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EFFECT OF HARIDRA GHRIT IN HEPATOTOXICITY INDUCED BY ANTITUBERCULOSIS DRUGS - ANANIMAL STUDY

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ABSTRACT

In recent times, considerable efforts are being made to develop protective agents to be used therapeutically in cases of liver toxicity originating from diverse causes. Drug induced hepatotoxicity has become a major clinical concern with the long-term administration of antituberculosis (Anti-TB) drugs such as rifampicin (RIF), isoniazid (INH) and pyrazinamide (PZA) specially when used in combination.[1] In the ATT regimen four chemicals are used in combination and the toxicity effect is seen in combination rather than individual use of drugs. Thus, with this reference the anti-tuberculosis drugs may be included in the Gara visha category. Yakrit vikar is also mentioned as a one of the manifestations of Garavishajanya vikriti.[2] In Ashtanga Sangraha Uttarsthan chapter 40/70 various formulations have been quoted for the treatment of ailments caused due to Garavishaktata. Haridra ghrit is one of them.[3] The main content, Haridra i.e Curcuma Longa has antioxidant activity which results in inhibition of lipid peroxidation[4] and shows hepatoprotective property too.[5] The current study was designed to find out Ayurvedic formulation to treat the hepatotoxicity with its in vivo study to screen its effectiveness in albino wistar rats. The pathological obtained results of conspicuous

observationhave been discussed with scientific reasoning.

KEYWORDS: Haridra Ghrit, Hepatotoxicity, Antituberculosis drugs, Silymarin, lipid peroxidation,oxidative stress.

INTRODUCTION

Garavisha is prepared artificially by mixing various substances; it produces gada (Disease). As it takes some kala (Time) for this type of poison to reach vipaka (Metabolized) and produce its toxic effects, it does not cause prompt death of person.[6] Ayurveda has no direct reference of hepatotoxicity caused due to drugs but as per the definition of Gara visha, all kritrim visha can be considered under the concept of Gara visha.[7]

Gara visha may enter the body by various routes, out of these methods Anna (food) is a very common route of administration of Gara visha.[8] The National Strategic Plan for TB in India integrates TB elimination through the pillars of Detect, Treat, Prevent, and Build. The recommended treatment regimen involves a combination chemotherapy including Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, and/or Streptomycin.[9] However, drug-induced hepatotoxicity poses a significant risk, potentially leading to treatment discontinuation and increased morbidity and mortality.[10] Different works are being done on drug induced hepatotoxicity but no consensus guidelines are available hence work on DIH should be done. In this study Haridra ghrit is used because both contents of Haridra ghrit i.e. Haridra and Ghrita are vishaghna[11], easily available, affordable & included in daily diet hence chances of side effects are minimized and cost will be also minimum.

MATERIALS AND METHODS

Study design: Experimental study (Animal experiment)

The present study was carried out in following two phases

★ Pharmaceutical Study

★ Animal Experiment

The Pharmaceutical study was conducted in three steps

I. Procurement and authentication of raw drugs

II. Preparation of test drug i.e. Haridra Ghrita

III. Analytical study of raw drugs i.e. Haridra rhizome, and Final Product/Test drug i.e.

Haridra Ghrit.

I. Procurement and Authentication of raw drugs

A. Collection, Identification and Authentication of raw drug/ Plant material

Haridra rhizomes were collected from the authorized vender. After collection, a sample of Haridra rhizome was identified and authenticated at the Botany department of the Authorized Institute.

Table No. 1: Analytical report: Haridra (Curcuma longa).

Test	Specifications	Result
Appearance	Fresh rhizome	Fresh rhizome
Colour	Yellowish brown	Yellow
Odour	Characteristic	Characteristic
Taste	Characteristic	Characteristic
Foreign matter	NMT 2%	NIL
Moisture content	NMT5%	42.05 %
Ash	NMT9%	3.01 %
Aia	NMT1%	0.14 %
A s e	NLT8%	9.04%
Wse	NLT 12 %	16.47 %
Volatile oil	NLT4%	4%

B. Collection of the animal product

Go-ghrita was collected from the authorized herbal & animal product supplier.

