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Efficacy and safety of quercetin and polyvinylpyrrolidone in treatment of patients with newly diagnosed destructive pulmonary tuberculosis in comparison with standard antimycobacterial therapy

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ABSTRACT

Objective/background: The objective/background of this work was to study the efficacy and safety of quercetin and polyvinylpyrrolidone (QP) in the treatment of patients with newly diagnosed destructive pulmonary tuberculosis in comparison with standard antimycobacterial therapy.

Materials and methods: The study involved 124 patients aged between 20 years and 70 years with newly diagnosed destructive pulmonary tuberculosis. Patients were allocated to two groups. The first (control) group of patients received standard antimycobacterial and pathogenetic therapy and included 31 (25.00 ± 3.89%) patients. The second (main) group of patients received QP therapy in addition to chemotherapy and included 93 (75.00 ± 3.89%) patients.

Results: Intoxication symptoms in the second group were reduced following 1.33 ± 0.15 months, whereas in the first group intoxication symptoms were reduced following 2.64 ± 0.20 months, $p < .001$.

Conclusion: Administration of QP combined with chemotherapy in patients with newly diagnosed destructive pulmonary tuberculosis resulted in a comparatively quick reduction of disease manifestation.

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Introduction

Tuberculosis (TB) is a re-emerging global public health problem, the incidence of which has increased in the Ukraine, as well as in other countries [1].

The therapeutic outcome in patients with pulmonary TB with bacterial excretion remains insufficient despite high efficacy of chemotherapy [2–4]. In 2013, in Ukrainian newly diagnosed patients, the frequency of cessation of bacterial excretion was 63% [5]. Thus, 37% of patients are contagious, which is favorable for TB circulation in a population [5]. In addition, the number of patients with primary drug-resistant *Mycobacterium tuberculosis* (MTB) has increased recently not only in Ukraine but all over the world [5–8]. In patients who excrete MTB, cavitary lesions are usually observed. It is impossible to achieve complete cure of a patient because without healing the cavitary lesions which are the main source of infection, allowing the maintenance of the microbial population leads to repeated bronchogenic spread of TB [9,10]. Modern regimens of antimycobacterial therapy have allowed the cessation of bacterial excretion to be reached in 67–96% of TB patients [11–13]. Development of new therapeutic technologies is one of the factors aimed to increase the treatment efficacy in patients with pulmonary TB [14]. Combined antibacterial therapy is deemed to be the main modern method for TB treatment [15,16]. Administration of antibacterial drugs is essential nowadays.

As defined by the World Health Organization, effective treatment results in the cessation of bacterial excretion without consideration of destruction healing in the lungs. Unhealed cavitary lesions are considered as residual changes [17,18]. However, it was shown [19–21] that unhealed cavitary lesions may cause TB recurrence under short courses of chemotherapy associated with no clinical and X-ray signs of TB improvement. Over the past years, TB recurrence tends to increase. Thus, the mortality rate related to TB recurrence increased by sevenfold [22,23].

Thus, the introduction of standard treatment regimens recommended by the World Health Organization does not provide a significant increase in the effectiveness of treatment [1].

Gaps in the understanding of the pathophysiologic networks between the human body and MTB is one of the reasons for low treatment efficacy. Consequently, combined therapeutic approaches aim to inhibit MTB and block the expansion of infected tissues. Thus, we should consider how to preserve unaffected tissues from further destruction and prevent any consequences related to TB.

When both myocardial hypoxia, triggered by the destruction of lung tissue, and TB progress, cardiopulmonary failure develops and may subsequently lead to the patient's death. Restoration of respiratory function in pulmonary TB is an essential hallmark for clinical cure, and medical and social rehabilitation of patients with respiratory diseases.

Regulation of the immune system in combined antibacterial therapy was found to be essential for higher efficiency of administered therapy [24–27]. Intensive antibacterial therapy reduces intoxication and improves the patient's general condition but does not reduce immune system impairment. Lung tissue destruction and immune system violations lead to further progression of inflammation [28,29]. TB outcome depends on the immunobiological status of the patient, as well as the complicated symbiotic interaction between MTB and the human body [30,31].

