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Efficacy of *Manjisthadi Yoga* in Paracetamol induced Hepatotoxicity in Wistar Rat

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ABSTRACT

The liver is one of the most essential organs in the body, as it regulates a variety of physiological functions. It plays a role in metabolism, secretion, storage and among other things. It has a high ability for detoxication and the creation of beneficial principles. A nutritious meal is essential for developing tissue and cells, however nowadays people avoid eating healthy meals in favor of fast food to save time and money. This junk food is jam-packed with pollutants like phthalates that are bad for the body, as well as excessive amounts of sugar, salt and trans-fat. Numerous metabolic illnesses and systemic issues like obesity, diabetes and liver disease are caused by them. This type of meal or cuisine is referred to as *Viruddha Aahara* in Ayurveda. *Viruddh Aahara*, when consumed in excess, agitates the *Doshas* at their locations and remains in the body, blocking channels (*Strotoavrodha*). This block prevents nutrients from reaching the *Dhatus* (tissue) and many *Dhatujanya Vikara* develop as a result. As a result, hepatotoxic chemicals' injury to the liver has serious consequences. Toxic substances, excessive alcohol intake, virus infections, medicines such as paracetamol, antibiotics and autoimmune disorders are the main causes of liver damage. Taking the all the above facts in consideration the selection of the study has been done.

Key words: *Hepatotoxicity, Paracetamol, Manjisthadi Yoga*

INTRODUCTION

The purpose of Ayurveda is to preserve the health of the healthy and cure the disease of the unhealthy.[1] Health is defined by WHO as "A state of complete physical, mental and social well-being of an individual and not merely an absence of disease or infirmity. Health is not an end in itself but the means to another end namely to lead socially and economically a productive life. As per the definition, health is three dimensional-the physical, the mental and the social. Nonmedical dimensions which can be included are spiritual, emotional, vocational and political dimensions. This 'modified' definition is divisible into three parts: (a) Public health is the science and art of preventing disease, prolonging life and promoting health and efficiency through an organized community effort; (b) for the sanitation of the environment, the control of communicable infections, the education of the individuals in the principles of hygiene, the organization of medical and nursing services for the early diagnosis and preventive treatment of disease and (c) the development of social machinery that will ensure to every individual in the community a standard

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of living adequate for the maintenance of health, so organizing the benefits as to enable every citizen to realize his birth right of health and longevity.[2]

The *Dosas, Agni* (digestive power), *Dhatus* (tissues), *Malas* (waste products) and their activities are normal. His soul, sense organs and mind are clear, is called *'Svastha'* (healthy person).[3] Apart from the concepts of *Dosha, Dhatu,* and *Mala*, there are express of other concepts such as *Strotas, Koshthanga, Ashaya, Anga Pratyanaga*, and so on. While each organ has its own significance. The Liver (*Yakrita*), as the largest organ is given special attention both anatomically and functionally. It conducts numerous metabolic functions and a functioning liver is necessary for an individual's health. Liver is the largest metabolic organ, which aids in the removal of waste materials, the creation of diverse bioactive chemicals and the location of the majority of metabolic processes. The present study deals with the Paracetamol induced hepatotoxicity review of *Yakrita* in terms of liver. *Yakriddalyudara* in terms of Hepatotoxicity, *Samprapti* formation of *Yakriddalyudara* due to *Virudhaahar, Dushivisha* and *Garavisha* in terms of Paracetamol (toxic chemical) and their inter relationship. The selection of the drug "*Manjisthadi Yoga*" has basically based on the classical reference and also on the consideration of the ingredients of the drug which are known to have great effect on liver, individually.[4] The purpose of this study has to test the hepatoprotective effects of various traditionally used polyherbal formulations for their usefulness in liver disease. The hepatoprotective effect of a given plant formulation (*Manjisthadi Yoga*) is screened by available In-vivo test model systems

Aims and Objectives

Phytochemical analysis and Pharmacognosy study of the *Manjisthaadi Yoga* in induced PCM.

To collect, compile and analyze the literary material regarding In vivo study of *Manjisthaadi Yoga* in wistar rats.

1. To study the Acute oral toxicity in wistar rats.
2. To study the efficacy of *Manjisthaadi Yoga* in Paracetamol induced Hepatotoxicity in wistar rats.

Materials and Methods

Preparation of drugs and solutions

Sample drug - The *Churna of Manjisthadi Yoga* 200mg/kg have mixed with CMC (carboxy methyl cellulose) solution mixed it well in mortar and pestle to form a uniform 1% solution of *Manjisthadi Yoga*.

Paracetamol - It has used at a dose of 1000mg/kg body weight mixed with distilled water and prepared 5% Solution of PCM.

Silymarin - It has used at a dose of 45 mg/kg body weight and mixed with distilled water, prepared 10% solution of silymarin to carry out the experiment.

