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RESEARCH ARTICLE

HEPATOPROTECTIVE AND ANTIOXIDATIVE POTENTIAL OF *ALLIUM SATIVUM* IN THE TREATMENT OF PULMONARY TUBERCULOSIS UNDER DOTS

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ABSTRACT

The anti-tubercular drugs Isoniazid and Rifampicin, the first line drugs used for tuberculosis therapy are associated with severe hepatotoxicity in Indian patients as compared to United State. Data reported that the combination of INH and RIF treatment in pulmonary tuberculosis patients taking ATD enrolled under DOTS, results in development of oxidative stress which has been considered as the most important mechanism of hepatotoxicity which results increase of MDA level decrease in body antioxidant level. MDA level is more in contrast to that observed in the normal GpI (48.21±12.13 n mol TBARS/ml blood Vs 13.56±2.06) & after treatment decreased significantly (** $p<0.001$). GSH levels in INH+RIF treated GpII and caused significant decrease in the blood GSH as compared to Normal GpI (169.95±96.4 Vs 218.51±121.5) while after treatment level increases (** $p<0.00$) vs normal (GpI). Similarly trends were recorded in SOD and Catalase level after treatment respectably (**$p<0.001$) vs normal group (GpI) & ** $p<0.001$ vs normal group (GpI). The postulated role of garlic organosulphur compounds in the prevention of INH and RIF hepatotoxicity was explained by their ability in free radical scavenging and prevention of hepatocyte GSH depletion. The aim of the study was to assess the role of garlic supplementation in the hepatoprotection of INH and RIF induced hepatotoxicity in pulmonary tuberculosis by monitoring the antioxidant levels.

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INTRODUCTION

Tuberculosis is one of the major health problems in developing countries like India. Most adult death in India is due to vascular disorder or pulmonary tuberculosis (Gajalakshmi *et al.,* 2003). Smoking and mortality from tuberculosis and other disease in India: respective study of 43000 adult male deaths and 35000 controls. INH and RIF, the first line drug used for tuberculosis chemotherapy are associated with hepatotoxicity (Tasduq *et al.,* 2005). The rate of hepatotoxicity has been reported to be much higher in developing countries (30%) compare to that in advanced countries (2%-3%) with an estimate dose schedule (Sharma, 2004). In England and Wales in 1992, there was a 2% increases incident of pulmonary tuberculosis over the period 1988-1992. The recommended treatment regimens for tuberculosis involved drugs which were potentially hepatotoxic; Thompson *et al.,* 1995 recommended regular monitoring for liver damage and hepatic dysfunction following anti-tuberculosis medication with INH and RIF.

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It was further reported that anti-tuberculosis chemotherapy is associated with abnormalities in liver function test in 10%-25% of patients. Clinical hepatitis in developing about 3% and in these patients there is likely to be significant morbidity and mortality. On the basis of reported cases of tuberculosis, 160 patients in England and Wales can be expected to be developed drug-induced hepatitis due to anti-tuberculosis therapy each year. There are published guidelines from the British and American Thoracic Society regarding choice of drug therapy for tuberculosis. Several anti-tuberculosis had been implicated has been hepatotoxic. Isoniazid (particularly in association with rifampicin) and pyrazinamide cause hepatic dysfunction more frequently than ethambutol. Isoniazid (INH) causes mostly acute hepatocellular type of injury which is a mixed hepatocellular-cholestatic picture (Black *et al.,* 1975). There are various metabolic products of Isoniazid, including monoacetyl hydrazine, hydrazine and isonicotinic acid, which had been suggested as being hepatotoxic. The onset of injury is usually after 6 weeks, and may be up to 1 year after beginning (Mouldings *et al.,* 1989; Garibaldi *et al.,* 1972; Mitchel *et al.,* 1976). Concomitant use of rifampicin leads to earlier more frequent injury, some in less than 10 days (Pessayre *et al.,*

1977). The incident of impaired liver function test, with raised transaminases, varies from 10 to 25% (Byrd *et al.,* 1979; Bailey *et al.,* 1974; Scharer, 1969; Yasuda *et al.,* 1990). It has been suggested that the elderly, pregnant women, malnourished patients are more prone to liver damage due to isoniazid (Berkani *et al.,* 1984; Gronhagen- Riska *et al.,* 1978; Black, *et al.,* 1975). It was observed up to 13 % mortality in patients who presented clinical evidence of hepatitis. Monldings, and Black *et al.,* 1989reported the most common incidence of hepatotoxicity such as "flu" like symptoms and non-specific gastrointestinal respect. Gronhagen; Riska *et al.,* 1978 found that the patients with pre-existing liver disease seem to be more likely to develop liver injury. (Stricker, 1987) reported that liver injury due to rifampicin is rare but rifampicin dose increases the hepatotoxicity of isoniazid (Yasuda *et al.,* 1990). This effect is thought to be due to enzyme induction, leading to an increase in hepatotoxic metabolites of isoniazid. Certain anti-tuberculosis drugs the following sign and symptoms.

