



# Effects of Silymarin in Methimazole Induced Hypothyroidism and Liver Dysfunction

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## ABSTRACT

**Introduction:** Research has shown 28% of hypothyroid patients to be at risk of developing cholestasis resulting in liver damage. Silymarin is an extract of Milk Thistle plant. Being hepatoprotective, it can regulate thyroid hormones by enhancing conversion of T<sub>4</sub> to T<sub>3</sub> in liver and improve thyroid and body functions. Bearing this in mind, a study was conducted to investigate the thyroid and hepatic therapeutic potential of silymarin in methimazole induced hypothyroidism and associated liver dysfunction. **Aims and Objectives:** Study the effects of Silymarin on thyroid functions and liver functions. **Place and Duration of Study:** The study was conducted in PGMI, Lahore and was completed in 38 days. **Material and Methods:** Rats were divided into 3 groups having 12 animals each. Group 1 served as negative control and was given water orally for 38 days. Remaining groups 2&3 were given methimazole orally 60mg/kg/day for 21 days to induce hypothyroidism and liver dysfunction. Post methimazole induction, group 3 was administered silymarin P.O 200mg/kg/day for 15days. Baseline thyroid and liver function tests were performed in all groups on day 1 and repeated on day 22 after methimazole administration and on day 38 following completion of treatment with silymarin to group 3. **Results:** At baseline, all groups showed normal thyroid and liver functions. After methimazole administration for 21days, group 2 &3 showed deranged TFTs and LFTs. Following 15 days of treatment with silymarin 200mg/kg/day, group 3 showed improvement in thyroid and liver functions (12.37 ± 0.44(T<sub>3</sub>), 3.10 ± 0.26(T<sub>4</sub>)ug/dl and 0.14 ± 0.109(TSH) ug/dl, LFTs 119.21 ± 24.14(AST), 87.78 ± 9.27 (ALT), and 148.25 ± 5.77 (ALP) and bilirubin levels of 0.44 ± 0.11 ug/dl with significant P value <0.05 from the healthy and diseased control groups 1&2. **Conclusion:** This study suggests that in the murine model, Silymarin intervention has therapeutic role in methimazole induced hypothyroidism and liver dysfunction which was displayed by improvement in thyroid and liver functions

**Key words:** Silymarin, Thyroxine, Methimazole

## INTRODUCTION

Hypothyroidism is the underproduction of the thyroid hormones T<sub>3</sub> and T<sub>4</sub>. Hypothyroidism is managed with hormone replacement therapy, like levothyroxine<sup>1</sup>. Methimazole inhibits the enzyme thyroperoxidase, which usually acts in thyroid hormone synthesis by converting the anion iodide (I-) to iodine (I). This causes hypothyroidism and liver dysfunction at high dosage<sup>2</sup>. Silymarin interestingly improves T<sub>3</sub>, T<sub>4</sub> and TSH by its hepatoprotective effects in rats exposed to carbon tetrachloride<sup>3</sup>. Chronic administration of hepatotoxic chemicals can reduce liver 5'DI enzyme

activity<sup>13</sup>. On the other hand, silymarin increases liver enzyme 5'DI (which converts T<sub>4</sub> to T<sub>3</sub>)<sup>4</sup>. As it has been reported, thyroid hormone replacement alone does not ensure euthyroidism in all tissues in thyroidectomized rats, silymarin might have the capacity to do so<sup>5</sup>.

The current study assesses these effects on thyroid and liver in the methimazole model. Silymarin, according to latest research is effective in reducing hepatotoxicity caused by carbon tetrachloride and xenobiotics such as isoniazid<sup>6</sup>. In this study, we assessed the therapeutic effects of silymarin in hypothyroidism and liver dysfunction induced by methimazole.

## MATERIAL AND METHODS

Rats, 6-8 weeks old, weighing 175-200gms were procured from University of Health Sciences, Lahore. Animals were kept under controlled environment having room temperature of  $22\pm 3^{\circ}\text{C}$ , humidity ( $50\pm 10\%$ ) and light and dark cycles of 12 hours each.

### Biochemical kits:

Kits for ALP, AST and ALT were purchased from Genway, Ltd.

Kits for T3, T4 and TSH were purchased from Randox.

### Medicines:

Silymarin and methimazole were purchased from Sigma company, Lahore.

### Grouping of animals and drug administration:

**Group 1:** Distilled water orally for 38 days (control)

**Group 2:** Methimazole 60mg/kg orally for 21 days and left for self recovery for 15 days.

**Group 3:** Silymarin 200mg/kg/day orally for 15 days. (in methimazole induced hypothyroid rats) Blood samples were taken by cardiac puncture at baseline, day 22 and day 38 at the end of the study. These were processed for serum on which LFTs and TFTs were conducted.