Every TB type is associated with immunopathological inflammation caused by the violation of microcirculation and trophopathy of lung tissue that may be complicated by matrix destruction, caseous mass excretion through the bronchi, and destructed region generation. This worsens the course of TB and may lead to partial or complete lung dysfunction if effective treatment is not administered. It was demonstrated that a new effective complex treatment in therapeutic conditions is required [28,32,33]. It was shown that treatment is primarily aimed at MTB elimination. There is no data available regarding the administration of therapy leading to lung tissue preservation through limiting pathological changes and matrix destruction prevention as well as rapid alleviation of intoxication syndrome associated with immune system restoration. We investigated the advantages of quercetin combined with polyvinylpyrrolidone (QP). QP is a capillary stabilizing agent and antioxidant (bioflavonoids) with immunomodulatory activity. We have shown that QP administration in TB-infected mice results in necrosis limitation from spreading to unaffected tissues [34]. Therefore, it allows localizing necrotic changes, limiting the pathological process, and preserving the affected lung. The fact that QP can influence the inflammatory process through necrosis limitation inspired us to investigate QP efficacy in TB patients.

Thus, the aim of our study was to investigate the efficacy and safety of QP in patients with newly diagnosed destructive pulmonary TB (NDTB) compared with standard antimycobacterial therapy.

Materials and methods

Patients

The study involved 124 patients with NDTB who were aged between 20 years and 70 years. All patients who presented with NDTB were enrolled in this study.

The patients were allocated to two groups. The first (control) group of 31 (25.00 ± 3.89%) patients received standard chemotherapy. The second (main) group of 93 (75.00 ± 3.89%) patients received QP therapy in addition to standard chemotherapy.

The first group included 27 (87.10 ± 6.02%) men and four (12.90 ± 6.02%) women. The second group included 64 (68.82 ± 4.80%) men and 29 (31.18 ± 4.80%) women. The difference between sex and age in both groups was statistically insignificant ($p > .05$).

All study patients presented with the active form of pulmonary TB. The most common symptoms were prolonged heavy cough, pain in the chest, subfebrile temperature fever, profuse night sweats, fatigue, dyspnea, and loss of weight and decreased appetite.

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Active pulmonary TB was defined by a medical history and clinical findings compatible with TB, a chest X-ray showing lung involvement, and a positive sputum smear for acid-fast bacilli and positive culture for MTB.

On the patients' admission to hospital, infiltrative TB was the most common type and was observed in every patient of the first group. In the second group, infiltrative TB was observed in 88 (94.62 ± 2.34%) patients. Moreover, five (5.38 ± 2.34%) patients of the second group were diagnosed with disseminated TB. Quantitative characteristics of TB cases within both groups of patients were evaluated and shown to be insignificant ($p > .05$). The difference between the spread of the TB process in the lungs and the number and size of destructions was insignificant ($p > .05$).

Ethics

The project was approved by the Ethics Committee of the Kharkiv National Medical University, Ukraine. It was conducted according to the Declaration of Helsinki standards. All of the patients provided written informed consent and explicitly provided permission for treatment and blood analyses, as well as for the collection of relevant clinical data.

Treatment regimen

All patients received standard chemotherapy, consisting of orally administered isoniazid (0.3 g), rifampicin (0.6 g), pyrazinamide (2 g), ethambutol (1.2 g), and/or an intramuscular injection of streptomycin (1 g) with a dose reduction after the intensive phase of the therapy. The anti-TB drugs were procured through the Ukraine's centralized national supply system.

QP was used in a dose of 0.5 g in 100 mL of 0.9% sodium chloride solution intravenously once per day for 10 days starting on admission to the hospital.

Laboratory evaluation

A standard microbiological examination of a sputum smear stained using the Ziehl–Neelsen and culture Löwenstein–Jensen methods was conducted prior to study entry and at Day 30, Day 90, and Day 150 from the start of treatment. Isolates of MTB were tested for sensitivity to first- and second-line anti-TB drugs with a commercially available kit (Tulip Diagnostics Pvt Ltd., Goa, India). The biochemical parameters were evaluated using standard routine techniques at baseline and repeated 2 months later.

The levels of cytokines (interleukin [IL]-1β, IL-4, and tumor necrosis factor-α [TNF-α]) in serum were evaluated using standard enzyme-linked immunosorbent assay kits (Vector-Best, Novosibirsk, Russian Federation). Serum samples for testing were taken during the 1st days of admission and after 1 month of in-patient treatment. Due to the peculiarities of the method, we included 20 apparently healthy donors into the study of cytokines.