MATERIALS AND METHODS

Total five hundred persons were enrolled in the study, in which 100 were normal healthy volunteers for control (standard LFT values), 100 DOTS patients who had been taken the medicine for at least 2 months and rest 300 patients are termed treated group who had been taken DOTS as well as the design medicine. The inform consent was obtained from all enrolled patients and healthy volunteers in this study. The treated groups are further classified into subheads for ease of study. For a baseline liver function and antioxidant study, blood will draw from normal, control and treated groups before and after administration of the different experimental design medicines respectively according to study design.

Sample size and study design

A total 500 tuberculosis patients will be taken for study. After sputum & case examination,

Patients was admitted in our study design as follows

Abbr.	Groups	Experimental Medicines Procedure
(GpI)	Normal	No medication
(GpII)	Control	DOTS Patients + Placebo
(GpIII)	Treated	DOTS Patients + Garlic (2 gm/day)
(GpIV)	Treated	DOTS Patients + Garlic (4 gm/day)
(GpV)	Treated	DOTS Patients + Garlic (6 gm/day)

Rational

Normal (GpI) Healthy volunteer considered as normal control. Control (GpII) Smear positive, TB patients, which does not receive experimental design medicine while taking schedule DOTS. Treated (GpIII) Smear positive TB patients, received DOTS & experimental design medicine; 2gm/day. Treated (GpIV) Smear positive TB patients, received DOTS & experimental design medicine; 4gm/day. Treated (GpV) Smear positive TB patients, received DOTS & experimental design medicine; 6gm/day.

RESULTS AND DISCUSSION

Lipid peroxidation (LPO)

Measurement of MDA showed a sensitive index of LPO and oxidative stress. Table-1 shows the mean values of MDA in the study groups. The INH + RIF treated GpII showed significantly higher mean values of MDA in contrast to that observed in the normal GpI (48.21±12.13 n mol TBARS/ml blood Vs 13.56±2.06). However, in the garlic treated 3 sub-groups there was a significantly decline in the activity of LPO levels as compared to INH-RIF treated GpII. Pre-treatment with different doses of garlic reduced the levels of LPO significantly. The hepato-protective effect of garlic as indicated by MDA on 0 day and after 180 days is shown in Table-1. In the treated sub-group I (i) the mean value of MDA decreased from 65.61±12.54 to 38.82±10.63. Similar trend was also recorded in sub-Gp II (ii).

Serum GSH

The response of GSH following INH+RIF drug treated and garlic treated group is shown in Table-2. The results showed that the metabolites of INH+RIF drugs appear to have adverse effects on the blood GSH levels in INH+RIF treated GpII and caused significant decrease in the blood GSH as compared to Normal GpI (169.95±96.4 Vs 218.51±121.5). Decrease in blood GSH level was correlated with increased oxidative stress in INH+RIF drug treated GpII. Pre-treated with various doses of garlic in GpIII (i,ii,iii) significantly improved the blood GSH levels in garlic GpIII. The role of garlic in the antioxidant defence system and deactivation of oxygen radicals is very well known which leads to significant increases and recovery of blood GSH levels in the garlic GpIII. In the treated Gp (sub-group i, receiving 2.0gm/day garlic) the level of blood GSH rose from 171.3±72.4 to 231.43±101.5). Similar increasing trend in blood GSH levels were also recorded in GpII (ii) and GpII (iii) sub-groups receiving 4.0gm/day and 6.0gm/day garlic respectively. (Table-2)

Blood SOD levels

This parameter which is a sensitive indicator of oxidative stress revealed significantly decreased value of SOD in the INH+RIF treated GpII as compared to the finding in the Normal GpI (1130.15±161.95 Vs 2117.65±207.21). In contrast to this drug treated Gp II, the administration of garlic in varying doses improved the levels of blood SOD in the garlic GpIII (Table-3). The activity of SOD increased significantly and correlated with the varying doses of garlic thereby confirming the role of garlic as a powerful antioxidant in this study. The treated GpIII (iii) receiving 6.0gm/day for 180 days showed near normal levels of blood SOD. (Table-3)

Blood Catalase

Catalase decomposes the H_2O_2 in cells and an increase in the activity of catalase indicates the active involvement in the decomposition of H_2O_2. The mean value of catalase decrease significantly in the INH+RIF drug treated GpII as compared to that found in the Normal GpI (26.55±7.95 Vs 41.65±9.76).