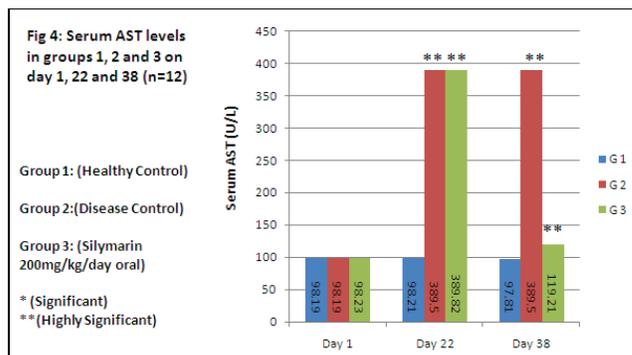
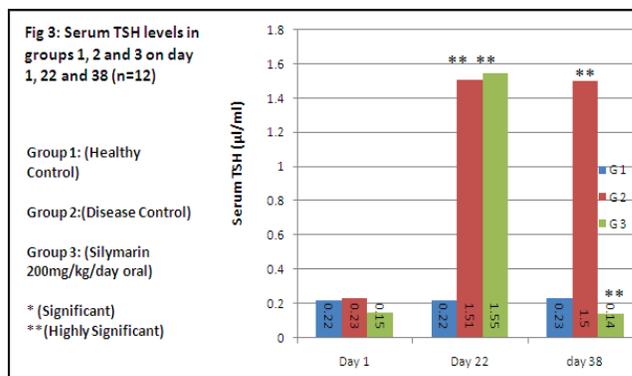
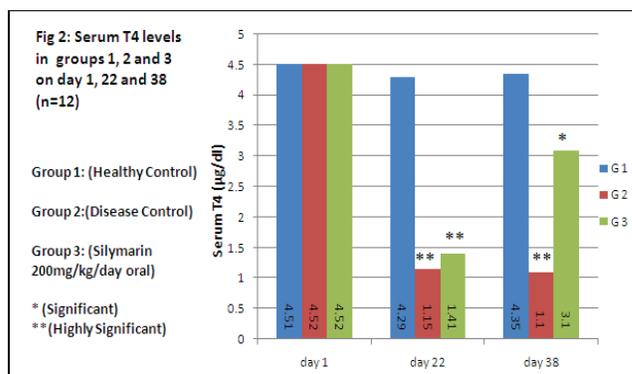
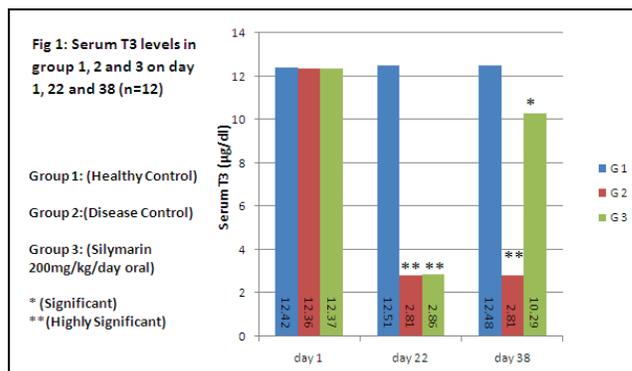
### Statistical Analysis:

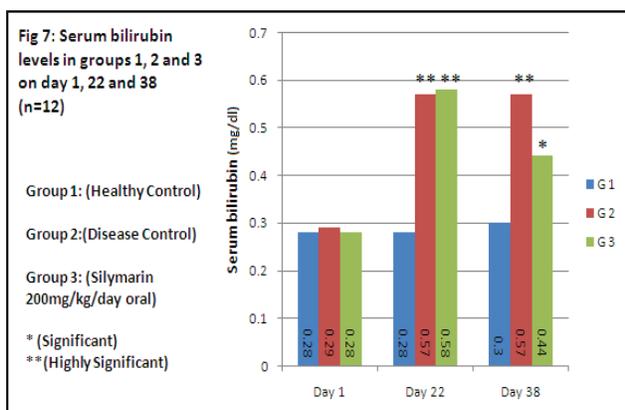
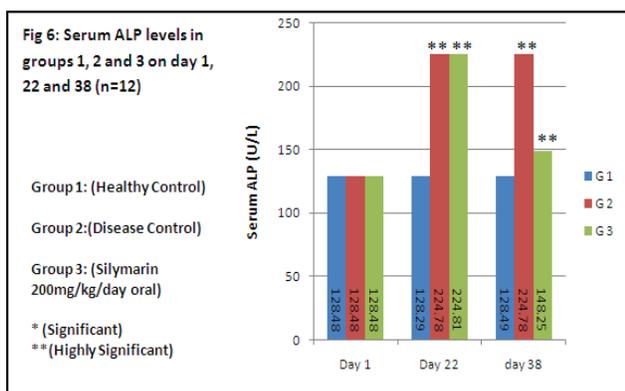
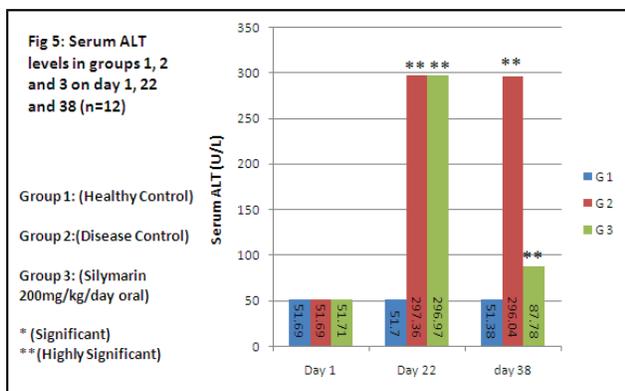
The data was entered and analyzed using SPSS 17.0. Mean  $\pm$  SEM was given for quantitative variables like T3, T4, TSH. One-way ANOVA was applied to compare the biochemical parameters among groups. Post Hoc Tukey's test was applied to determine difference in group means. A p-value of  $< 0.05$  was considered statistically significant.