C. Collection of Toxicant i.e. antitubercular drugs (Isoniazid, Rifampicin and Pyrazinamide) and Standard drug i.e. Silymarin

Antitubercular drugs (Isoniazid, Rifampicin and Pyrazinamide) and Standard drug i.e. Silymarin of a renowned pharmaceutical company was procured from a pharmacy.

II. Preparation of test drug

A. Ghrita murchana

Raw drugs (Murchana dravya) viz., Amalaki (Embelica officinalis), Haritaki (Terminalia chebula), Bibhitak (Terminalia bellerica), Musta (Cyprus rotundus), Haridra (Curcuma longa) were procured from renowned vendor and Matulunga (Citrus indica) i.e. Nimboo was purchased from the local market.

Table No. 2: Showing the ingredients, Ratios, Parts used, Quantity, by Sharangdhar SamhitaAyurveda Deepika Tika.

Ingredients	Latin Name	Family	Part used	Quantity
Amalaki	Emblica Officinalis	Euphorbiaceae	Pericarp	1 Pala
Bibhitaki	Terminaliabellerica	Combretaceae	Pericarp	1 Pala
Haritaki	Termineliachebula	Combretaceae	Pericarp	1 Pala
Haridra	Curucuma longa	Zingiberaceae	Rhizome	1 Pala
Musta	Cyprus rontandus	Cyperaceae	Rhizome	1 Pala
Matulunga	Citrus medica	Rutaceae	Swarasa	1 Pala
Goghrita				1 Prastha
Jala				4 Prastha

According to Modern Measurements1 Pala means = 48 gm

1 Prastha means = 768 gm

Preparation of murchana dravya kalka

The murchana dravya were taken in above quantity and were dried in sunlight till theybecame moisture less and then were subjected to grinding with the help of mortar and pestleto convert into coarse powder form. Further, an appropriate quantity of Matulunga swaras (Fresh juice) was added to prepare kalka.

Procedure

- All Murchana Dravya were taken in Bharad form.
- Kalka was prepared by adding Matulung swarasa.
- Goghrita was taken in a steel vessel and heated on Madhyamagani up till complete evaporation of moisture content.
- The Kalka was added in Ghrita after slight cooling
- When Kalka becomes light brown in color, water was added in proportion to 4 times of Ghrita.
- After addition of water, it was heated on Mandagni with intermediate stirring.
- Heating duration was adjusted to complete the Sneha paka till Sneha Siddhi Lakshana appeared.
- Then the vessel was taken out from the fire and Ghrita was filtered through clean clothin its mild hot stage.

Table No. 3: Sneha siddhi lakshana during ghrita murchana.

Sr. No.	Sneha siddhi lakshana	Kalka	Ghrita
1.	Shabda hino agni nikshipta	-	+
2.	Phenashanti	-	+
3.	Gandh varna rasotpatti	-	+

Table No. 4: Ingredients and their weight used for Haridra Ghrita preparation.

Dravya	Latin Name	Quantity of dravya
Haridra kalka	Curcuma longa	42gm
Murchita Ghrita	-	750ml
Jala	-	3000ml

Procedure

- Haridra was taken in Bharad form.
- Kalka was prepared by adding Jala into it.
- Murchita ghrita was taken in a steel vessel and heated on Madhyamagani until complete evaporation of moisture content.
- The Haridra Kalka was added in Murchita Ghrita after slight cooling
- When Kalka became light brown in color, water was added in proportion to 4 times of Ghrita.
- After addition of water, it was heated on Mandagni with intermediate stirring.
- Heating duration was adjusted to complete the Sneha paka till Sneha Siddhi Lakshana appeared.
- Then the vessel was taken out from the fire and Ghrita was filtered through clean cloth in its mild hot stage.
- Continuous stirring was carried out to prevent the burning of kalka, especially in the last stage.

