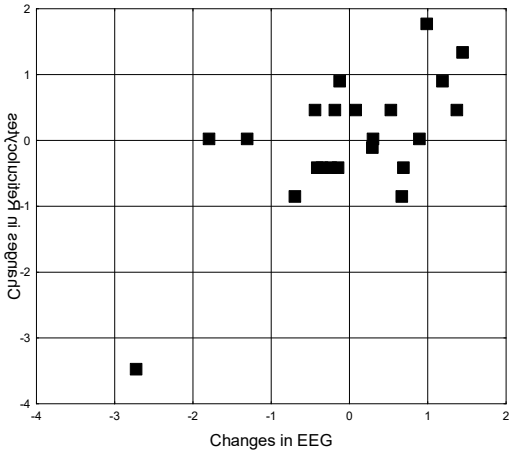


R=0,455; R^2=0,207; $\chi^2_{(2)}$=4,4; p=0,111; Λ Prime=0,793

Fig. 13. Scatterplot of canonical correlation between the changes in HRV&EEG (X-line) and B-lymphocytes (Y-line)

Table 7. Regression Summary for change in Reticulocytes
R=0,676; R^2=0,457; Adjusted R^2=0,329; $F_{(4,2)}$=3,6; p=0,027; SE: 1,9 ‰

N=22		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(17)}$	p-level
Change in Variables	r		Intercpt	-0,703	0,467	-1,51	0,150
Fp2-θ PSD, %	**-0,48**	-0,241	0,210	-0,102	0,088	-1,15	0,267
T5-θ PSD, %	**-0,46**	-0,303	0,203	-0,097	0,065	-1,49	0,154
T4 PSD Entropy	**-0,24**	-0,226	0,182	-2,395	1,923	-1,25	0,230
O1-δ PSD, %	**0,49**	0,304	0,194	0,026	0,017	1,57	0,135

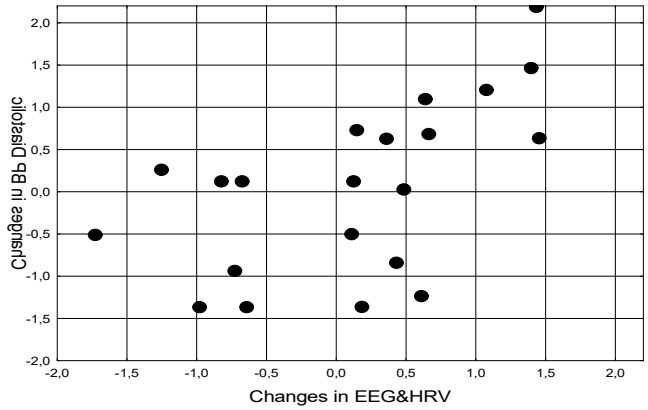


R=0,676; R^2=0,457; $\chi^2_{(4)}$=11; p=0,027; Λ Prime=0,543
Fig. 14. Scatterplot of canonical correlation between the changes in EEG (X-line) and Reticulocytes (Y-line)

Changes in diastolic blood pressure (Table 8 and Fig. 15) and associated glomerular filtration rate (Table 9 and Fig. 16) are also expected to be subject to neural determination.

Table 8. Regression Summary for change in BP diastolic
R=0,608; R^2=0,370; Adjusted R^2=0,265; $F_{(3,2)}$=3,5; p=0,036; SE: 5,9 mmHg

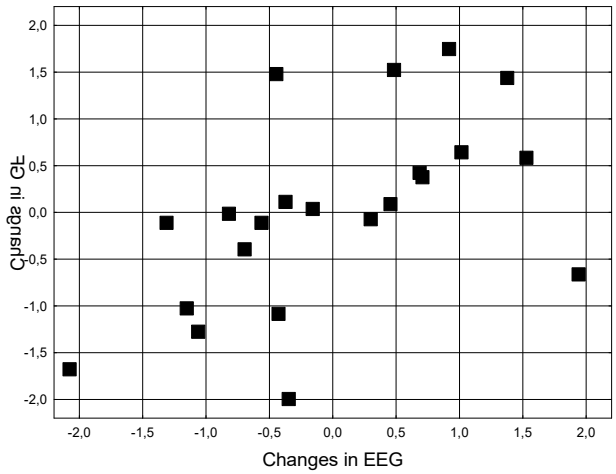
N=22		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(18)}$	p-level
Change in Variables	r		Intercpt	2,239	1,427	1,57	0,134
F8-θ PSD, %	**0,48**	0,326	0,202	0,348	0,216	1,61	0,125
T5-θ PSD, %	**0,36**	0,381	0,214	0,358	0,201	1,78	0,092
ULF PSD, %	**-0,23**	-0,327	0,206	-0,344	0,216	-1,59	0,130



