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Hepatoprotective effect of few Ayurvedic herbs in patients receiving antituberculus treatment

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Under the antituberculosis treatment (ATT) drug therapy, inclusion of a hepatoprotective drugs is not mandatory but in Indian scenario these are prescribed by most of the physicians. In present clinical trial three groups of patients receiving antituberculosis treatment have been studied to evaluate the hepatoprotective effect of few Ayurvedic herbs. The first group of 10 patients was given capsules Liv-600 containing hydroalcoholic extract of *Daruharidra* (*Berberis aristata*) roots, *Kakmachi* (*Solanum nigrum*) whole plant, *Ghritakumari* (*Aloe vera*) ariel parts. Second Group was given a standardized decoction of herb *Bhumyamalaki* (*Phyllanthus fraternus*). Third group was kept on ATT and a placebo starch capsule for equal duration. The trial was conducted for 12 weeks from initiation of ATT and liver functions were periodically evaluated to assess the hepatoprotective effect of drugs under trial. At the end of trial, Group first and second exhibited their hepatoprotective efficiency over the placebo.

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With the 15 million new cases of tuberculosis being diagnosed per year, tuberculosis is a major health problem in India and is far from being controlled. Treatment dropouts and defaulters are major source of continuous spread of disease in society. Antituberculosis drugs have hepatotoxicity, which frequently becomes cause of withdrawal of treatment. In India, presently Direct Observation Therapy (DOT) form of antituberculosis treatment is fighting the tuberculosis. It is observed that due to drug related toxicity, the incident of withdrawal of drug and dropout is significant. Hepatotoxicity of primary drugs is a major problem. Mostly drug-induced hepatotoxicity has been thought to be self-limiting event but drug withdrawal is fraught with reactivation of focus as well as risk of developing multi drug resistance. This has lead to the idea of providing some hepatoprotective remedies to minimize the hepatotoxicity related dropouts, particularly, with the use of some herbal hepatoprotectives.

Kutki (*Picrorhiza kurroa Royle ex Benth.*), a well recognized hepatoprotective herb, is on the list of endangered Himalayan herbs. This necessitates research on other hepatoprotective herbs and exploration of

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Ayurvedic literature. The present clinical work concerns clinical trial on such identified hepatoprotective herbs, namely *Daruharidra* (*Berberis aristata*), *Kakmachi* (*Solanum nigrum*), *Ghrita kumari* (*Aloe vera*), and *Bhumyamalaki* (*Phyllanthus fraternus*). It is the combined hydroalcoholic extract of first three herbs in a dose of 200 mg each in a capsule form (named Liv-600), has been used in Group-I, while decoction of whole plant was used in Group-II. For standard evaluation, Placebo Group received starch in capsules. All the selected trial drugs are bitters and are considered hepatoprotectives and cholegouges. In Ayurvedic pharma-copoeia, they are considered as *Katu Ras* predominant drugs, and as *Pitta Virechaka* (help in secretion of bile) and thus protect liver damage.

Methodology

The present clinical research was undertaken at Rajiv Gandhi Post Graduate Government Ayurvedic Hospital in Post Graduate department of Kayachikitsa, Paprola. The patients under trial were selected from OPD and IPD of Hospital.

Patients of tuberculosis who were to be put on Anti-Tuberculosis Treatment (ATT), aged between 15-70 years were confirmed to have normal liver function tests (LFT) at the initiation of treatment and trial (Normal Serum Bilirubin, ALT, AST, Alkaline Phosphatase). They were confirmed to have normal liver anatomy under ultrasound and were not on any other hepatoprotective or hepatotoxic drug at the initiation of trial. All the patients agreeing for trial gave a written consent for the same.

With the initiation of ATT, trial drugs were administered to the patients, and the period of trial covered 90 days in all patients. The periodic evaluation of liver function was done at every 15 days, of trial. Those trial patients where ATT induced hepatotoxicity appeared during periodic evaluation of 15 days were asked to stop ATT and last LFT report was considered to be the cut-off day of their treatment and the values of LFT were taken for evaluation of results.

Fresh raw drugs were procured from market. After botanical identification from Department of Pharmacognosy (*Dravyaguna*), hydroalcoholic extracts of *Berberis aristata* DC., *Solanum nigrum* Linn. and *Aloe vera* Tourn. ex Linn. were got prepared from Ayush Herbs, Nagrota Bagwan, Himachal Pradesh. The standard of purity, quality and packing was maintained as per Good Manufacturing Practice. The capsules of drug were filled in automatic plant and packed in airtight plastic containers.