Observations during haridra ghrita preparation

- ❖ When Haridra Ghrita was moisture free, the color of Ghrita was slightly changed to light yellow from dark yellow.
- ❖ Bubble and sound appear during Sneha Paka.

III. Analytical study

A. Analytical evaluation of raw drugs

Haridra rhizome and go-ghrita were evaluated by using organoleptic, physicochemical and chromatographical parameters. The analytical study was carried out according to the standard

guidelines given in Ayurvedic Pharmacopoeia of India, in an authorized laboratory. All the experiments were performed in triplicates and average value was calculated.

I. Organoleptic tests

Haridra and go-ghrita both were subjected to various sensory characteristics such as color, odour, taste etc. and the results were carefully noted down.

II. Physicochemical tests

a) Physicochemical evaluation of Haridra was done using following parameters

- Foreign Matter
- Total Ash Value
- Acid Insoluble Extractive
- Water Insoluble Extractive
- Alcohol Soluble Extractive

B. Analytical study of test drug (HG)/ Finished product

Finished product in Haridra ghrita (HG) was subjected to organoleptic, physico-chemical and chromatographic evaluation.

I. Organoleptic tests

NG was subjected to various sensory characters such as color; odor, taste etc. and the results were carefully noted down.

II. Physicochemical tests

Physicochemical analysis of HG was carried out according to the guidelines given in Laboratory Protocol for Testing of ASU drugs. And the following parameters were assessed

- Refractive Index
- Viscosity
- Acid Value
- Iodine Value
- Peroxide Value
- Saponification Value
- Test for Aflatoxins (B1, B2, G1, G2)
- Microbial Contamination

Animal experiment

A. Study design: Animal experiment
B. Study setting: Authorized laboratory with animal house facility
C. Ethical consideration: The protocol of study was approved by the Institutional Ethical Committee (IEC) and permission of Institutional Animal Ethical Committee (IAEC)was obtained prior to initiation of experiment.

Sample preparation

1) Haridra Ghrita: 0.8ml/kg/day (0.16ml/200g rat)
2) Silymarin: 25 mg/kg of Silymarin in distilled water.
3) Isoniazid: 100mg/kg/day of Isoniazid in distilled water.
4) Rifampicin: 300mg/kg/day of Rifampicin in distilled water.
5) Pyrazinamide: 700mg/kg/day of Pyrazinamide in distilled water.

Test System and Management

- Species: Rat
- Strain: Wistar
- Source: Crystal Biological Solutions.
- Sex: Male & Female (Female were non-pregnant & nulliparous)
- Body weight range: 180- 200 g
- Identification: Identification mark to animals and cages
- No. of animals: 24 (12M & 12F)
- Acclimatization: The rats were Acclimatized at test environment for 7 days.
- Environmental conditions: Room temperature maintained between 22 +3oC, relative humidity 55 + 5 % and 12-hours light and 12 hours dark cycle was maintained.
- Accommodation: Three rats in each cage with clean paddy husk.
- Diet: Pelleted feed supplied by Nutrivet Pvt. Ltd. ad libitum during the study.
- Water: RO filtered water was provided ad libitum.

Study design

Six rats (3 male & 3 female) in each group were used for this study, Test samples were given orally as per standard protocol and animals were observed for signs and symptoms along with weekly Body weight.

Procedure

This hepatotoxicity study was conducted in 12 male wistar rats & 12 nonpregnant and nulliparous female wistar rats weighing 180-200 gm having age between 6-10 weeks. Animals were kept for acclimatization under standard conditions for 7 days. The rats were identified by color marking.