R=0,608; R^2=0,370; $\chi^2_{(3)}$=8,5; p=0,036; Λ Prime=0,630
Fig. 15. Scatterplot of canonical correlation between the changes in EEG&HRV (X-line) and BP diastolic (Y-line)

Table 9. Regression Summary for change in Glomerular Filtration
R=0,551; R^2=0,304; Adjusted R^2=0,230; $F_{(2,2)}$=4,1; p=0,032; SE: 15 mL/min

N=22		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(19)}$	p-level
Change in Variables	r		Intercpt	-4,415	3,502	-1,26	0,223
T4 PSD Entropy	**-0,47**	-0,498	0,192	-39,59	15,27	-2,59	0,018
T5-θ PSD, %	**-0,24**	-0,281	0,192	-0,674	0,461	-1,46	0,160



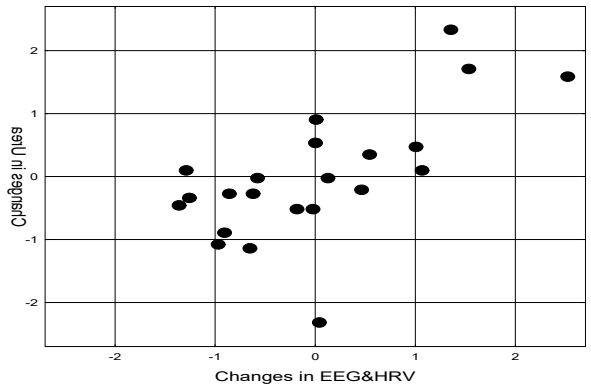
R=0,551; R^2=0,304; $\chi^2_{(2)}$=6,9; p=0,032; Λ Prime=0,696

Fig. 16. Scatterplot of canonical correlation between the changes in EEG (X-line) and Glomerular Filtration (Y-line)

It is interesting that the multiple urea-neural correlation turned out to be maximal in this series and at the same time statistically insignificant (Table 10 and Fig. 17).

Table 10. Regression Summary for change in plasma Urea
R=0,655; R^2=0,429; Adjusted R^2=0,205; $F_{(6,2)}$=1,9; p=0,151; SE: 1,5 mM/L

N=22		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(15)}$	p-level
Change in Variables	r		Intercpt	0,595	0,378	1,57	0,136
O1-δ PSD, %	**-0,41**	-0,606	0,322	-0,037	0,020	-1,88	0,080
LF PSD, %	**0,32**	0,347	0,220	0,033	0,021	1,58	0,135
T4 PSD Entropy	**0,30**	0,679	0,321	5,077	2,402	2,11	0,052
Frequency-β, Hz	**0,28**	-0,350	0,289	-0,108	0,089	-1,21	0,245
T6 PSD Entropy	**0,26**	-0,593	0,385	-4,130	2,681	-1,54	0,144
Fp2-θ PSD, %	**0,25**	0,468	0,261	0,139	0,078	1,80	0,093