X-ray evaluation

Pathological peculiarities, for example, the severity of the disease and changes in localization, were assessed through X-ray. Chest fluorography was performed in the out-patient department for every patient involved in the study. In cases of pathological findings, we conducted a chest X-ray (two views). Targeted tomography of the destructed area on selected sections was performed in every patient. Interpretation of the thorough X-ray examination allowed us to estimate newly TB diagnosis, specifically, to detect localization, severity, and peculiarities of TB cavities in the lungs. X-ray monitoring of patients was repeated every 2 months following the start of treatment until the end of the continuation phase (8 months).

Statistical evaluation

The obtained data were statistically analyzed using standard Student t test [35]. The difference was considered to be significant at $p < .05$.

Results and discussion

Regression of intoxication and respiratory symptoms were the hallmarks of estimating how rapidly disease manifestation terminates under QP administration. Intoxication symptom regression was evaluated regarding subjective symptoms (increased appetite, general revival, fatigue, and sweating alleviation), normalization of body temperature, and body weight, which were considered as symptoms of TB intoxication. Respiratory symptoms were evaluated through dyspnea, cough, and chest pain reduction or alleviation. Data are shown in Table 1. Therefore, in the second group, patients demonstrated more rapid intoxication and respiratory symptom alleviation than the first group. Coughing and dyspnea are mainly related to the severity of the specific process in the lungs and bronchial lesions. They attenuated more rapidly in patients of the second group in comparison with the first group.

Weight gain is a crucial sign of patient's recovery that may indicate not only total weight restoration but also the overall regeneration of affected regions in the human body. Weight changes following 1 month of treatment in comparison with weight parameters prior to treatment were as follows: first group: before treatment 62.35 ± 2.12 kg, 1 month after treatment 64.97 ± 2.03 kg, $p = .37$; second group: before treatment 64.40 ± 1.07 kg, 1 month after treatment 69.24 ± 1.06 kg, $p = .002$. It was found that weight parameters in the second group were higher in comparison with the first group following 1 month of treatment.

Thus, QP treatment resulted in more rapid regression of intoxication following 1.33 ± 0.15 months in the second group and following 2.64 ± 0.20 months in the first group ($p < .001$). Complete regression of respiratory symptoms in patients of the second group was observed following 1.43 ± 0.30 months, and following 2.33 ± 0.30 months in patients of the first group ($p < .05$).

Adverse reactions to anti-TB drugs during treatment were observed in 17 (13.71 ± 3.09%) patients: nine (29.03 ± 8.15%) in the first group and eight (8.60 ± 2.91%) in the second group ($t = 2.36$, $p < .05$). In the second group, side effects of anti-TB drugs were observed only at the early phase of treatment.

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Table 1 – Period of reduction of tuberculosis clinical signs in patients of the groups.

Clinical symptoms	First group			Second group			p
	No. at the beginning of treatment, (M ± m)		Terms of disappearance of clinical signs (mo), (M ± σ)	No. at the beginning of treatment, (M ± m)		Terms of disappearance of clinical signs (mo), (M ± σ)	
	n	%		n	%		
Intoxication symptoms							
Weakness	21	67.74 ± 8.40	2.73 ± 1.11	41	44.09 ± 5.15	0.86 ± 0.57	<.05
Loss of appetite	7	22.58 ± 7.51	2.42 ± 0.53	5	5.38 ± 2.34	0.58 ± 0.2	<.05
Fatigue	12	38.71 ± 8.75	3.25 ± 0.45	13	13.98 ± 3.60	2.2 ± 0.44	<.05
Night sweats	17	54.83 ± 8.84	3.23 ± 0.66	24	25.81 ± 4.54	1.28 ± 0.46	<.05
Increased body temperature	19	61.29 ± 8.75	2.05 ± 0.91	21	22.58 ± 4.34	0.55 ± 0.32	<.05
Respiratory symptoms							
Cough	26	83.87 ± 6.61	3.38 ± 0.8	44	47.31 ± 5.18	1.84 ± 0.6	<.05
Dyspnea	20	64.52 ± 8.59	1.3 ± 0.41	19	20.43 ± 4.18	0.25 ± 0.15	<.05
Pain in the chest	3	9.68 ± 5.31	2.33 ± 0.32	25	26.88 ± 4.60	1.57 ± 0.53	<.05

Note. The *p* value is the significance of difference between parameters in Groups 1 and 2. mo = months.
σ - mean square deviation value of the indicator; m - arithmetic mean error.