1. Isoniazid (100 mg/kg/day), Rifampicin (300mg/kg/day) and pyrazinamide (700mg/kg/day) was administered to each rat except control group (Group 1) for 21 days by oral route taking with the help of oral gavage.
2. All the animals were weighed before (day 1), and weekly thereafter till day 21.
3. Isoniazid (100 mg/kg/day), Rifampicin (300mg/kg/day) and pyrazinamide (700mg/kg/day) were given to the Disease control group (Group 2) for 21 days.
4. Isoniazid (100 mg/kg/day), Rifampicin (300mg/kg/day) and pyrazinamide (700mg/kg/day) was given to Standard Group for 21 days. And also Standard drug (Silymarin) was given to Standard group (Group3) for 21 days.
5. Test drug Haridra ghrit was given orally to Test group (Group4) for 21 days.
6. Anesthesia was provided to animals after completion of treatment and Collection of blood was done.
7. Blood sample was collected on 0, 15th and 21th days and serum biochemical was done.
8. Biochemical estimations of various parameters such as serum glutamic- oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase (ALP), Serum Bilirubin, and Serum Albumin will be assessed.
9. All animals were weighed, and visual observations for death, behavioral patterns, and physical appearance changes are observed. Throughout the 21-day testing period, food and water intake were also assessed weekly.
10. Animals from each group were sacrificed and Liver were removed, weighed, and perfused in formalin solution for histopathology studies.

Table No. 5: The 4 groups (n= 6, 3 male & 3 females per group) were as follows.

Sr. No.	Animal Group	Animal Specification	Drug Specification	Dose in animal
1.	Group 1	Normal Control (NC)	No treatment	-
2.	Group 2	Disease Control (DC)	Isoniazid Rifampicin Pyrazinamide	100mg/kg/day 300mg/kg/day 700mg/kg/day

3.	Group 3	Standard (STD)	Isoniazid Rifampicin Pyrazinamide + Silymarin	100mg/kg/day 300mg/kg/day 700mg/kg/day + 25 mg/kg/day
4.	Group 4	Test	Isoniazid Rifampicin Pyrazinamide + Haridra ghrit	100mg/kg/day 300mg/kg/day 700mg/kg/day + 0.8 ml/kg/day

Dose calculation

Dose Calculation for anesthesia

75 + 10 mg/kg of ketamine & xylazine was given intraperitoneally (i.p) for anesthesia at the time of bleed.

Dose calculation of haridra ghrit

Dose of Haridra ghrit in human = 48 gram/dayConversion factor of rat (200g) = 0.018

Dose of Haridra ghrit in rat = 48 X 0.018.

=0.864 gram/day

I.e. dose in rat = 0.8 ml/kg/day.

= 0.16ml/200g/day

OBSERVATIONS AND RESULTS

Table no. 6: Mean biochemical parameter- Day 0.

Groups	Bilirubin	Albumin	SGPT
NormalControl	0.46±0.06	3.37±0.37	44.87±2.50
Diseasecontrol	0.47±0.04	3.33±0.14	45.76±1.39
Standard	0.49±0.02	3.31±0.26	46.57±2.77
Test	0.47±0.02	3.31±0.30	46.93±2.11

Groups	SGOT	ALP
Normal Control	117.20±2.78	87.41±2.26
Disease control	121.01±4.86	87.99±4.84
Standard	119.91±3.24	89.62±2.68
Test	123.10±2.81	88.42±4.38

The pair-wise comparison of serum biochemical parameters on day 0 shows

- No significant differences between the Test group and Normal Control (NC), Disease Control (DC), or Standard Control (SC) groups in serum bilirubin and albumin levels.
- In terms of SGPT and ALP levels, there were no significant differences between the Test

group and NC, DC, or SC groups. However, there was a significant difference in SGOT levels between the Test group and NC, indicating variations in liver enzyme activity.

Table No. 7: Mean biochemical parameter- Day 15.

