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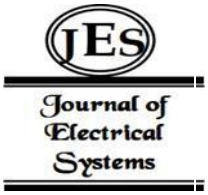
Burdock Root Extract in Combined Therapy of Lymphoproliferative Diseases: Clinical Trial



Abstract: - The importance of identifying effective ways of dealing with endogenous intoxication in Lymphoproliferative disorders is acknowledged. Proper nutrition helps fight infection and provides the body with a sufficient amount of energy. For centuries, burdock root has been used for cleansing and detoxifying. In this study, we assessed the efficacy of two biologically active food supplements with nutrient-rich burdock root extract in combined therapy for LPDs. For the trial, people with stages II-IV non-Hodgkin lymphomas or with stages II-III multiple myeloma were selected. The participants were divided equally into two groups: the main group and the comparison group. The participants for both groups possessed similar characteristics and clinical data. The participants of the main group were prescribed to take supplements with concentrated burdock root extract between three treatment cycles of polychemotherapy. The supplements with burdock root extract were found to significantly reduce the severity of endogenous intoxication and improve the tolerability of systemic chemotherapy.

Keywords: Lymphoproliferative disorders, Burdock root, Supplement, Clinical trial

I. INTRODUCTION

Lymphoproliferative disorders (LPDs) are characterized by endogenous intoxication, which is an abnormal condition with a non-specific response of the body and a homeostasis imbalance. Endogenous intoxication can be caused by several factors, including tissue hypoxia, disrupted cellular destruction and renewal processes due to the spread of cancer cells to surrounding tissues, disrupted functioning of internal organs, and general inflammatory response of the immune system to tumor cells. The inflammatory response affects the whole human body, activating catabolic processes, increasing the number of metabolic products in serum, worsening health status, and reducing tolerability. The most common causes of endogenous intoxication in patients with LPDs include the toxic effect of cytostatic therapy and the systemic inflammatory response syndrome triggered by the increased activity of the immune system.

Given the importance of proper nutrition in fighting infection and providing the body with a sufficient amount of energy, it is important to consider different approaches to nutritional care for patients with LPDs. For centuries, burdock root has been used for cleansing and detoxifying. Studies have shown that arctiin and arctigenin have a cytotoxic effect on tumor cells [1-3, 4] and asparagines prevent cancer cells from growing [1, 5, 6]. Burdock root has an antioxidant effect and is beneficial for metabolic processes [7-10]. The nutritional value and potential health benefits of burdock root can be used: (a) in antitumor therapy as a detoxifying agent in patients with

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hemoplastic diseases when treated with polychemotherapy, (b) for enhancing drug therapy, (c) in cancer rehabilitation programs, (d) for preventing cancer.

II. MATERIALS AND METHODS

We performed a clinical trial to examine the efficacy of two new biologically active food supplements with concentrated burdock root extract. The studied supplements, namely Arktavit and Toksidont-May+, are manufactured by Biolit in the city of Tomsk. Both products are thick brown liquids (syrups) with a sweet-and-sour taste and a pleasant smell. They are nutrient-rich and include macro- and micro-elements, asparagine, resins, inulin, phytosterol, protein, stigmasterol, essential bardan oil, sitosterol, tannins, stearic and palmitic acids, and bitters.

Arktavit and Toksidont-May+ supplements meet the requirements of international standards on food safety management (ISO 22000) and current Good Manufacturing Practices and are included in the Federal Register for food supplements of the Russian Federation.

Sixty subjects, 16 males (42.5%) and 34 females (57.5%) between 44 and 72 years of age, with B-cell lymphoproliferative disorders, were selected for the trial. The participants included 31 individuals (51.7%) diagnosed with stages II-IV non-Hodgkin lymphomas (NHL) and 29 individuals (48.3%) diagnosed with stages II-III multiple myeloma (MM). The participants were provided with information about the study and signed an informed consent to be included in the trial.

The participants were divided equally into two groups: the main group and the comparison group. The participants in both groups possessed similar characteristics and clinical data. The participants of the main group were prescribed to take Arktavit or Toksidont-May+ supplements between three treatment cycles of polychemotherapy. The supplements were taken for a period of 14 days (the total number of days amounted to 44 days). A half of measuring spoon of the supplement was diluted in a glass of warm water and taken on an empty stomach three times a day. The participants in the comparison group were treated with polychemotherapy only.