Housing and feeding conditions

The experimental animal room had a temperature of 22°C (plus 3°C). Except for when cleaning the room, the relative humidity should be between 50 and 60 percent, even though it had been at least 30 percent and should not exceed 70 percent. Artificial lighting should be used, with 12 hours of light and 12 hours of darkness. Regular laboratory diets and an endless supply of drinking water may be employed for feeding.

Preparation of animals

The animals are randomly selected, marked with Picric acid H (mark on head), B (Mark on Back), T (mark on Tail) for individual identification and kept in their cages for at least 5 days prior to dosing to allow for acclimatization to the laboratory conditions. Indusial rat had been marked with picric acid.

Study design

A. **Acute oral toxicity test :** 6 albino Wister rats were divided in two groups each group have 3 wistar rats.

Group 1 - 3 Wister rats had received test sample 1 at dose 300 mg/kg/ orally

Group 2 - 3 Wister rats had received test sample 1 at dose 2000 mg/kg/ orally

B. **Evaluation of Hepatoprotective Activity of *Manjisthadi Yoga***

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Eighteen healthy albino wistar rats had been selected in this animal model and divided in three groups each group contain six rats. All rats orally received 1000 mg/kg of PCM for7 days for induce hepatoxicity.

Group - 1 : Six Hepatotoxicity induced albino wistar rats had been received distilled water 5 ml/kg/P.O. for 30 days.

Group - 2 : Six Hepatotoxicity induced albino wistar rats had been received Test sample 200 mg/kg/P.O. for 30 days

Group - 3 : Six Hepatotoxicity induced albino wistar rats had been received Standard drug Silymarin 45 mg/kg/P.O. for 30 days.

Administration of doses

The test substance has been administered in a single dose by gavage using an oral feeding needle. Animals had been fasted prior to dosing (e.g., with the rat, food but not water should be withheld over-night, with the mouse, food but not water should be withheld for 3-4 hours). Following the period of fasting, the animals should be weighed and the test substance administered. After the substance has been administered, food may be withheld for a further 3-4 hours in rats.

OBSERVATION

Observations should include changes in Behavioral changes, Biochemical changes_and Histopathological changes.

Parameters for assessment

a) **Blood -** Liver function test (Serum Bilirubin, SGOT, SGPT, Total Protein) with help of automatic biochemistry analyzer. Blood sample have collected under all aseptic precautions. All blood specimens had collected by orbital puncher in Eppendorf tube.

b) **Collection of organs -** At the end of trial period, the animals have euthanized and liver has isolation from rat for observe histopathological changes.

c) **Histopathological studies -** At the end of experimental period, one animal of each group was sacrificed and observed for gross lesions of internal organs.

Statistical analysis

The results are expressed as mean ± SEM Comparison between Before and after treatment were performed Student t test paired and Comparison between the treatment groups and control have performed by analysis of variance (ANOVA) followed by Dunnett's multiple tests.

OBSERVATION

Animals are observed individually after dosing at least once during the first 30 minutes, periodically during the first 24 hours, with special attention given during the first 4 hours, and daily thereafter.

- **Behavioral changes -** Skin and fur, eyes, mucous membranes, salivation, Lethargy, sleep, coma, convulsions, tremors, diarrhea, morbidity, mortality are observed.
- **Biochemical changes -** Serum Bilirubin, SGOT, SGPT, Total Protein) with help of automatic biochemistry analyzer.
- **Histopathological changes -** liver dissected out, washed with saline and preserved in formalin for histopathological studies.

RESULTS AND DISCUSSION

Acute oral toxicity study-

Table 1: Showing hematological and biochemical parameter in acute oral toxicity study

SN	Parameters	Group 1	Group 2	Normal Range
1.	Hemoglobin	15.36	15.21	11.5-16.1 grams per deciliter
2.	WBC	9.56	8.93	6.6-12.6 x $10^3/mm^3$
3.	RBC	7.94	8.43	6.76-9.75 x $10^6/mm^3$
4.	Neutrophils	2.09	2.46	1.77-3.38 x$10^3/mm^3$

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5.	Lymphocytes	7.95	8.41	4.78-9.12 x 10^3/ mm^3
6.	Eosinophils	0.05	0.06	0.03-0.08 x 10^3/ mm^3
7.	Monocytes	0.04	0.03	0.01-0.04 x 10^3/ mm^3
8.	Basophils	0.00	0.00	0.00-0.03 x 10^3/ mm^3
9	SGOT (IU/ml)	185.96	180.34	5-40 unit per liter of serum
10	SGPT (IU/ml)	91.03	95.30	7-56 unit per liter of serum
11	Total Bilirubin (mg/dl)	0.78	0.85	0.2-0.8 mg/dl

The data presented in Table no 30 show the effect of the test drugs on hematology analysis (Hemoglobin, WBC, RBC, Neutrophils, Lymphocytes, Eosinophils, Monocytes, Basophils) SGOT, SGPT and total bilirubin.