Side effects of antimycobacterial drugs completely alleviated following two to three injections of QP. Considering these data, we can assume that QP diminishes adverse reactions to anti-TB drugs (cardiotoxic disorders, toxic hepatitis, and allergic dermatitis). Thus, QP provides higher tolerance to anti-TB drugs by 20.42%. Side effects of QP administration were not observed. Some patients had more than one side effect to anti-TB drugs.

A biochemical study through the course of treatment did not reveal any significant changes of cholesterol, total bilirubin, and protein concentrations (thymol test; Table 2). Either before the start of the therapeutic regimen or following 2 months of treatment these parameters were within normal limits, except rare cases. Nevertheless, we should also consider alanine aminotransferase and aspartate aminotransferase concentrations. As shown in Table 2, the toxic effect on the body in the second group of patients was more prominent compared with the first group prior to the treatment of TB. Following 2 months of treatment, patients of the first group demonstrated a significantly higher concentration of these proteins due to liver and heart-related side effects of the anti-TB drugs. By contrast, the opposite trend was observed in patients of the second group, due to the cardioprotective and hepatoprotective effects of QP in TB and drug intoxication as we have already shown in mice [34].

In order to elucidate the mechanisms of caseous necrosis limitation and reduction observed in the experiment [34] and the immunomodulatory effect of QP, we conducted further research aimed at the estimation of cytokine IL-1β, TNF-α, and IL-4 levels (Table 3).

Prior to treatment, patients of both groups demonstrated a significant increase in cytokine levels in comparison with apparently healthy donors (control group in the cytokine study). Following 1 month of therapy, concentrations of these cytokines changed significantly. Thus, the levels of IL-1β and TNF-α significantly decreased. Consequently, a decrease of TNF-α and IL-1β levels was observed through the course of standard therapy. QP administration resulted in a more pronounced decrease of TNF-α and IL-1β levels. In contrast to the reduction of the above-mentioned cytokine levels, IL-4 level increased significantly through the course of treatment. Standard monthly therapy was associated with an IL-4 level increase, whereas QP administration resulted in higher IL-4 levels.

Considering the parameters mentioned above, we accentuate a pronounced reduction of IL-1β and TNF-α levels in the second group of patients compared with the first group. Reduction of IL-1β and TNF-α due to QP administration improves the growth of endothelial cells and induces the activation of microcirculation at the inflammatory site, reduces blood clotting, and reduces the MTB population. These cytokines decrease nitric oxide (NO) production in peripheral blood, as evidenced by the reduction of its metabolites in patients of the second group. This is supported by the prevention of cell damage and death, as well as the activation of microcirculation at the inflammatory site where NO increases and eliminates MTB whereas in peripheral blood the NO level decreases. Moreover, a rapid increase of IL-4 induced by QP administration reduces the production of reactive oxygen species by macrophages and indicates an increase of T-helper population, because these cells predominantly produce IL-4. Consequently, the caseation process is prevented.

The frequency of bacterial excretion cessation is a crucial parameter used to evaluate the efficacy of pulmonary NDTB treatment (Tables 4 and 5). The obtained data demonstrate that bacterial excretion cessation is observed following a significantly shorter period of treatment in the second group compared with the first group that was confirmed with both microscopic study and culture.

Furthermore, healing of cavitary lesions and the elimination of infiltrative changes is one of the most important indicators in evaluating the efficacy of pulmonary NDTB treatment (Table 6). Throughout the period of observation, the healing of cavities was more common in patients of the second group.

Both groups showed similar results for the duration period when infiltrative changes decline (Table 6) and cavitary lesions completely close up. The only exceptions were a few

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Table 2 – Dynamics of the main biochemical parameters in observed patients (M ± σ).