Groups	Bilirubin	Albumin	SGPT
Normal control	0.49±0.04 ****	3.38±0.06 ****	46.35±1.74 ****
Diseasecontrol	2.09±0.37	3.56±0.09	88.34±4.93
Standard	1.37±0.29 ***	3.47±0.03	70.88±4.95 ****
Test	1.60±0.28 *	3.49±0.04 *	75.06±2.83 ****

Groups	SGOT	ALP
Normal control	119.78±1.22 ****	86.13±2.35 ****
Disease control	237.41±5.32	259.70±6.20
Standard	184.86±5.29 ****	159.94±5.14 ****
Test	187.75±4.51 ****	168.89±5.37 ****

The pair-wise comparison of serum biochemical parameters on day 15 shows

- Significant differences between the Test group and the Normal Control (NC), Disease Control (DC), and Standard Control (SC) groups in serum bilirubin, albumin, SGPT, SGOT,and ALP levels. Specifically, the Test group shows highly significant deviations in bilirubin, SGPT, SGOT, and ALP levels compared to NC and DC, highlighting substantial alterations in liver function.

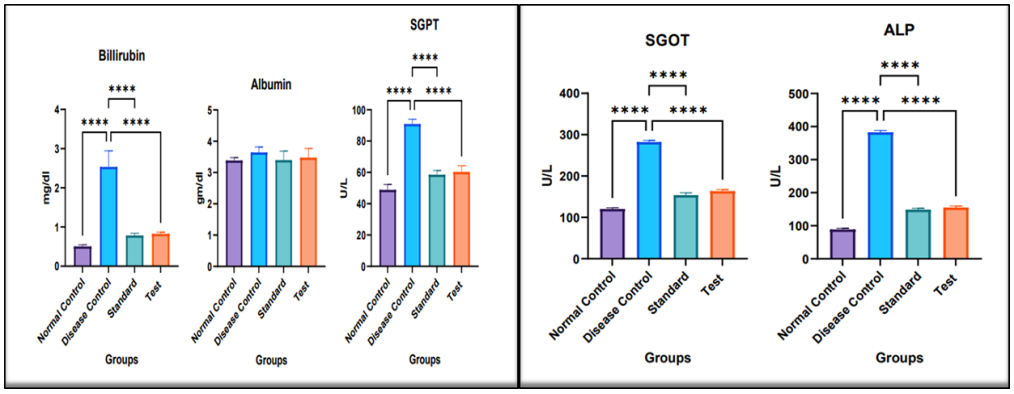
Table No. 8: Mean biochemical parameter- Day 21.

Groups	Bilirubin	Albumin	SGPT
Normal control	0.50±0.04 ****	3.39±0.09	48.90±3.39 ****
Diseasecontrol	2.53±0.41	3.64±0.17	90.99±2.99
Standard	0.79±0.05 ****	3.40±0.29	58.53±2.72 ****
Test	0.83±0.05 ****	3.48±0.30	60.30±3.99 ****

Groups	SGOT	ALP
Normal control	120.45±2.75 ****	88.96±3.49 ****
Disease control	282.07±3.89	382.53±5.50
Standard	153.83±5.62 ****	148.76±3.75 ****
Test	163.34±4.06 ****	155.09±4.76 ****

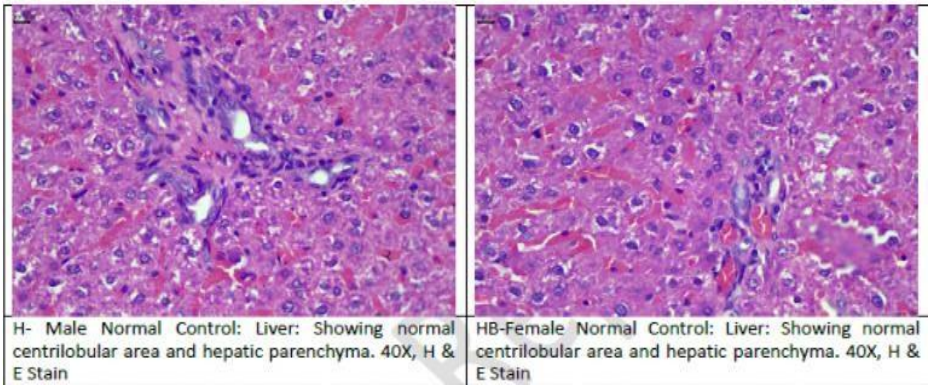
The pair-wise comparison of serum biochemical parameters on Day 21 shows