The clinical trial was performed at the premises of City Hospital 2 of Novosibirsk City and the central research laboratory of Novosibirsk State Medical University. The study was supervised by T.I. Pospelova, Professor, Doctor of Medical Science, and Head of the Department of Therapy, Haematology, and Transfusiology at Novosibirsk State Medical University. The clinical trial was performed following the Guidelines for Good Clinical Practices and the Declaration of Helsinki on medical research.

We assessed the following before, during, and after the clinical trial:

- The intensity of endogenous intoxication (generalized weakness, fatigue, lack of physical or muscle strength, loss of sleep or appetite, weight loss, muscle pain, headaches, sweating, and emotional lability);
- The severity of endogenous intoxication (C-reactive protein level (CRP), fibrinogen, creatinine, urea, uric acid, lactate dehydrogenase (LDH), alkaline phosphatase, the cytokine profile). The data on twenty healthy individuals (the control group) was used to examine the cytokine profile;
- the changes in the intensity and severity of endogenous intoxication;
- tolerability of the studied supplements and side effects.

The treatment results were assessed by both doctors and patients.

The concentration of pro-inflammatory cytokines (IL-1ß, IL-6, and TNF-α) was studied with the enzyme-linked immunosorbent assay technique. The Thermo Labsystems Multiskan and Vector-Best test systems were used. The control group was comprised of 20 participants who had neither neoplastic processes nor exacerbations of chronic diseases at the time when the concentrations of cytokines were studied.

For statistical analysis, the standard application package Statistica 7.0 (StatSoft, USA) and SPSS Statistics (version 16.0) were applied.

To summarise the data, we applied a descriptive analysis ($M \pm \sigma$), where M represents the arithmetic mean and σ represents the standard deviation.

The statistical significance of differences was assessed using the student's t-test for the means of two groups and the Mann-Whitney test for the distributions.

To compare qualitative characteristics, we applied Pearson's chi-square test ($\chi 2$), when the total number of observations was ≥ 50 and the number of each variant of values was ≥ 5. The criterion for statistical significance was $P < 0.05$.

III. RESULTS AND DISCUSSION

In this study, we assessed the efficacy of two supplements with burdock root in combined therapy for LPDs. Only 58 out of 60 subjects completed the clinical study. The course of polychemotherapy was temporarily suspended for two subjects with non-Hodgkin lymphomas (one from the main group and the other from the comparison group) as they got infected with coronavirus. Therefore, the subjects were excluded from the clinical trial. The remaining subjects completed the clinical trial following the protocol.

Before the start of the clinical trial, all subjects in both groups complained about weakness, fatigue, headaches, and emotional lability. Complaints about a low-grade fever were made by 34.5% of the patients from the main group and 31% of the patients from the comparison group. Sleeping troubles and weakness were recorded in 41.5% and 34.6% of the patients; lack of appetite, muscle weakness, and health-related low performance were recorded in 31% and 34.5% of the patients, respectively.

Upon treatment, the subjects reported improved general well-being. The most significant improvements were reported for (a) weakness – with a decrease from 100% to 31% in the main group and a decrease from 100% to 58.6% in the comparison group ($\chi 2=21.1$; $p_{2-4}<0.001$), (b) generalized weakness – from 41.4% to 6.9% and from 34.5% to 17.2% ($\chi 2 = 4.7$; $p_{2-4}=0.03$), (c) emotional lability – from 100% to 24.1% and from 100% to 48.3 % ($\chi 2=12.5$, $p_{2-4}<0.001$), (d) health-related low performance - from 31% to 6.9% and from 34.5% to 17.2% ($\chi 2 = 4.73$; $p_{2-4}=0.03$), (e) nausea – from 31% to 3.4% and from 34.5% to 10.3% ($\chi 2 = 4.03$, $p_{2-4} = 0.045$). The data is presented in **Table 1**.