R=0,655; R^2=0,429; $\chi^2_{(6)}$=9,5; p=0,146; Λ Prime=0,571

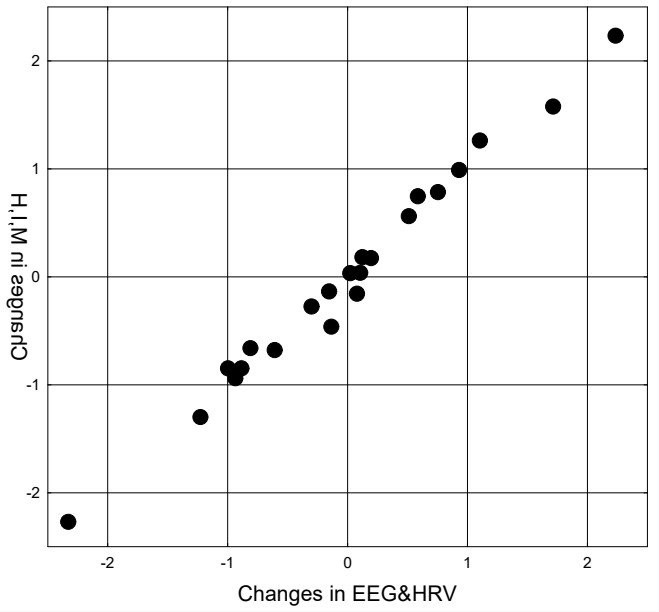
Fig. 17. Scatterplot of canonical correlation between the changes in EEG (X-line) and Glomerular Filtration (Y-line)

Table 11. Factor structure of Canonical Roots

EEG&HRV	R
T6 PSD Entropy	-0,638
F8-θ PSD, %	-0,627
Fp2-θ PSD, %	-0,603
T5-θ PSD, %	-0,484
T4 PSD Entropy	-0,362
LF PSD, %	-0,038
O1-δ PSD, %	0,348
O2-δ PSD, %	0,229
ULF PSD, %	0,069
Frequency-β, Hz	0,067
Other	**R**
BP Diastolic, mmHg	-0,698
Urea, mM/L	-0,416
T-helpers, %	-0,449
B-Lymphocytes, %	-0,145
Reticulocytes, ‰	0,640
Glom Filtration, mL/min	0,564
Malondyaldehid, µM/L	0,311

Finally, a canonical correlation analysis was performed between changes in EEG&HRV parameters, taken as factors, and metabolic and hemato-immune parameters, taken as responses.

It was found that changes in nervous regulation caused by balneofactors determine changes in diastolic pressure, glomerular filtration, plasma concentration of urea, malondialdehyde, as well as the content of T-helpers, B-lymphocytes and reticulocytes in the blood by 98.6% (Table 11 and Fig. 18).



R=0,993; R^2=0,986; $\chi^2_{(70)}$=101; p=0,009; Λ Prime=0,0002

Fig. 18. Scatterplot of canonical correlation between the changes in EEG&HRV (X-line) and metabolic, immune and other (Y-line) parameters

There is a well-founded opinion that the adaptogenic properties of classical phytoadaptogens are caused by polyphenolic compounds [26]. The latter are also present in the phytocomposition "Balm Kryms'kyi" [1] and Naftussya bioactive water [3][17][18][43], which also have adaptogenic ability [1][25][29][30]. It is interesting that ozokerite, an integral

component of the standard balneotherapy complex of the Truskavets resort, has a number of effects similar to those of Naftussya, both when taken orally and when applied to the skin, as well as in vitro [18][28][34]. According to the hypothesis of the Truskavetsian Scientific School of Balneology [29], polyphenolic compounds of adaptogens of various nature are ligands of aryl hydryl receptors (AHR), which are known to be expressed by almost all types of cells of all organisms, starting from unicellular [4][24].

Taking into account literature data on the direct neurotropic effect of phytoadaptogens in vitro and in vivo [26], previously published data on changes in EEG&HRV parameters as well as relationships between EEG and HRV, EEG&HRV and adaptogene hormones, EEG&HRV and immunity parameters [5][6][7][9][20][23], the neurogenic mechanism of the revealed effects of balneotherapy factors seems to be very real.

At the same time, there is a right to the hypothesis that the primary target of polyphenolic compounds are immunocytes, which through their cytokines affect neurons of the central and autonomic nervous system [29][30].

The results of a discriminant analysis [19] testify in favor of the alternativeness of primary targets, according to which the characteristic effects of balneofactors are both neurotropic and immunotropic. In addition, the forward stepwise program also included PWC and bilirubin level in the discriminant model (Tables 12 and 13).

