

Effect of Phytotherapy on Prevention and Elimination of Hepatotoxic Reactions in Patients with Pulmonary Tuberculosis and Carriers of Hepatitis B Virus Markers

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Viral hepatitis is 10-25 times more common in tuberculosis patients than in the population as a whole (3). In present day conditions, the frequency of infection with the hepatitis B virus, determined based on all the markers of infection, is 49.0% in TB patients prior to in-patient treatment and 83.1% after in-patient treatment (7). Factors such as the presence of viral hepatitis in the medical history of the patient, and the presence of markers of viral hepatitis B in TB patients during in-patient treatment, significantly increase the incidence of liver disorders (6). Hepatotoxic reactions to a specific therapy have been observed in 70% of TB patients who have had viral hepatitis. As a result, a complete cure for TB is impossible in 30-40% of the cases (7). In 83% of the cases, a preventive course of phytoformulations decreases the toxic action on the liver, of carbon tetrachloride and other damaging factors (1).

The aim of the present investigation is to study the possibility of using a preventive hepatoprotective phytotherapy as prophylaxis and treatment for hepatotoxic reactions in patients with pulmonary TB during in-patient treatment with a specific therapy. A comparative study was also made of the effectiveness of the TB treatment in the groups observed. The 1st group under observation comprised 54 patients with infiltrative (57.4%) and disseminated (42.6%) destructive pulmonary TB with bacterial discharge, detected for the first time. The patients were in the age range of 19 to 48 years and included 37 men and 17 women. Viral hepatitis B markers were detected during hospitalisation. Serum indices of liver function were determined on a weekly basis on a 'Spectrum' autoanalyser. These included alanine and aspartatamino transferase (AlAT, AsAT), alkaline phosphatase (AP), haemagglutamil-transpeptidase (HGTP), leucinaminopeptidase (LAP), total bilirubin, and malone dialdehyde level in blood serum, determined using the M. Uchigama and M. Mirava (1978) method as modified by L. I. Andreyeva (1987). When these indices exceeded the normal value by 1.5 times or more, an ultrasound investigation of the hepatobiliary system was carried out once in two months using the 'Aloka SSD-260' machine. Serodiagnosis of viral hepatitis B was done using the immunoferment solid phase method and special diagnostic equipment developed by a Nizhegorod company, 'Diagnostic Systems'. This included determination of the following markers: surface antigen (HBsAg), antibodies of e antigen (anti-HBe), antibodies of nuclear antigen of immunoglobulins (Ig) G and M (anti-HBc-IgG, M). The following markers of viral hepatitis B infection and their combinations were detected: anti-HBc-IgG in 57.4%, anti-HBc-IgG+anti-Hbe in 27.8%, HbsAg+anti-HBc-IgG+anti-Hbe in 11.1%, and HbsAg in 3.7%.

Almost throughout the entire course of anti-TB therapy, the patients received infusions of herbs specially selected for each individual case (10-15 g of dry herbs per day). The infusions were prepared by pouring 0.7- 0.8 l of boiling water over 1.5 - 2 tablespoons of herbs and standing it in a water bath for 10-15 min, followed by 8-10 hours in a thermos. 100 - 150 ml of warm infusion was recommended 6 times a day. In all, 100 types of herbs were used. The

combinations contained 17-51 herbs, on an average 25 herbs. The most commonly used herbs and the frequency of their use in the combinations are listed below:

1. Root of Ural licorice (glycyrrhiza)- 100%
2. Flowers of filipendula (with elm-like leaves) - 93%
3. Leaf of dioecius nettle (urtica) - 90%
4. Leaf of rubus idaeus (raspberry) - 89%
5. Tanacetum grass (tansy) - 87%
6. Fruit of rosa - 81%
7. Mentha piperita grass - 80%
8. Leaf of white birch (betula) - 77%
9. Leaf of salix (willow) - 72%
10. Origanum vulgare grass - 71%
11. Fruit of anethum graveolens (common dill) - 71%
12. Bidens (bur marigold, four-sectional) grass - 71%
13. Leaf of narrow leaved epilobium (willow herb) - 64%
14. St. John's wort (perforated) grass (Hypericum) - 58%
15. Leaf of salvia officinalis (sage) - 58%
16. Flowers of calendula officinalis - 56%
17. Flowers of helichrysum arenarium - 55%
18. Flowers of matricaria chamomilla - 55%
19. Icelandic moss - 46%
20. Root of aralia (manchurian) - 46%
21. Leaf of taraxacum officinalis (dandelion) - 43%
22. Leaf of plantago major - 41%
23. Equisetum arvense grass - 38%
24. Fruit of sorbus - 36%
25. Zingiberaceae rhizome - 36%
26. Beans of gleditschia (prickly leaved) - 35%
27. Leonurus quinquelobatus gilib grass - 35%
28. Fruit of pimpinella anisum - 33%
29. Fruit of Siberian catnip (nepeta) - 33%

Since the primary purpose of the present investigation was to achieve a hepatoprotective effect, only the main herbs of the combinations have been identified. They are similar to those in the extensive 'polyphytochol' prescription (9), viz. glycyrrhiza, filipendula, tansy, mentha, rosa, helichrysum, betula, anethum graveolens, calendula, hypericum, taraxacum, zingiberaceae. These herbs, which can be substituted one for the other or combined for greater effect, were used in 43-100% of the combinations. Another aspect of the therapy can also be formally identified, viz. the effect on the TB process of the anti-inflammatory properties of the following herbs (mainly during the alteration stage): glycyrrhiza, filipendula, rubus idaeus, betula, salix, bidens, salvia, hypericum, chamomilla, Icelandic moss, taraxacum, plantago etc. (1,4). However, such an interpretation of the action of herbs would amount to accepting the mechanistic approach of the currently predominant tendency to treat using active, chemically pure substances with a strictly directed action (anti-bacterial, anti-exudative etc.). Practically all the infusions made from the herbs mentioned above, are pharmacologically very valuable. They increase the resistance of various organs and tissues to alteration, accelerate repair, and have a clear hepatoprotective, antioxidant, antihypoxant, detoxifying, immunomodulating and other actions. We have shown earlier, that some herbs have background adaptogenic properties (1). At the same time, additional properties of classical phytoadaptogens can be used in phthisiology: aralia root and ginseng are good

expectorants, detoxifiers, hepatoprotectors, immunomodulators, and they can intensify the contractions of fibroblasts (i.e. closed caverns), etc. (8,11). The tuberculo-static and immunocorrective action of herbs conventionally used in the treatment of TB can be relied upon - glycyrrhiza, betula, aralia, taraxacum, zingiberaceae, origanum, hypericum, sorbus, nepeta, juniperus, artemisia vulgaris (20%), artemisia vulgaris (23%), thyme creeper (23%), prickly eleuterococcus (23%) (4,5,11). We have shown that acid heteropo-lysaccharides from herbs (althea officinalis, plantago, pulmonaria, chamomilla, tussilago farfara, malva, althaea rosea etc.) are suppliers of the monosaccharides required for producing secretion of proper mucus in the bronchi (1).

The moment alanine, aspartat aminotransferase, hemagglutamyltranspeptidase, alkaline phosphatase and leucineamino-peptidase activity (all or any one of them) exceeded the normal level by 1.5 times, potentially hepatotoxic anti-TB preparations (pyrazinamide, isoniazid, rifampicin) were discontinued, until normal levels of these enzymes, with the exception of hemagglutamyltranspeptidase, were restored.