Table 1. Effect of blood status of lipid peroxides (MDA) on control and treated groups (*p<0.001)**

Groups	MDA (n mol TBRS/ml blood)	Range
Normal (GpI)	13.56±2.06	(07.43-14.82)
Control (GpII)	48.21±12.13	20.68-82.51
Treated groups		
(GpIII) Treated with 2gm/day *Allium sativum*.	38.82±10.63***	(30.68-61.66)
(GpIV) Treated with 4gm/day *Allium sativum*.	26.02± 09.93***	(20.94-43.55)
(GpV) Treated with 6gm/day *Allium sativum*.	15.82±10.03	(10.67-27.31)

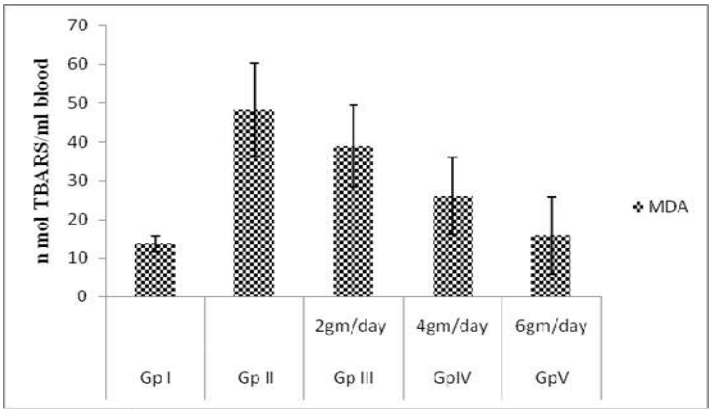


Figure 1. Effect of *Allium sativum* on MDA on GpIII, GpIV & GpIV (2gm/day, 4gm/day & 6gm/day respectively)

Table 2. Effect of Glutathione (GSH) level in normal (GpI), control (GpII), & treated groups (GpIII) (GpIV) & (GpV) after treatment with Allium sativum (p<0.001 vs normal group (GpI)**

Groups	Glutathione level (µg/ml blood)	
	mean±SD	range
Normal (GpI)	218.51+121.5	110-437
Control (GpII)	169.95±96.4**	149-213
Treated groups		
(GpIII) Treated with 2gm/day *Allium sativum*.	231.43±101.5	215-337
(GpIV) Treated with 4gm/day *Allium sativum*.	301.69±96.5	280-361
(GpV) Treated with 6gm/day *Allium sativum*.	267.51±87.7***	250-309

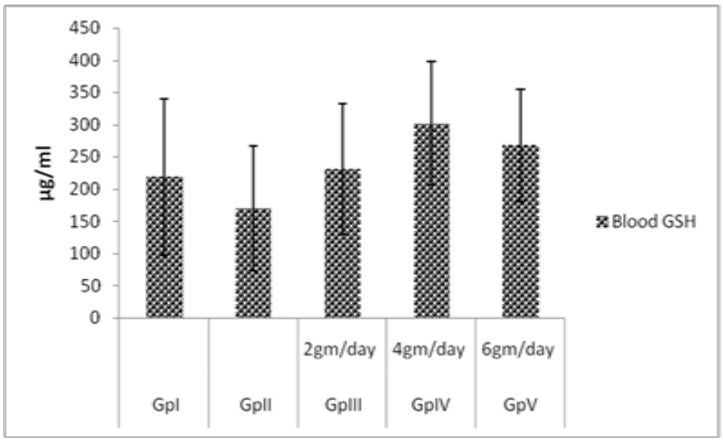
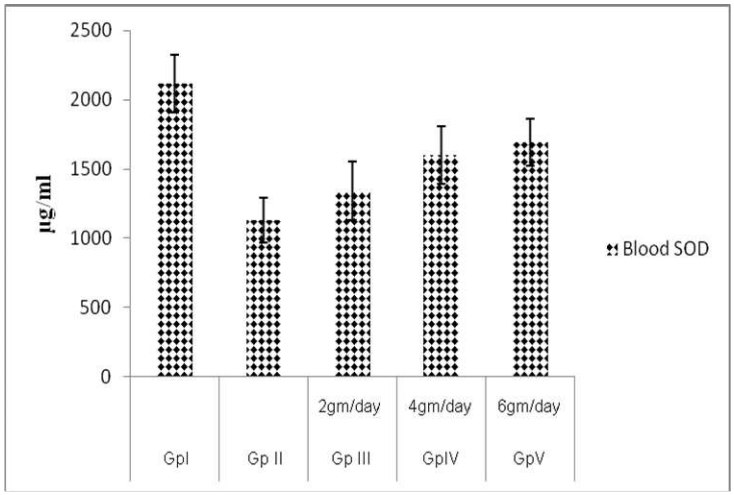