Table 12. Summary of the analysis of discriminant functions

Step 10, N of vars in model: 10; Grouping: 3 grps; Wilks' Λ: 0,2094; approx. $F_{(21)}$=3,8; $p<10^{-4}$

Variables currently in the model	Groups (n) and Means±SE			Parameters of Wilks' Statistics					
	Before Standard therapy (22)	After Standard Therapy + Balm (11	After Standard therapy (11)	Wilks' Λ	Partial Λ	F-remove (2,32)	p-level	Tolerancy	Norm Cv
F8-θ PSD, %	10,1 0,8	6,3 0,9	8,2 1,2	0,258	0,813	3,68	0,036	0,606	9,8 0,492
Fp2-θ PSD, %	10,7 1,1	7,6 1,7	8,2 1,3	0,249	0,842	2,99	0,064	0,612	9,9 0,620
T6 PSD Entropy	0,778 0,025	0,697 0,057	0,772 0,044	0,228	0,919	1,41	0,259	0,549	0,825 0,149
LF PSD, %	38,8 1,8	29,1 3,9	42,6 3,9	0,276	0,757	5,13	0,012	0,871	27,2 0,381
Heart Rate, beats/min-	65,9 2,2	60,8 2,7	79,9 2,2	0,280	0,747	5,42	0,009	0,572	68,5 0,118
B-Lymphocytes, %	19,0 1,0	19,8 1,3	17,7 0,8	0,238	0,879	2,21	0,127	0,738	21,5 0,196
T-helper Lymphocytes, %	25,6 1,5	28,4 1,5	29,1 2,0	0,260	0,804	3,90	0,030	0,656	33,2 0,196
Bilirubin, μM/L	9,66 0,89	10,12 0,68	8,81 0,89	0,269	0,779	4,53	0,018	0,544	11,7 0,355
Reticulocytes, ‰	5,09 0,35	5,82 0,64	4,48 0,37	0,230 4262	0,908 5783	1,609 93	0,215 6739	0,583 8795	6,9 0,403
Physical Working Capacity, W/kg	2,28 0,16	2,56 0,17	1,47 0,11	0,239 9976	0,872 3431	2,341 408	0,112 4597	0,434 8455	2,67 0,333

Table 13. Summary of stepwise analysis of discriminant variables ranked by criterion Λ

Variables currently in the model	F to enter	p-level	Λ	F-value	p-level
Heart Rate, beats/min-	12,7	10^{-4}	0,618	12,7	10^{-4}
LF PSD, %	4,77	0,014	0,499	8,32	10^{-5}
F8-θ PSD, %	4,54	0,017	0,404	7,44	10^{-5}
T-helper Lymphocytes, %	2,11	0,136	0,364	6,24	10^{-5}
Bilirubin, µM/L	1,96	0,155	0,329	5,50	10^{-4}
Fp2-θ PSD, %	2,24	0,121	0,293	5,09	10^{-5}
T6 PSD Entropy	1,29	0,288	0,273	4,58	10^{-5}
B-Lymphocytes, %	1,35	0,272	0,253	4,21	10^{-4}
Physical Working Capacity, W/kg	1,58	0,221	0,230	3,97	10^{-4}
Reticulocytes, ‰	1,61	0,216	0,209	3,79	10^{-4}

Other variables were left out of the discriminant model, apparently due to duplication/redundancy of separating information (Table 14).

Table 14. Variables currently not in the model

Variables	Groups (n) and Means±SE			Parameters of Wilks' Statistics					
	Before Standard therapy (22)	After Standard Therapy + Balm (11	After Standard therapy (11)	Wilks' Λ	Partial Λ	F to enter	p-level	Tolerancy	Norm Cv
Frequency-β, Hz	20,9 0,9	17,5 1,0	19,8 1,4	0,207	0,990	0,16	0,855	0,775	17,9 0,244
T4 PSD Entropy	0,826 0,025	0,770 0,052	0,839 0,030	0,208	0,993	0,11	0,894	0,868	0,844 0,137
T5-θ PSD, %	8,3 0,7	5,8 0,7	6,6 0,9	0,207	0,989	0,17	0,843	0,477	9,7 0,471
O1-δ PSD, %	20,3 3,0	34,4 8,4	20,5 3,7	0,208	0,994	0,10	0,908	0,674	23,5 0,655
O2-δ PSD, %	15,0 2,3	27,9 8,6	18,4 3,1	0,207	0,989	0,17	0,843	0,133	22,8 0,720
ULF PSD, %	7,7 0,8	8,2 1,8	4,5 1,1	0,207	0,990	0,16	0,851	0,848	4,8 0,735
Blood Pressure Diastolic, mmHg	76,7 1,6	75,1 1,1	80,0 1,8	0,207	0,987	0,21	0,815	0,007	78,7 0,054
Glomerular Filtration, mL/min	95,6 4,0	103,5 6,6	83,8 3,9	0,209	0,996	0,06	0,939	0,502	127 0,200
Creatinine, µM/L	83,5 2,3	80,6 3,7	91,0 4,1	0,198	0,944	0,92	0,409	0,618	78,3 0,167
Urea, mM/L	5,60 0,29	4,95 0,44	6,57 0,46	0,207	0,989	0,17	0,843	0,501	5,57 0,281
Malondyaldehid, µM/L	74,8 5,6	78,2 7,0	67,5 7,5	0,201	0,958	0,68	0,514	0,564	77,5 0,339
Gamma-globulins, g/L	11,13 0,97	13,15 0,54	11,49 1,44	0,203	0,970	0,49	0,616	0,481	13,88 0,348