Evaluation of Hepatoprotective Activity of *Manjisthadi Yoga*

- Present study was aimed to check the Hepatoprotective study of *Manjisthadi Yoga* on Paracetamol induced hepatotoxicity.
- After oral administration PCM 1000 mg/kg for 7 days hepatoxicity was induced and determined by increasing in Liver function tests, behavioral observations and treatment was orally administration for 30 days and observe as follow.

Table 2: Showing Direct bilirubin parameters

Direct Bilirubin	H	B	T	HB	BT	HT
Group 1	2.21	2.45	2.67	2.34	2.45	2.67
Group 2	0.89	0.78	0.87	0.67	0.70	0.67
Group 3	0.45	0.35	0.34	0.42	0.36	0.45

The data presented in Table no. 2 show the effect of the test drugs on Direct bilirubin activity. Administration of paracetamol leads to a remarkable and statistically significant increase in the direct bilirubin. Administration of test drug dose leading to statistically significant decrease in direct bilirubin activity in comparison to paracetamol control group. In reference standard group also a marked significant decrease in direct bilirubin activity was observed in comparison to paracetamol control group.

Table 3: Showing Total Protein parameters

Total Protein	H	B	T	HB	BT	HT
Group 1	51.34	48.85	52.34	45.43	44.56	48.45
Group 2	69.43	71.34	69.43	78.43	54.54	61.34
Group 3	67.43	68.324	62.23	65.46	65.43	61.33

The data presented in Table no. 3, showing the effect of the test drugs on total protein activity. Administration of paracetamol leads to a remarkable and statistically significant decrease in the total protein activity. Administration of test drug dose leading to statistically significant increase in total protein activity in comparison to paracetamol control group. In reference standard group also a marked significant increase in total protein activity was observed in comparison to paracetamol control group.

Table 4: Showing SGOT parameters

SGOT	H	B	T	HB	BT	HT
Group 1	234.54	245.43	298.43	276.45	289.42	291.34
Group 2	214.56	232.34	216.64	254.567	209.45	232.45
Group 3	198.45	179.45	188.45	193.45	199.23	204.52

The data presented in Table no. 4 show the effect of the test drugs on SGOT activity. Administration of paracetamol leads to a remarkable and statistically significant increase in the SGOT activity. Administration of test drug dose leading to statistically significant decrease in SGOT activity in comparison to

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paracetamol control group. In reference standard group also a marked significant decrease in SGOT activity was observed in comparison to paracetamol control group.

Table 5: Showing SGPT parameters.

SGPT	H	B	T	HB	BT	HT
Group 1	198.32	189.32	210.34	189.34	197.34	217.34
Group 2	134.54	143.45	153.45	124.57	132.45	145.67
Group 3	110.32	98.33	112.43	99.34	103.43	110.34

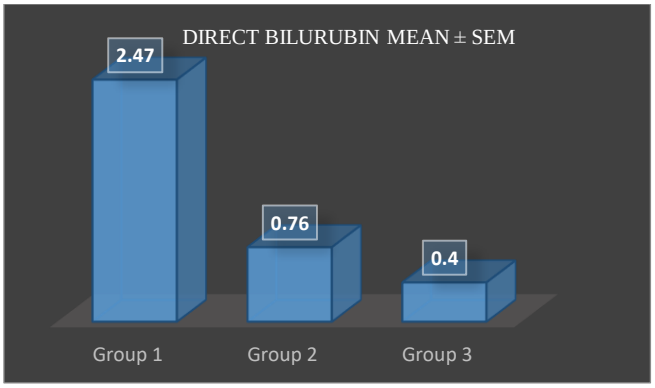
The data presented in Table no. 5, show the effect of the test drugs on SGPT activity. Administration of paracetamol leads to a remarkable and statistically significant increase in the SGPT activity. Administration of test drug dose leading to statistically significant decrease in SGPT activity in comparison to paracetamol control group. In reference standard group also a marked significant decrease in SGPT activity was observed in comparison to paracetamol control group.

Table 6: Showing mean value of all parameter.