Figure 2. Effect of Glutathione (GSH) level in normal (GpI), control (GpII), & treated groups (GpIII) (GpIV) & (GpV) after treatment with Allium sativum (* p<0.5 vs normal group (GpI), significant decrease, ** p<0.001 vs normal (GpI)

Table 3. Effect of Superoxide dismutase (SOD) level in normal (GpI), control (GpII), and treated groups (GpIII) (GpIV) & (GpV) after treatment with Allium sativum (*p<0.001)**

Groups	Blood SOD level (µg/ml blood)	
	mean±SD	range
Normal (GpI)	2117.65±207.21	(2019-2415)
Control (GpII)	1130.15±165.95***	(1079-1317)
Treated groups		
(GpIII) Treated with 2gm/day *Allium sativum*.	1339.25±211.69**	(1219.5-1615.5)
(GpIV) Treated with 4gm/day *Allium sativum*.	1599.67±208.91***	(1503-1715.9
(GpV) Treated with 6gm/day *Allium sativum*.	1691.13±171.66***	(1585.7-1829.5)



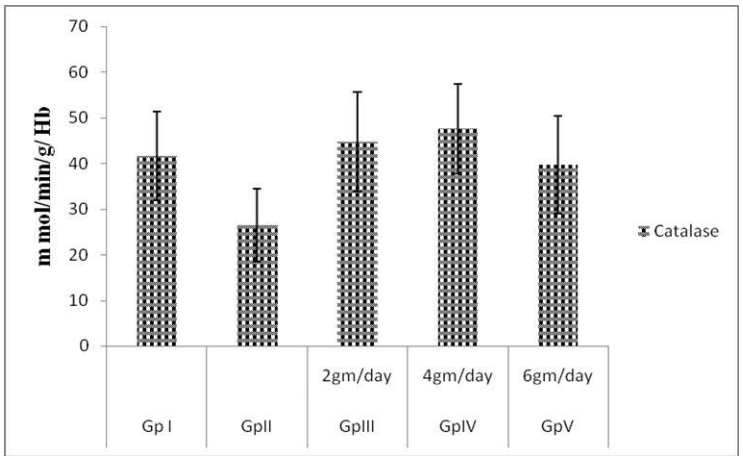
* p<0.05 vs GpI, ** p<0.001 vs normal group (GpI), ** p<0.001 vs normal group (GpI)

Figure 3. Effect of Superoxide dismutase (SOD) level in normal (GpI), control (GpII), & treated groups (GpIII) (GpIV) & (GpV) after treatment with Allium sativum

Table 4. Effect of Catalse level in treated groups (GpIII), (GpIV) & (GpV) after treatment with Allium sativum, compare to normal (GpI) & control (GpII) groups

Groups	Blood Catalase level (m mol/min/g Hg)	
	mean±SD	range
Normal (GpI)	41.65±9.76	(25-73)
Control (GpII)	26.55±7.95**	(20-37)
Treated groups		
(GpIII) Treated with 2gm/day *Allium sativum*.	44.79±10.93***	(37-69)
(GpIV) Treated with 4gm/day *Allium sativum*.	47.65±09.79***	(40-74)
(GpV) Treated with 6gm/day *Allium sativum*.	39.66±10.65	(32-61)

p<0.05;*p<0.001



** p<0.05 vs normal group (GpI), ** p<0.001 vs normal group (GpI)

Figure 4. Effect of Catalse level in treated groups (GpIII), (GpIV) & (GpV) after treatment with Allium sativum, compare to normal (GpI) & control (GpII) groups