The identifying information contained in the 10 discriminant variables is condensed into two roots. The major root contains 69,7% of discriminatory opportunities (r*=0,796; Wilks'

Λ=0,209; $\chi^2_{(20)}$=57; $p<10^{-4}$), while minor root 30,3% (r*=0,655; Wilks' Λ=0,571; $\chi^2_{(9)}$=20; p=0,015).

Table 15. Standardized and raw coefficients and constants for discriminant variables

Coefficients	Standardized		Raw	
Variables	Root 1	Root 2	Root 1	Root 2
Heart Rate, beats/min-	0,647	0,644	0,069	0,069
LF PSD, %	0,620	-0,285	0,057	-0,026
F8-0 PSD, %	0,038	-0,847	0,010	-0,229
T-helper Lymphocytes, %	-0,120	0,822	-0,019	0,129
Bilirubin, µM/L	-0,794	0,125	-0,227	0,036
Fp2-0 PSD, %	-0,380	-0,623	-0,083	-0,136
T6 PSD Entropy	0,369	0,379	2,563	2,636
B-Lymphocytes, %	-0,488	0,177	-0,115	0,042
Physical Working Capacity, W/kg	-0,584	0,426	-0,032	0,023
Reticulocytes, ‰	-0,199	0,554	-0,118	0,329
	Constants		0,378	-10,97
	Eigenvalues		1,728	0,751
Cumulative Proportion			0,697	1

Calculating the values of discriminant roots for each patient by coefficients and constants given in Table 15 allows visualization of each patient in the information space of roots (Figs. 12-14).

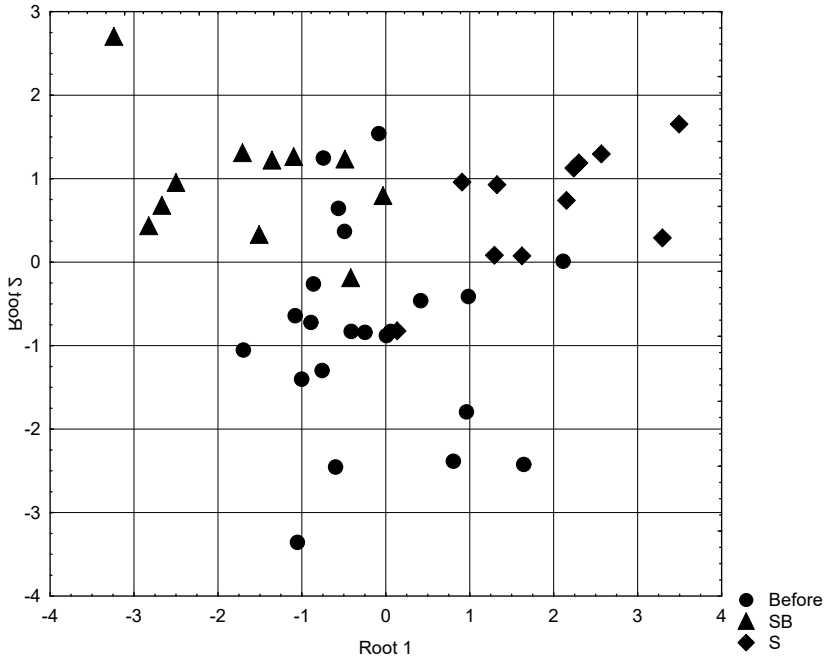


Fig. 12. Scattering of individual values of the first and second discriminant roots of patients before (circles) and after the course of standard balneotherapy (rhombuses) and in combination with Balm "Truskavets'" (triangles)