Table 1. The changes in the clinical signs of endogenous intoxication in patients with LPDs: before and after treatment

Clinical signs	Main group (n=29)		Comparison group (n=29)	
	Before treatment 1	After treatment 2	Before treatment 3	After treatment 4
Weakness	29 (100%)	9 (31%)	29 (100%)	17 (58.6%) $\chi 2=21.1$ $p_{2-4}<0.001$
Fatigue	29 (100%)	6 (20.1 %)	29 (100%)	15 (51.7%) $\chi 2=21.9$ $p_{2-4}<0.001$
Generalised weakness	12 (41.4%)	2 (6.9 %)	10 (34.5%)	5 (17.2%) $\chi 2=4.7$ $p_{2-4}=0.03$
Emotional lability	29 (100%)	7 (24.1 %)	29 (100%)	14 (48.3 %) $\chi 2=12.5$ $p_{2-4}<0.001$
Muscle weakness	9 (31%)	2 (6.9 %)	10 (34.5%)	4 (13.8%) $\chi 2=2$ $p_{2-4}<0.158$
Low-grade fever	10 (34.5%)	0	9 (31%)	2 (6.9%) $\chi 2=7.25$ $p_{2-4}<0.008$
Headache	29 (100%)	5 (17.2 %)	29 (100%)	5 (17.2%) $\chi 2=0$ $p_{2-4}=1$

Sleeping troubles	12 (41.4%)	3 (10.3%)	16 (34.5%)	6 (20.7%) $\chi 2$=3.92 p_{2-4}=0.048
Health-related low performance	9 (31%)	2 (6.9%)	10 (34.5%)	5 (17.2%) $\chi 2$=4.73 p_{2-4}=0.03
Nausea	9 (31%)	1 (3.4%)	10 (34.5%)	3 (10.3 %) $\chi 2$=4.03 p_{2-4}=0.045

The analysis of biochemical markers, which was undertaken prior to treatment, indicated that important biochemical markers (fibrinogen, urea, uric acid) were outside of the reference range. Higher levels of biochemical markers signaled increased catabolism in patients with NHL and MM.

Upon treatment, lower levels of biochemical markers were registered in both groups **(Table 2)**.

Table 2. The changes in biochemical markers in patients with LPDs: before and after treatment

Biochemical markers	Main group (n=29)		Comparison group (n=29)	
	Before treatment 1	After treatment 2	Before treatment 3	After treatment 4
CRP (mg/l) reference range (0-5.0)	6.43±2.14	1.72±0.22 p_{1-2}<0.001	Before treatment 3	3.24±0.53 p_{3-4}<0.05 p_{2-4}<0.006
LDH (U/L) reference range (195-450)	410.8±171.9	210.5±41.2 p_{1-2}<0.001	5-94±1.93	342.9±67.1 p_{3-4}<0.08 p_{2-4}<0.043
Fibrinogen(g/L) reference range (2,0-4,0)	6.62±0.52	2.11±0.41 p_{1-2}<0.001	443.6±201.4	4.7±1.52 p_{3-4}<0.05 p_{2-4}<0.004
Urea (mmol/L) reference range (2,9 - 8,2)	10.31±1.8	5.4±1.7 p_{1-2}<0.001	6.24±1.21	7.9±2.4 p_{3-4}<0.07 p_{2-4}<0.032
Uric acid (mmol/L) reference range (200-420)	567.3±43.1	250.1±34.8 p_{1-2}=0.005	9.8±3.12	346.3±28.1 p_{3-4}<0.05 p_{2-4}<0.042
Creatinine (µmol/L) reference range (40-115)	112.1±21.4	74.5±1.33 p_{1-2}=0.008	597.3±23.8	101.6±2.67 p_{3-4}<0.8 p_{2-4}<0.048
Alkaline phosphatase (U/L) reference range (70-270)	245.8±193.7	94.2±43.4 p_{1-2}<0.005	125.3±11.8	135.2±31.4 p_{3-4}<0.05 p_{2-4}<0.081

Upon completion of three treatment cycles of polychemotherapy, the changes in biochemical markers before and after therapy were statistically less significant in patients from the comparison group. The results obtained confirm the effectiveness of the two supplements with burdock root.