Formulation A: (Cap. Liv-600): Each capsule contained 200 mg each of hydroalcoholic extract of *Daruharidra* (*Berberis aristata* DC.), *Kakmachi* (*Solanum nigrum* Linn.) and *Ghritkumari* (*Aloe vera* Tourn. ex. Linn.). In Group I, 13 patients were registered and 10 patients completed full course of trial. These patients were given Cap. Liv 600 or Formulation "A", one capsule thrice a day.

Formulation B: Freshly prepared decoction of *Bhumyamalki* (*Phylanthus fraternus* Webster), from 10 gm of aerial

plant. The powder of crude drug was boiled with 16 times the volume of water by weight on mild fire till the contents of liquid were reduced to 1/8 of pre boiling volume and the liquid part was filtered. The filtrate was administered to patients while still warm. OPD patients were explained the procedure thoroughly and told the importance of therapy. In Group II, 12 patients were registered, of which 10 completed full course of trial. The group was given *Bhumyamalki* decoction or Formulation "B".

Formulation C: 600 mg of starch powder in each capsule. In Group III (control group), 15 patients were registered, of which 10 completed full duration of trial. The patients of this group were given a placebo starch powder filled capsules of Formulation "C".

Results

For evaluation of hepatoprotective effect of the formulations after use for 90 days in patients taking ATT, both subjective and objective evaluation criteria were applied. The reliable amongst them was liver function test including, serum bilirubin, ALT, AST and alkaline phosphates.

The trial patients were randomly scattered over the groups but administration of trial drugs and results were monitored by Scientific Research Committee of department from time to time. The observations regarding liver function test of the patients over the trial are as given in Table 1.

No significant increase in AST was observed after ATT course initiation in trial groups. The mean difference of AST of trial groups was found to be non significant with –31.29 ± 54.28 and 1.278 ± 11.22 in trial group II and I, respectively. Both groups showed insignificant increase in AST with $p>0.05$. Whereas in control group significant increase in AST during ATT administration was observed. The mean difference in serum AST in control group was –82.52 ± 121.53, which was statistically significant with p being < 0.05. It is worth recording that in ATT, induced hepatotoxicity appeared on periodic evaluation of 15 days and treatment with ATT had to be stopped the last day of taking ATT was taken as final cut off day of after treatment for inclusion of values of liver enzymes in trial evaluation.

Effect of drugs on serum SGPT (ALT) in patients of tuberculosis receiving ATT is given in Table 2.

No significant increase in ALT was observed after ATT course initiation in trial groups. The mean difference of AST of trial groups was found to be non significant with -39.63 ± 68.58 and1.914 ± 8.87 in trial groups II and I, respectively. Both groups showed insignificant increase in ALT with $p>0.05$, whereas in control group, significant increase in ALT during ATT administration was observed. The mean difference in serum AST in control group was -78.243 ± 106.45, which was statistically significant with p being < 0.05.

Effect of trial drugs on serum total bilirubin in different groups is given in Table 3.

Table 1—Effect of drugs on serum AST (SGOT) in patients of T.B. receiving ATT

Groups	Serum AST (SGOT) in I.U./dl			Paired t/p
	Before Treatment Mean ± S.D.SE	After Treatment Mean ± SD SE	Difference Mean ± SD SE	
Trial Group I	29.99 ± 5.53 SE = 1.750	61.28 ± 57.13 SE = 18.06	-31.29 ± 54.28 SE = 17.166	T = 1.823 P >0.05
Trial Group II	29.67 ± 7.144 SE = 2.259	28.39 ± 5.919 SE =1.872	1.278 ± 11.22 SE = 3.55	T = 0.3600 P >0.05
Control Group	30 ± 6.95 SE = 2.199	112.69 ± 121.95 SE = 38.46	-82±121.53 SE = 38.43	T = 2.14 P <0.05

Table 2—Effect of drugs on serum SGPT (ALT) in patients of tuberculosis receiving ATT

Groups	Serum ALT (SGPT) in I.U./dl			Paired t/p
	Before Treatment Mean ± S.D.SE	After Treatment Mean ± SD SE	Difference Mean ± SD SE	
Trial Group I	25.45± 7.851 SE = 2.483	65± 69.69 SE = 22.04	-39.63± 68.58 SE = 21.68	t= 1.827 P >0.05
Trial Group II	27.96 ± 6.538 SE = 2.067	26.064 ± 6.140 SE =1.942	1.914 ± 8.87 SE = 2.807	t = 0.6820 P >0.05
Control Group	28.93 ± 6.124 SE = 1.937	107.18 ± 103.70 SE = 32.79	-78.243± 106.45 SE = 33.66	t = 2.32 P <0.05