- Significant differences between the Test group and the Normal Control (NC), Disease Control (DC), and Standard Control (SC) groups in bilirubin, SGPT, SGOT, and ALP levels.Particularly, the Test group exhibits very significant deviations in these parameters compared to NC and DC, indicating substantial alterations in liver function following the administered treatment regimen.



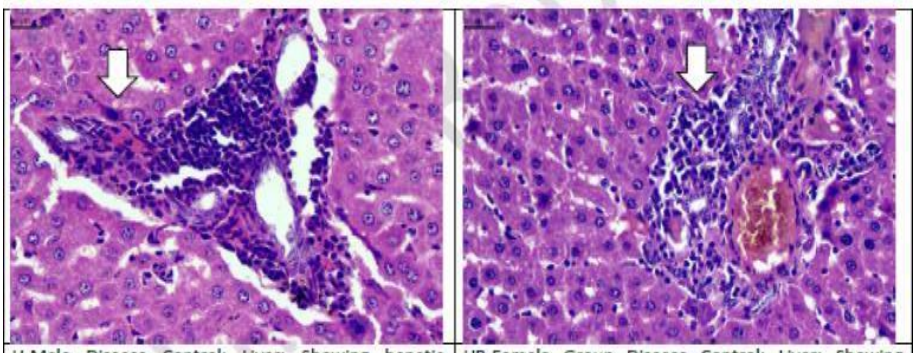
Histopathology

The NC group shows normal histological architecture. While in the DC group, it shows significant hepatotoxicity changes presented as hepatic degeneration with infiltration of inflammatory cells. STD groups treated with Silymarin show normal centrilobular area and hepatic parenchyma. The Test group treated with Haridra Ghrita showed normal hepatic architecture, along with normal centrilobular area and hepatic parenchyma. These findings were suggestive of hepatoprotective actions as well as hepatocytes repairing action of Haridra Ghrita.



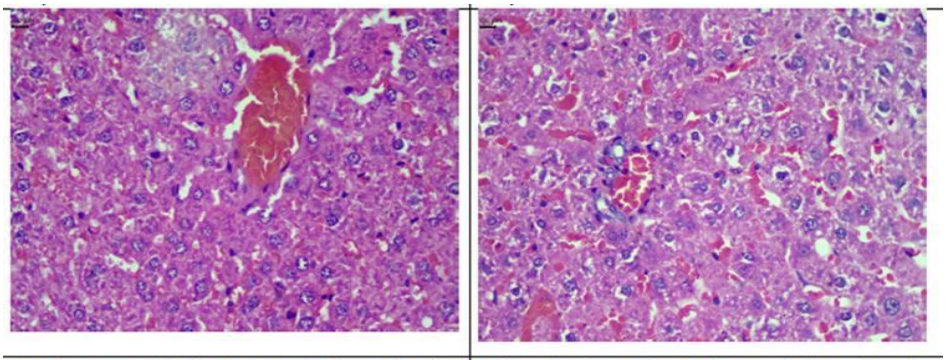
H- Male Normal Control: Liver: Showing normal centrilobular area and hepatic parenchyma. 40X, H & E Stain

HB-Female Normal Control: Liver: Showing normal centrilobular area and hepatic parenchyma. 40X, H & E Stain