## RESULTS

On day 1, all groups had normal thyroid and liver functions. After methimazole administration, group 2 and 3 were found to have the deranged TFTs and LFTs. However following silymarin intervention for 15 days, on day 38, group 3 had improved thyroid and liver function tests significantly ( $P = < 0.05$ ). These results indicated therapeutic effects of silymarin in reducing the thyroid and hepatic toxicity induced by

methimazole. Results are presented in the following figures 1-7:





## DISCUSSION

Hypothyroidism is a disease affecting 5.8% of population and its prevalence is increasing in Pakistan every year due to iodine deficiency and multiple drugs<sup>7,8,9</sup>. Thyroid hormones regulate the basal metabolic rate of hepatocytes; the liver in turn metabolizes the thyroid hormones and regulates their systemic effects.

Methimazole is an anti thyroid drug; It inhibits the enzyme thyroperoxidase which is required for the synthesis of thyroid hormones. In high dosage it may cause hypothyroidism and liver

dysfunction<sup>10</sup>.

Silymarin (flavonolignan obtained from seeds of milk thistle) contain a number of different active principles like flavonoids having potential prophylactic and therapeutic activity against many liver diseases<sup>11,12</sup>. Thyroid aspects of Silymarin had not been investigated much, our proposed research project was to investigate its beneficial effects against methimazole induced hypothyroidism and liver dysfunction.

On day 1, all groups had normal thyroid and liver functions. After methimazole administration for 21 days, groups 2 and 3 were found to have the deranged T3, T4, TSH and LFTs. However following silymarin intervention for 15 days, on day 38, group 3 had improved thyroid and liver function tests significantly ( $P < 0.05$ ). On day 38, group 3 showed 3 times increase in the levels of T<sub>3</sub> & T<sub>4</sub>, with significant fall in TSH. Whereas LFTs showed improvement by decreasing to one third of their previous levels. These results indicated therapeutic effects of silymarin in reducing the thyroid and hepatic toxicity induced by methimazole. Previous literature indicates that silymarin has therapeutic effects on the early stages of liver damage, reversing fatty changes and recovering liver histopathology in a dose-dependent manner. Research supported the beneficial action of Silymarin on hepatic dysfunction caused by acetaminophen and isoniazid due to acceleration of growth factors, and increased collagen<sup>15</sup>.

Silymarin possibly augmented the physiological activity of both hepatocytes directly and the thyroid indirectly by promoting the activity of 5'DI enzyme in the liver that enhanced conversion of T<sub>4</sub> into T<sub>3</sub><sup>12</sup>. Studies propose that silymarin has cell-regulating and metabolic effects namely carrier-mediated regulation of cell membrane permeability, inhibition of the 5-lipoxygenase pathway, scavenging of reactive oxygen species (ROS) and action on DNA-expression, for example, via suppression of nuclear factor (NF)-kappaB<sup>13,14,15</sup>. All these mechanisms would have a positive impact and further enhance hepatic and thus thyroid function. Silymarin have cell-regulating and metabolic effects namely carrier mediated regulation of cell membrane permeability, inhibition of the 5-lipoxygenase pathway, scavenging of reactive oxygen species (ROS) and action on DNA-expression, for example, via suppression of nuclear factor (NF)-kappaB.

## CONCLUSION

Silymarin could ameliorate the hypothyroidism and liver dysfunction induced by methimazole. Oral Silymarin 200mg/kg for 15 days showed good therapeutic activity in methimazole induced hypothyroidism and liver dysfunction which resulted in improvement of thyroid and liver function.

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