The 2nd (control) group comprised 58 patients. Traditional hepatoprotectors (essentiale, legalon, Liv. 52) and detoxification therapy (glucose, hemodese) were used in this group during the period when specific preparations were discontinued. All other parameters of the patients in the 2nd group, including extent of affection of the lungs and drug resistance of the TB microbacteria, were comparable with those of the 1st group. A comparative analysis of the nature and dynamics of the hepatotoxic reactions (see table 1) showed that phytotherapy decreases the occurrence of hepatotoxic reactions by more than 4 times (20.4% of the patients in the 1st group as against 84.5% in the 2nd group, $p < 0.01$). Statistically ($p < 0.05$), hepatotoxic reactions appeared 2.3 times earlier in patients of the 2nd group (25.8 ± 0.5 days) than in patients of the 1st group (59.5 ± 1.5 days). When the anti-TB preparations mentioned above were withdrawn and phytotherapy and detoxication therapy were introduced, complete arrest of the hepatotoxic reactions was 2.1 times slower in the 2nd group than in the 1st group (29.7 ± 0.5 days and 14.3 ± 1.3 days, respectively; $p < 0.05$). The average number of hepatotoxic reactions was similar (2.7 ± 0.1 in the 1st group and 2.3 ± 0.3 in the 2nd group; $p < 0.05$). The weightage of cases where hepatotoxic reactions were completely eliminated was also similar: 87.8% in the 2nd group and 90.9% in the 1st group, $p < 0.05$. In 6 patients of the 2nd group and 1 patient of the 1st group, hemagglutamyltranspeptidase activity remained at a high level for a long time (upto 22.4 days on an average), after alanine and aspartat aminotransferases, alkaline phosphatase and leucineaminopeptidase activity returned to normal levels. According to the literature (10), this does not come in the way of continuing the basic therapy. The higher mean levels of increase in activity of these enzymes during the period of hepatotoxic reactions in the 2nd group of patients attract attention. The differences are statistically reliable: for alanine (AlAT) and aspartat aminotransferases (AsAT), alkaline phosphatase (AP) and leucineaminopeptidase (LAP) $p < 0.05$; for hemagglutamyltranspeptidase (HGTP) $p < 0.01$. Analysis of the dynamics of malone dialdehyde levels in the blood showed the following: in patients of the 1st group, this parameter decreased by a factor of 1.5 to return to normal during the treatment (4.1 ± 0.2 at the time of hospitalisation and 2.2 ± 0.1 nmol/ml at the time of discharge; $p < 0.05$). In patients of the 2nd group, malone dialdehyde level at the time of discharge was 1.8 times higher than in the 1st group (4.0 ± 0.1 nmol/ml for the 2nd group against 2.2 ± 0.1 nmol/ml for the 1st group; $p < 0.05$).

Table 1: Comparative analysis of indicators of hepatotoxic reaction (HTR) and malone dialdehyde (MDA) level in groups of TB patients (M ± m)							
Group of patients	No. of patients with complete elimination of HTR		Time of appearance of initial HTR, day	No. of HTR during the course of treatment	Time taken for elimination of HTR, days	No. of patients with complete elimination of HTR	
	Absolute	%				Absolute	%
1 st (n=54)	11	20.4	59.5±/1.5	2.3±/0.3	14.3±/1.3	10	90.9
2 nd (n=58)	49	84.5	25.8±/0.5	2.7±/0.1	29.7±/0.5	43	87.8
<i>P</i>	<0.01		<0.05	>0.05	<0.05	>0.05	
Group of patients	Average level of increase in activity					Malone dialdehyde level, nmol/ml	
	AIAT (U/l)	AsAT (u/l)	AP (iu/l)	HGTP (iu/l)	LAP (iu/l)	At hospitalisation	At discharge
1 st (n=54)	67.8±/1.9	55.3±/2.8	100.8±/3.1	69.7±/1.7	41.3±/1.4	4.1±/10.2	2.2±/0.1
2 nd (n=58)	81.8±/1.8	70.1±/1.8	124±/3.8	132.4±/2.2	77.4±/1.5	4.2±/0.2	4.0±/0.1
<i>P</i>	<0.05	<0.05	<0.05	<0.01	<0.05	>0.05	<0.05

In order to determine the effect of phytotherapy on changes in the hepatobiliary system, established through echography, two more groups of patients with hepatotoxic reactions were identified (3rd and 4th groups). These groups underwent a dynamic ultrasound investigation of the hepatobiliary system. The 3rd group comprised 11 patients, who had received phytotherapy, while the 4th group comprised 20 patients, who had received conventional hepatoprotective and detoxifying treatment.