Biochemical parameters			Thymol test, (un SH)	Total bilirubin (μmol/L)	ALT (μmol/L)		AST (μmol/L)		Total protein (g/L)	Cholesterol (mmol/L)
Group 1	No. on admission	*n*	31	31	3[a]	28	9[a]	22	31	31
		%	100	100	9.7[a]	90.3	29[a]	71	100	100
	On admission to hospital	1.63 ± 0.91	9.8 ± 1.26	1.26 ± 0.51[a]	0.3 ± 0.15	0.82 ± 0.39[a]	0.26 ± 0.12	78.76 ± 9.23	4.51 ± 0.92	
	No. in 2 mo of treatment	*n*	31	31	11[a]	20	17[a]	14	31	31
		%	100	100	35.4[a]	64.6	54.8[a]	45.2	100	100
	In 2 mo of treatment	2.21 ± 1.21	10.24 ± 1.91	1.14 ± 0.57[a]	0.26 ± 0.13	0.84 ± 0.38[a]	0.26 ± 0.17	79.92 ± 8.63	4.69 ± 1.04	
Group 2	No. on admission	*n*	93	93	16[a]	77	42[a]	51	93	93
		%	100	100	17[a]	83	45[a]	55	100	100
	On admission to hospital	1.95 ± 0.97	9.93 ± 1.4	1.93 ± 1.4[a]	0.36 ± 0.17	1.07 ± 0.89[a]	0.23 ± 0.097	80.04 ± 7.72	4.39 ± 0.92	
	No. in 2 mo of treatment	*n*	93	93	6[a]	87	11[a]	82	93	93
		%	100	100	6[a]	94	12[a]	88	100	100
	In 2 mo of treatment	1.62 ± 0.88	9.53 ± 1.23	1.16 ± 0.63[a]	0.24 ± 0.15	0.96 ± 0.5[a]	0.26 ± 0.11	80.96 ± 7.63	4.66 ± 0.91	
p		>.05	>.05	>.05[a]	>.05	>.05[a]	>.05	>.05	>.05	>.05
p in mo of treatment		>.05	>.05	>.05[a]	>.05	>.05[a]	>.05	>.05	>.05	>.05

Note. The *p* value is the significance of difference between parameters in Groups 1 and 2.
σ - mean square deviation value of the indicator; un SH - Shank-Hoagland units, unit of measurement of this indicator.
ALT = alanine transaminase; AST = aspartate transaminase; mo = months.
a The parameters increased above normal.

Table 3 – Levels of interleukin (IL)-1β, IL-4, and tumor necrosis factor-α (TNF-α) in tuberculosis patients compared with apparently healthy donors.

Groups of patients	*n*	IL-1β (pg/L)		TNF-α (pg/L)		IL-4 (pg/L)	
		Before treatment	After 1 mo of treatment	Before treatment	After 1 mo of treatment	Before treatment	After 1 mo of treatment
1	30	166.8 ± 5.2*	78.07 ± 3.1**	185.4 ± 5.57*	125 ± 5.84**	62.63 ± 2.61*	85.19 ± 3.01**
2	89	168.7 ± 5.02*	67.92 ± 2.1**	202 ± 4.72*	127.4 ± 4.63**	57.51 ± 1.56*	97.46 ± 3.02**
Relatively healthy	20	55.91 ± 5.21		34.73 ± 3.68		30.75 ± 1.13	

Note. mo = month.
* Difference is significant ($p < .001$) in comparison with apparently healthy donors.
** Difference is significant ($p < .001$) in comparison with group prior to treatment and following 1 month of treatment.

Table 4 – Indicators of bacterial excretion cessation as evidenced by microscopic examination of sputum and bronchial washing.

Stages of treatment (mo)[a]	Group 1		Group 2	
	n	%	*n*	%
On admission to hospital	27	87.10 ± 6.02	86	92.47 ± 2.74
1	15	55.56 ± 9.75	76	88.37 ± 3.46*
3	5	18.52 ± 7.62	8	9.30 ± 3.13
5	7	25.93 ± 8.59	2	2.33 ± 1.63*

Note. mo = months.
a Index value at each stage is calculated based on previous values.
* Difference is significant ($p < .05$) in comparison with Group 1.

cases when infiltration diminished prior to cavitary lesions healing, or when cavities were healed prior to a complete reduction of infiltration.

Thus, the second group of patients demonstrated a considerably shorter period of cavitary lesion healing than the first group.

Treatment efficacy should be evaluated considering not only the immediate human body response to treatment but also residual changes following the completion of the main course of antimycobacterial therapy in both groups.