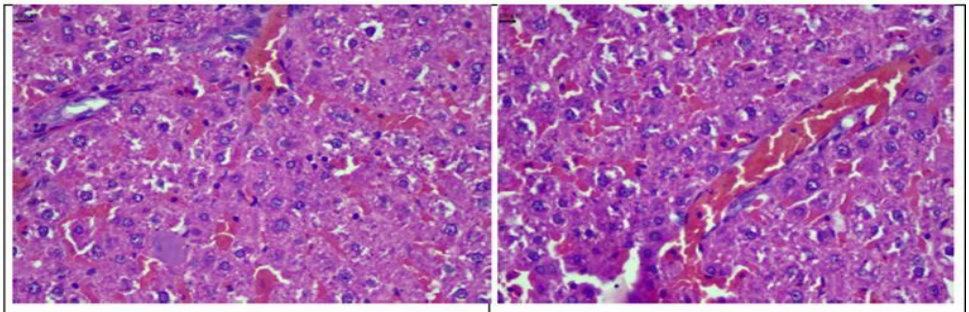
H-Male Disease Control: Liver: Showing hepatic degeneration with infiltration of inflammatory cells (arrow). 40X, H & E Stain

HB-Female Group Disease Control: Liver: Showing hepatic degeneration with infiltration of inflammatory cells (arrow). 40X, H & E Stain



B-Male Group Standard Control: Liver: Showing normal centrilobular area and hepatic parenchyma. 40X, H & E Stain

BT-Female Group Standard Control: Liver: Showing normal centrilobular area and hepatic parenchyma. 40X, H & E Stain



H-Male Group Test item Control: Liver: Showing normal centrilobular area and hepatic parenchyma. 40X, H & E Stain

HB-Female Group Test item Control: Liver: Showing normal centrilobular area and hepatic parenchyma. 40X, H & E Stain

DISCUSSION OF RESULT

There were significant changes in biochemical markers of liver function tests as summarized in table 7 & 8. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Bilirubin, Albumin and Alanine phosphatase (ALP) levels were raised in disease control groups. Statisticaldifferences were observed in day 0, day 15 and day 21 biochemical parameters.

Before induction (Day 0) of antitubercular drugs the biochemical parameters did not show anysignificant ($p>0.05$) change in their value when compared to the value of disease control. After induction (Day 15) of antitubercular drugs the values of SGPT, SGOT and ALP, Bilirubin,Albumin were high in disease control group.

The values of SGPT, SGOT, Bilirubin and ALP were reduced in standard and test group after Standard Silymarin and Test *Haridra ghrit* Treatment (Day 21). Normal control, standard Silymarin and test group animals showed significantly reduced levels of SGPT, SGOT, BILIRUBIN and ALP when compared with the disease control group. So it concluded that no statistically changes were observed before induction, however SGPT, SGOT, BILIRUBIN, Albumin and ALP were slightly increased after induction of antitubercular drugs whereas

SGPT, SGOT, BILIRUBIN and ALP decreased after treatment of Standard Silymarin and Test *Haridra ghrit.* Silymarin treated standard group showed significant decrease when compared to disease control group.

The test *Haridra ghrit* group was found to be more effective like the Silymarintreated group.

CONCLUSION

Antitubercular drugs Isoniazid, Pyrazinamide and Rifampicin are potent hepatotoxic for rats. It is also known to produce marked liver damage in exposed animals. There were highly significant changes observed in that group of animals which received antitubercular drugs for 21 days (Disease control group). Also, there was a marked increase in the weight of the liver of group 2 (Disease Control) animals. Various Histopathological and biochemical changes were also recorded in the animals that received antitubercular drugs. Hence, based on the results, it can be concluded that the deleterious effects of antitubercular drugs were observed.

In the present study treatment with *Haridra ghrit* was found to significantly reverse the hepatotoxicity induced by antitubercular drugs. Biochemical parameters like SGPT, SGOT, Bilirubin, Albumin and ALP levels were controlled due to treatment by standard as well as test drug. During a 21 days observation period, we found that0.8ml/kg *Haridra ghrit* showed efficacy in liver damage.

In the present study it is concluded that *Haridra ghrit* effectively protects against liver damage.

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