When the cytokine profile was examined before the treatment, the concentration of all studied pro-inflammatory cytokines (IL-1ß, TNF-α, IL-6) in patients with LPD was higher than in the control group **(Table 3)**. Our findings correlate with existing research on cytokines and their broad functions in inflammation and immunity [11-16]. Higher levels of pro-inflammatory cytokines, increased tumor mass, and metabolic changes contribute to a higher level of endogenous intoxication.

Table 3. The concentration of pro-inflammatory cytokines in patients with LPDs before the treatment

Cytokines	All patients with LPDs before treatment (n = 58)	The control group (n = 20)	Statistical significance, p
IL-1ß (pg/ml)	2.81 [1.3; 4.5]	1.6 [0; 11]	p = 0.032

TNF-α (pg/ml)	2.84 [1.62; 16.7]	0.5 [0; 6]	p = 0.008
IL-6 (pg/ml)	11.5 [3.6; 41.4]	2 [0; 10]	p= 0.002
Note: Data are presented as median [25th; 75th percentile]			

The increase in the concentration of the pro-inflammatory cytokines in LPD is explained by the interaction between tumor cells and the immune system. Macrophages are known to contribute to inflammation by secreting IL-6, IL-1β, and TNF-α. [3, 8, 17-21]

Tumor cells (atypical lymphoid and plasma cells) promote the secretion of cytokines, which may cause chronic inflammation and support tumor growth in both autocrine and paracrine manners [22-28].

Upon treatment, lower levels of cytokines were registered in patients with LPDs from the main group **(Table 4)**. The results obtained confirm the positive impact of burdock root extract and its ability to act as an anti-inflammatory and detoxifying agent and, thus, reduce the manifestations of a systemic inflammatory response in patients with LPDs.

Table 4. The concentration of pro-inflammatory cytokines in patients with LPDs after the treatment

Cytokines	Main group (n=29)	Comparison group (n=29)	The control group (n = 20)	Statistical significance, p
	1	2	3	
IL-1ß (pg/ml)	2.02 [1.32; 3.7]	3.65 [2.15; 4.5]	1.6 [0; 11]	$p < 0.01$ [1.2.3]
TNF-α (pg/ml)	2.3 [1.62; 8.51]	6.49 [2.62; 12.7]	0.5 [0; 6]	$p < 0.01$ [1.2.3]
IL-6 (pg/ml)	10.6 [3.72; 35.1]	25.5 [5.64; 40.2]	2.0 [0; 10]	$p < 0.01$ [1.2.3]

Note: Data are presented as median [25th; 75th percentile]
1. The differences are statistically significant between the main and comparison groups of patients with LPDs;
2. The differences are statistically significant between the main group with LPDs and the control group;
3. The differences are statistically significant between the comparison group with LPDs and the control group.
n is the number of patients in the group.

When assessing the results of the treatment, four patients (13.8%) stated significant improvement and twenty-two (76%) stated moderate improvement in general well-being, while three patients (10.3%) stated no improvement.

The doctors, who were assessing the results of the treatment, stated improvement in general well-being and reduction in endogenous intoxication in twenty-two patients (76%) and lack of improvement in seven patients (24%). Lack of improvement might also be due to the toxic side effects of chemotherapy.

Most patients noted the good organoleptic properties of both supplements with burdock root extract and confirmed the absence of side effects. The maximum effect of burdock root extract was registered at the end of the second two-week period (for some patients) and at the end of the third two-week period.

The findings of our study demonstrate the effectiveness of using supplements with burdock root in combined therapy since they can significantly reduce the severity of endogenous intoxication and improve the tolerability of systemic chemotherapy.

IV. CONCLUSION

1. The two examined supplements with burdock root extract have anti-inflammatory and detoxifying properties and can be used with chemotherapy for patients with LPDs (NHL and MM).
2. The two examined supplements with burdock root extract help reduce clinical and biochemical manifestations of endogenous intoxication in 76% of patients.
3. The use of Arktavit and Toksidont-May+ supplements in the combined therapy of patients with LPDs allows for cytostatic therapy to be performed without reducing the dose, and, therefore, increases the effectiveness of an antitumor therapy.
4. Taking into account good tolerability and the absence of side effects, we can recommend the studied supplements for treating and preventing endogenous intoxication in patients with LPDs between courses of chemotherapy.

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Conflict of interest

None.

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Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki.

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