Table 3—Effect of trial drugs on serum total bilirubin in different groups

Groups	Serum Total Bilirubin in mg/dl			Paired t/p
	Before Treatment Mean ± S.D.SE	After Treatment Mean ± SD SE	Difference Mean ± SD SE	
Trial Group I	.8870 ± .1532 SE = .04844	1.11 ± 0.3969 SE = 0.1255	-0.2290 ± 0.517 SE = 0.1637	T = 1.399 P >0.05
Trial Group II	1.00 ± 0.2028 SE = .06414	.9660 ± .1120 SE =0.3541	.0340 ± .2524 SE = .07982	T = 0.4259 P >0.05
Control Group	1.020 ± 0.1819 SE = .05752	1.217 ± .6634 SE = .2098	-.1970 ± .7707 SE = .2437	T = .8083 P >0.05

Table 4—Effect of trial drugs on serum alkaline phosphatase in different groups

Groups	Serum Total Alkaline phosphatase I.U./dl			Paired t/p
	Before Treatment Mean ± S.D.SE	After Treatment Mean ± SD SE	Difference Mean ± SD SE	
Trial Group I	161.46 ± 66 SE = 20.87	132.34 ± 83.08 SE = 26.27	29.12 ± 103.68 SE = 32.78	t = 0.8882 p >0.05
Trial Group II	97.097 ± 20.98 SE = 6.637	101.36 ±3.182 SE = 1.006	-4.263 ± 21.85 SE = 6.912	t = .6167 p >0.05
Control Group	95.89± 43.83 SE = 13.86	149.56± 102.49 SE = 32.409	-53.668 ±107.58 SE = 34.019	t = 1.578 p >0.05

No significant increase in serum total bilirubin was observed after ATT initiation in trial groups. The mean difference of serum total bilirubin in trial groups and control group was found to be insignificant with values -0.2290 ± 0.517, .0340 ± 0.2524, -0.1970 ± 0.7707 in trial group I, trial group II and control group, respectively. The entire three groups showed overall statistically insignificant rise in total serum bilirubin during trial period.

Effect of trial drugs on serum alkaline phosphatase in different groups is given in Table 4.

No significant increase in serum alkaline phosphatase was observed during ATT course in trial groups as well as control group.

Discussion

The front line drugs to fight tuberculosis have common toxicity associated as hepatotoxicity. Isoniazid causes liver damage due to its reactive metabolites generated from the acetyl hydrazine. Rifampicin is an enzyme inducer and enhances formation of reactive metabolites and hence hepatotoxicity in form of impairment of uptake of bilirubin and acute cellular necrosis[1]. Pyrazinamide also has potential to produce hepatocellular damage[2]. The concomitant use of hepatoprotectives was always recommended. Variety of herbal drugs has been tried in India and elsewhere[3,4]. Use of herbal drugs like *Kutki* (*Picrrohiza kurroa*)[5], Silimiron, *Kalmegh* (*Andrographis paniculata* Wall. ex Nees), *Bhumyamalaki* (*Phyllanthus fraternus* Webster) is well documented and standardized[6]. The present trial is exploration of ancient Ayurvedic literature[7-9] to screen and dose standardization of the extract of Ayurvedic bitters in reducing the hepatic damage. The trial drugs *Bhumyamalki* (*Phyllanthus fraternus* Webster), *Daruharidra* (*Berberis aristata* DC.), *Kakmachi* (*Solanum nigrum* Linn.), and *Ghritakumari* (*Aloe vera* Tourn. ex Linn.) showed definitive hepatoprotective effect over the trial period of 90 days of initiation of anti-tuberculosis treatment in patients of tuberculosis. This is the period when the patient is on multi-drug intensive treatment and the chances of developing hepatotoxicity are high. The patients of control group using starch as placebo hepatoprotective, showed statistical rise in marker enzymes of hepatotoxicity i.e. ALT and AST, where as patients of Group I taking Liv. –600 and Group II taking decoction of *Bhumyamalki* did not show any significant rise in these enzymes, establishing their hepatoprotective effect. In further post trial analysis, it was observed that in efficiency to protect liver during ATT therapy, the effect of fresh decoction of *Bhumyamalki* was better than the combination of extract of three herbs used as Liv. –600. The activity has been attributed to their anticholestatic action, reduction in free radicals andreduction in cell proteins necrosis as well as immune suppression and glutathione depletion reduction potential. No significant rise in serum bilirubin and alkaline phosphatase was observed in any group.

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