Table 2: Comparative analysis of echography changes in the hepatobiliary system in patients with HTR (3rd and 4th groups), at the end of hospitalisation for treatment of TB (M ± m)								
Group of patients	Distance between edge of costal arch and lower edge of liver, cm	Height		Diameter of hepatic veins of the 1st order, cm				Portal vein diameter, cm
		Left lobe, cm	Right lobe, cm	Right	Left	Central	Overall	
Standard	0.5	8.0	13.0	1.0	0.9	1.0	2.9	13.0
3 rd (n=11)	1.1±/0.1	8.8±/0.4	15.6±/0.1	1.1±/0.1	0.8±/0.2	0.9±/0.2	2.8±/0.3	14.2±/0.2
4 th (n=20)	2.3±/0.1	10.1±/0.3	18.9±/0.2	1.1±/0.2	0.6±/0.1	2.3±/0.1	2.3±/0.1	15.4±/0.3
<i>p</i>	<0.05	>0.05	<0.05	>0.05	<0.05	<0.05	<0.05	>0.05

Note: The reliability indices pertain to the differences within the groups.

Analysis of the data in table 2 showed that absolutely all the patients in both the groups had some sort of pathological changes in the hepatobiliary system. These changes were particularly well defined in the patients of the 4th group. For instance, it is statistically significant that enlargement of the liver is more clearly defined in patients of the 4th group than in the 3rd group; the lower edge of the liver projected from under the costal arch by 2.3 ± 0.1 and 1.1 ± 0.1 cm ($p < 0.05$), the height of the right lobe was 18.9 ± 0.2 and 15.6 ± 0.1 cm ($p < 0.05$), respectively. Similarly, narrowing of the hepatic veins of the 1st order was more pronounced in patients of the 4th group than in the 3rd group: diameter of the central vein was 0.6 ± 0.1 and 0.9 ± 0.2 cm ($p < 0.05$), of the left vein - 0.6 ± 0.1 and 0.8 ± 0.2 cm ($p < 0.05$), respectively. The most serious changes were noted in the central hepatic vein. This indicates a poor prognosis and conforms to data from the literature (2). These factors are reflected in the difference between the sum total diameter of the central, left and right hepatic veins, which is 1.2 times higher for the 3rd group ($p < 0.05$). The difference in the diameter of the right hepatic

vein of the 1st order, the portal vein, and in the height of the left lobe of the liver, were statistically unreliable ($p>0.05$).

Group of patients	Achieved abacillary status		Patients without cavities of degeneration		Mean duration of in-patient treatment, months
	Absolute no.	%	Absolute no.	%	
1st (n=54)	52	96.3	52	96.3	6.4±/0.2
2nd (n=58)	56	96.6	49	84.5	8.3±/0.1
<i>P</i>	>0.05		<0.05		<0.05

There was no significant difference in the number of patients achieving a bacillary status in the two groups (96.3% in the 1st group and 96.6% in the 2nd; $p>0.05$). A higher level of closure of cavities of degeneration was observed in the 1st group as compared to the 2nd (96.3 and 84.5%, respectively). This difference was statistically significant ($p<0.05$). The mean duration of in-patient treatment in the 1st group was 1.3 times less than in the 2nd group (6.4 ± 0.2 and 8.3 ± 0.1 months, respectively; $p<0.05$).

CONCLUSIONS

1. Among patients with pulmonary tuberculosis, carriers of the hepatitis B virus markers, hepatotoxic reactions have been noted in 84.5% of the cases, against the background of specific therapy. Hepatotoxic reactions affect the parenchyma as well as the vascular system of the liver and are accompanied by increased levels of (per)oxidation of lipids.
2. Continuous preventive hepatoprotective phytotherapy during the entire course of in-patient treatment of TB reduces the occurrence of hepatotoxic reactions by a factor of 4.1, helps eliminate these reactions faster, by a factor of 2.1, reduces by a factor of 2.2 the period of forced withdrawal of potentially hepatotoxic anti-TB preparations, and helps to normalise the level of (per)oxidation of lipids. This leads to more effective treatment of destructive tuberculosis.

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