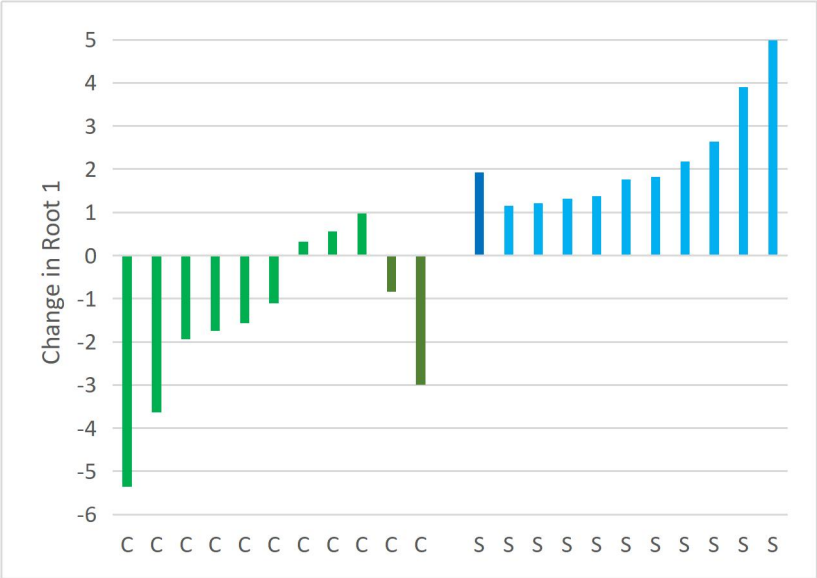


Fig. 13. Changes in individual values of the first discriminant root of patients after the course of standard balneotherapy and in combination with Balm "Truskavets'". Women are highlighted in shades of colors

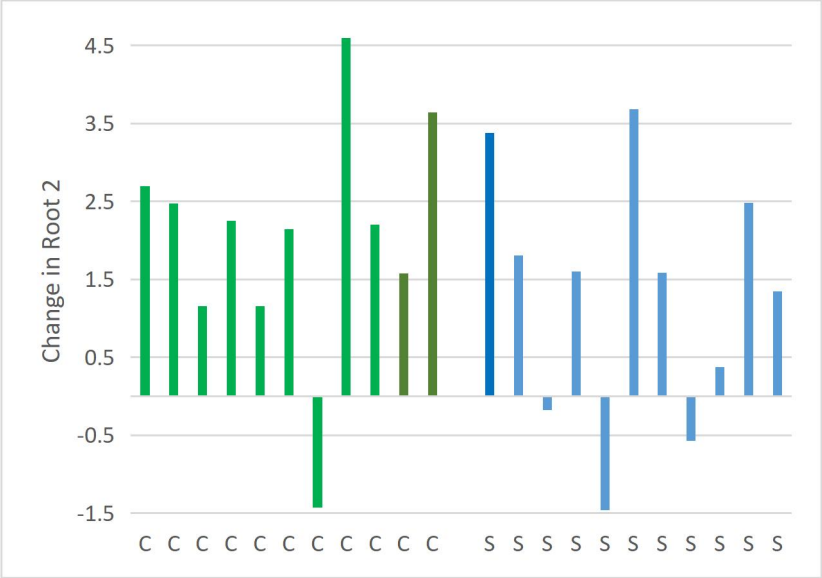


Fig. 14. Changes in individual values of the second discriminant root of patients after the course of standard balneotherapy and in combination with Balm "Truskavets'". Women are highlighted in shades of colors

The separation of patients who received two schemes of balneotherapy is more clearly manifested by the centroids of the discriminant roots (Fig. 15).