However pre-treatment with garlic improved significantly the mean values of blood catalase (Table-4). The mean value of catalase rose significantly from 24.43±10.65 to 44.79±10.93 in the garlic treated group receiving 3.0gm/day garlic for 180 days. Similar observations were also recorded in the two other sub-groups receiving 4.0 gm/day and 6.0gm/day garlic (Table-4). Therefore a significant increase in catalase activity observed in the present study following pre-treated with garlic suggests increased functional efficiency of these antioxidants in hepato-toxicity induced by INH+RIF drugs.

DISCUSSION

The results of the study showed significant increase in the activity of MDA enzyme and corresponding decreases in the GSH activity in the INH and RIF treated cases in GpII thereby indicating that the increased lipid per-oxidation was primarily due to a disturbance in the balance of pro-oxidant and antioxidant cycle, resulting from excess formation and release of oxygen free radicals (OFRs) in the blood circulation. The decrease levels of GSH following ATD treatment may be due

to cell damage (hepatocytes) caused by the damaging effects of peroxides formed and through ROS reactions. However, the changes both in MDA (increased lipid peroxidation; LPO and GSH are associated with liver dysfunction resulting from hepatotoxicity by the given drugs. Supplementation with garlic preparation for 180 days showed significant decrease in the activity of MDA and recovery of GSH levels near normal in GpIII cases thereby supporting the earlier studies claiming strong antioxidant properties of *Allium sativum* (Tadi *et al.,* 1991; Wang *et al.,* 1998; Boreck, 2001; Yuang,, 1954). Studies in mice showed that SAC and SAMC, the major organosulphur compounds present in garlic have potent antioxidant activity (Amagase, 1997; Ide *et al.,* 1997; Imai *et al.,* 1994; Wei and Lau, 1998). The content of SAC and SAMC in garlic preparations is high because they are produced during the process of aging. Other compounds in garlic include diallyl sulphide (DAS) and diallyl disulfide (DADS). These lipid soluble compounds also show antioxidant effects (Awazu *et al.,* 1997; Okada *et al.,* 2005). The recovery of GSH following garlic supplementation in the hepatocytes may be due to protective action of garlic on cellular constituents from the damaging effects of ROS reactions. The other antioxidant enzymes such as SOD, CAT also increased significantly in our study following therapeutic role of *Allium sativum*. It has been reported that the organosulphurs present in the garlic preparations cause rapid scavenging of ROS release due to oxidative stress induced by INH and RIF induced hepatotoxicity and also prevent hepatocyte depletion of GSH. Allicin is a major component of garlic organosulphurs and its antioxidant properties confirmed by many investigators (Vimal, 2004).

Because the garlic contains many other antioxidants, the supplementation of garlic neutralizes several types of ROS (Pal *et al.,* 2006). Moreover, garlic compounds absorb from gastro-intestinal system to circulation and can effect on body organs effectively. Many previous researchers and investigators showed that garlic organosulphur compounds prevent hepatotoxicity induced by isoniazid and rifampicin (Andres and Cascales, 2002). The biochemical changes occurred in INH and RIF induced hepatotoxicity suggests the pivotal role of oxidative stress. Consequently any mechanism which decreases oxidative stress may limit the hepatotoxicity and this was done by garlic supplementation which has strong antioxidant potential. The INH and RIF causing hepatotoxicity through oxidative stress mechanism in hepatocytes confirms other studies that showed the antioxidants can prevent such type of hepatotoxicity (Mostafavi-Pour *et al.,* 2008; Durak *et al.,* 2004; Wu *et al.,* 2001). The antioxidant action of garlic's organosulphur compounds prevents the formation of lipid peroxides. The garlic compounds DAS, DADS and DAT were shown to play a differential modulator role on GSH related antioxidant system in liver and red blood cells and increased hepatic GST activity.

Conclusion

Our study showed that the supplementation with garlic preparation in anti-tuberculosis drug treated cases (INH+RIF) can provide hepato-protection as it contains a wide range of antioxidants that can act in synergetic or additive fashion and protect cells against oxidative damage thus helping the rise of hepatotoxicity. The tremendous recovery of various cellular enzymes like SOD, CAT, GSH and MDA strongly indicate the hepatoprotective role of *Allium sativum* in drug-induced hepatotoxicity.

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