Slight residual changes were observed following the administration of anti-TB drugs in combination with QP in patients with pulmonary NDTB. Slight residual changes at the site of healed cavities, or even no signs were found in 84 (90.32 ± 3.07%) patients of the second group compared with 22 patients (70.97 ± 8.15%) in the first group ($t = 2.22$, $p < .05$). Pronounced residual changes were found in nine (9.68 ± 3.07%) patients of the second group and in nine (29.03 ± 8.15%) patients of the first group ($t = 2.22$, $p < .05$).

It should be noted that QP administration affects the incidence of residual changes following a completed course of antimycobacterial therapy and reduces the number of pronounced residual changes by increasing the frequency of slight residual changes. We deem that these changes occurred due to the hepatoprotective and immunomodulatory properties of QP.

It should be accentuated that the treatment of pulmonary NDTB by the application of QP in combination with antimycobacterial therapy accelerates the normalization of the clinical manifestation of TB, and reduces the incidence of adverse reactions to antimycobacterial drugs and the progress of the specific process. The drug caused no adverse effects in observed patients. The drug reduces the period of cessation of bacterial excretion, increases the frequency of healing of cavities and frequency of complete clinical and radiological cure, and decreases the number of pronounced residual changes after treatment.

This pathogenic effect of treatment will further improve the patient's life after curing TB, prevent TB recurrence, and

Table 5 – Indicators of bacterial excretion cessation as evidenced by bacteriologic examination of sputum and bronchial washing.

Stages of treatment (mo)[a]	Group 1		Group 2	
	n	%	*n*	%
On admission to hospital	29	93.55 ± 4.41	86	92.47 ± 2.74
3	21	72.41 ± 8.45	84	97.67 ± 1.63*
5	8	27.59 ± 8.45	2	2.33 ± 1.63*

Note. mo = months.
a Index value at each stage is calculated based on previous values.
* Difference is significant ($p < .05$) in comparison with Group 1.

Table 6 – Indicators of cavitary lesion healing and infiltrative change alleviation in pulmonary tissue.

Stages of treatment (mo)[a]	Group 1		Group 2	
	n	%	*n*	%
2	10	32.26 ± 8.40	58	62.37 ± 5.02*
4	15	48.39 ± 8.98	3	78.49 ± 4.26*
6	20	64.52 ± 8.59	82	88.17 ± 3.35*
Total: 8	26	83.87 ± 6.61	91	97.85 ± 1.50*

Note. mo = months.
a Index value at each stage is calculated based on previous values.
* Difference is significant ($p < .05$) in comparison with Group 1.

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prevent disability from TB, which in turn will reduce the cost of TB treatment in the future.

Conclusion

Administration of QP combined with chemotherapy in patients with NDTB resulted in a comparatively quick reduction of disease manifestation. Specifically, intoxication symptoms in the second group were reduced following 1.33 ± 0.15 months, whereas following 2.64 ± 0.20 months in the first group, $p < .001$. Moreover, respiratory symptoms regression in the second group was observed following 1.43 ± 0.30 months, whereas following 2.33 ± 0.30 months in the first group, $p < .05$. The bacillary excretion period evaluated within 3 months was reduced by 97.67 ± 1.63% in the main group compared with 72.41 ± 8.45%, $p < .05$, in the control group. In addition, the period of destructed cavity healing was reduced to 2.86 ± 0.15 months in the main group compared with 3.43 ± 0.20 months, $p < .05$, in the control group. Residual abnormal X-ray findings (mild or slight or even no signs) were observed in 84 (90.32 ± 3.07%) patients of the main group versus 22 (70.97 ± 8.15%) patients in the control group. Significant residual findings were observed in nine (9.68 ± 3.07%) patients of the main group and in nine (29.03 ± 8.15%) patients of the control group, $p < .05$.

QP in patients with NDTB does not cause side effects. Furthermore, QP provides a higher tolerance to anti-TB drugs by 20.42%.

QP administration in patients with pulmonary TB can increase the concentration of IL-4 and reduce the levels of IL-1β and TNF-α in serum which is evidence of the immunotherapeutic effect of QP.

Indications for QP administration with antimycobacterial therapy in patients with NDPB include side effects of antimycobacterial drugs, reduced immunological reactivity, severity of the case, and TB intoxication.

Conflicts of interest

The authors declare that no competing interests exist.

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