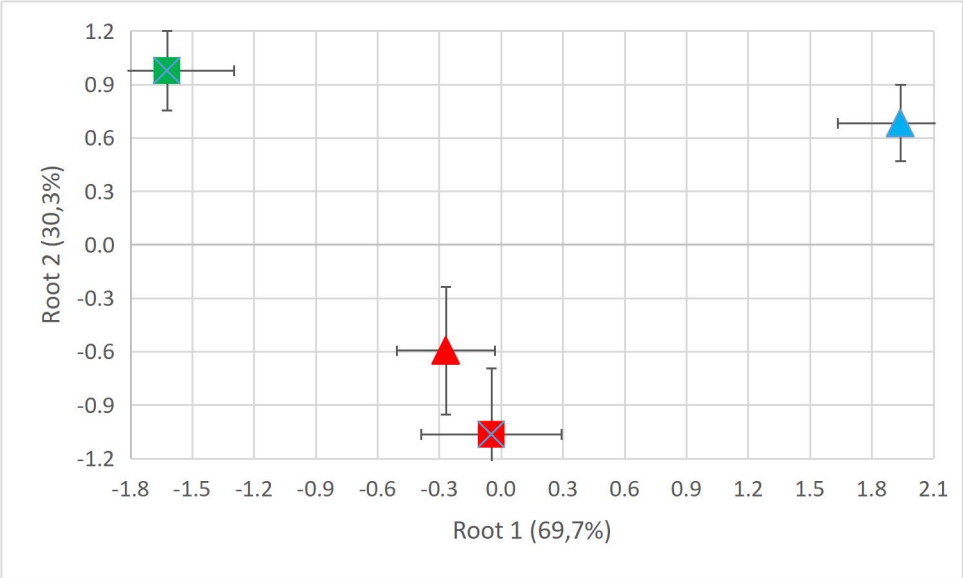


Fig. 15. Scattering of average values (M±SE) of the first and second discriminant roots of patients before and after the course of standard balneotherapy (triangles) and in combination with Balm "Truskavets'" (squares)

The shift along the axis of the first root of the centroid of the control group to the right relative to its initial localization reflects both an increase in the parameters that are positively correlated with the root, and a decrease in the parameters associated with it inversely. Instead, the opposite shift of the centroid of patients who received combined phytobalneotherapy reflects its opposite effects on these parameters (as well as on those not included in the model, but presented in Table 16 and Fig. 1).

An additional, but less tangible, delimitation of groups occurs along the axis of the second root. The top position of the main group of patients reflects, more deeply than in the control group, a decrease in EEG parameters inversely related to the root (as well as not included in the model, but included in the fifth cluster - Fig. 1).

In addition, it is worth noting three parameters of the sixth cluster (Fig. 1), which deviate in opposite directions relative to the initial levels, but are not visualized in the information field of the roots, since they were not included in the model.

Table 16. Correlations between variables and roots, centroids of clusters and Z-scores of clusters. Clusters are separated by spaces

Variables	Correlations Variables-Roots		After Standard ther +Balm (11	Before Standard therapy (22)	After Standard therapy (11)	Efect of Balm (11)	Effect of The-rapy (11)
Root 1 (69,7 %)	**Root 1**	**Root 2**	**-1,62**	**-0,16**	**+1,94**	**-3,56**	**+2,10**
Heart Rate	**0,587**	0,177	**-0,94±0,33**	**-0,30±0,28**	**+1,42±0,29**	**-2,36**	**+1,72**
LF PSDr	**0,330**	-0,222	**+0,16±0,36**	**+1,16±0,19**	**+1,59±0,41**	**-1,43**	**+0,43**
T6 PSD Entropy	**0,130**	-0,204	**-1,04±0,46**	**-0,39±0,20**	**-0,43±0,36**	**-0,61**	**+0,04**
T4 PSD Entropy			**-0,77±0,46**	**-0,28±0,22**	**-0,16±0,27**	**-0,61**	**+0,12**
BP Diastolic			**-0,84±0,28**	**-0,49±0,33**	**+0,27±0,38**	**-1,11**	**+0,76**
Creatinine			**+0,20±0,25**	**+0,39±0,17**	**+0,93±0,30**	**-0,73**	**+0,54**
Urea			**-0,57±0,40**	**+0,02±0,27**	**+0,93±0,42**	**-1,50**	**+0,91**
T-helper Lymph	**0,054**	0,285	**-0,74±0,22**	**-1,17±0,22**	**-0,64±0,31**	**-0,10**	**+0,53**

ULF PSDr			+1,06±0,52	+0,95±0,25	+0,07±0,35	+0,99	-0,88
PWC$_{150}$	-0,301	-0,006	-0,12±0,19	-0,44±0,18	-1,35±0,13	+1,23	-0,91
Glomerular Filtr			-0,93±0,26	-1,24±0,16	-1,70±0,15	+0,77	-0,46
Reticulocytes	-0,217	0,062	-0,39±0,23	-0,65±0,13	-0,87±0,13	+0,48	-0,22
B-Lymphocytes	-0,143	-0,115	-0,40±0,30	-0,58±0,24	-0,91±0,19	+0,51	-0,43
Bilirubin	-0,106	-0,014	-0,38±0,16	-0,49±0,21	-0,70±0,21	+0,32	-0,21
Malondyaldehid			+0,03±0,26	-0,10±0,21	-0,38±0,29	+0,41	-0,28
Root 2 (30,3 %)	Root 1	Root 2	+0,98	-0,83	+0,68	+0,30	+1,51
F8-θ PSDr	0,102	-0,481	-0,72±0,18	+0,06±0,17	-0,34±0,25	-0,38	-0,40
Fp2-θ PSDr	0,007	-0,372	-0,37±0,19	+0,14±0,17	-0,27±0,22	-0,10	-0,41
T5-θ PSDr			-0,68±0,18	-0,06±0,16	-0,49±0,21	-0,19	-0,43
Frequency-β			-0,11±0,23	+0,68±0,21	+0,43±0,31	-0,54	-0,25
O2-δ PSDr			+0,28±0,56	-0,55±0,15	-0,33±0,20	+0,61	+0,22
O1-δ PSDr			+0,70±0,55	-0,21±0,20	-0,20±0,24	+0,90	+0,01
Γ-globulins			-0,15±0,11	-0,57±0,20	-0,49±0,30	+0,34	+0,08

Although the distinction between the integrated states of patients at admission and after the two therapy schemes is not sufficiently clear, the differences are statistically significant, which is documented by the calculation of Mahalanobis distances (Table 17).

Table 17. Squares of Mahalanobis distances between groups (above the diagonal) and F-criteria (df=10,3) with p-levels (below the diagonal)

Groups	Before ST (22)	After ST + Balm (11)	After ST (11)
Before therapy	***	5,41	6,68
After Combined therapy	3,10; p=0,007	***	12,8
After Standard therapy	3,83; p=0,002	5,48; p=10^{-4}	***

Selected discriminant variables were used to identify the affiliation of a patient to a particular groups. This goal of discriminant analysis is realized with the help of classification functions (Table 18).

Table 18. Coefficients and constants of classification functions

Groups	Before Standard therapy	After Standard Therapy + Balm	After Standard therapy
Variables	p=,50	p=,25	p=,25
Heart Rate, beats/min-	2,208	2,231	2,457
LF PSD, %	0,200	0,069	0,279
F8-θ PSD, %	-1,716	-2,145	-2,040
T-helper Lymphocytes, %	1,873	2,134	2,029
Bilirubin, μM/L	3,204	3,602	2,781
Fp2-θ PSD, %	-1,292	-1,416	-1,670
T6 PSD Entropy	79,97	80,98	89,33
B-Lymphocytes, %	2,356	2,600	2,178
Physical Working Capacity, W/kg	1,492	1,580	1,460
Reticulocytes, ‰	10,82	11,58	11,07
Constant	-253,5	-276,0	-271,7

The classification accuracy is quite high (Table 19).

Table 19. Classification Matrix

Group	Rows: Observed classifications Columns: Predicted classifications			
	Percent Correct	Before therapy p=,50	After comb therapy p=,25	After stand therapy p=,25
Before	86,4	19	2	1
Comb therapy	81,8	2	9	0
Stand therapy	90,9	1	0	10
Total	86,4	22	11	11

CONCLUSION

Phytocomposition "Balm Truskavets'" by modulating the parameters of the nervous system limits the adverse effects of standard balneotherapy at the Truskavets' Spa in patients with post-radiation encephalopathy.

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ACCORDANCE TO ETHICS STANDARDS

Tests in patients are carried out in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, and directive of National Committee on ethics of scientific researches. During realization of tests from all participants the informed consent is got and used all measures for providing of anonymity of participants.

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