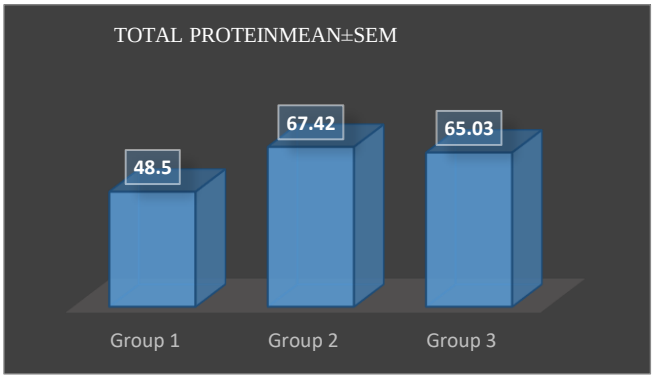
Groups	Direct Bilirubin Mean± SEM	Total Protein Mean ± SEM	SGOT - Mean ±SEM	SGPT - Mean ±SEM
Group 1	2.47±0.074	48.50±1.263	272.60±10.806	200.33±4.635
Group 2	0.76±0.040	67.42±3.404	226.67±6.801	139.02±4.259
Group 3	0.40±0.021	65.03±1.133	193.93±3.654	105.70±2.504

It indicates that *Manjisthadi Yoga* sample have similar action to standard drug (Silymarin) biological act - SGPT reduction response, SGOT reduction response, Direct Bilirubin reduction response and Total protein increasing response.

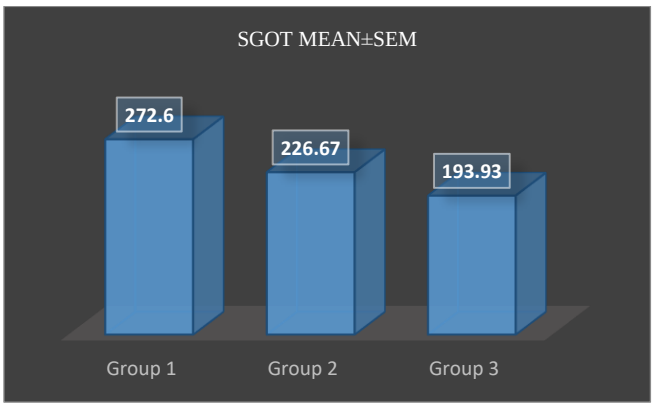
Graph 1: Showing mean value of Direct Bilirubin



Graph 2: Showing man value of total protein



Graph 3: Showing mean value of SGOT



Graph 4: Showing mean value of SGPT

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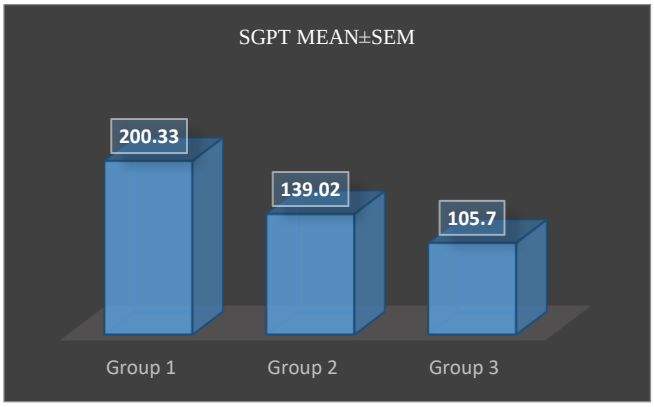

Table 7: Statical comparison of SGPT

Dunnett's multiple comparisons test	Mean Diff.	95.00 % CI of diff.	Significant?	Summary	Adjusted P Value
Group 1 vs. Group 2	61.31	47.82 to 74.80	Yes	****	<0.0001
Group 1 vs. Group 3	94.64	81.14 to 108.1	Yes	****	<0.0001

After statical comparison in between group 1 (Negative control) group 2 (Test drug) was found statical significant P value is less than 0.0001 and comparison between group 1 (Negative control) group 3 (Standard drug) P value is less than 0.0001.

Table 8: Statical comparison of SGOT.

Dunnett's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Summary	Adjusted P Value
Group 1 vs. Group 2	45.93	19.48 to 72.38	Yes	**	0.0014
Group 1 vs. Group 3	78.68	52.23 to 105.1	Yes	****	<0.0001

After Statical comparison in between group 1 (negative control) and group 2 (test drug) was found statical significance P value 0.0014 and comparison between group 1, group 3 (standard drug) was found statical significant P value < 0.0001.

Table 9: Statical comparison of Direct Bilirubin.

Dunnett's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Summary	Adjusted P Value
Group 1 vs. Group 2	1.702	1.528 to 1.875	Yes	****	<0.0001
Group 1 vs. Group 3	2.070	1.897 to 2.243	Yes	****	<0.0001

After statical comparison in between Group 1, group 2 was found statical significance P value less than 0.0001, and Group 1, group 3 was found statical significance P value less than 0.0001.

Table 10: Statical comparison of Total Protein

Dunnett's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Summary	Adjusted P Value
Group 1 vs. Group 2	-18.9	-26.50 to -11.35	Yes	****	<0.0001
Group 1 vs. Group 3	-16.5	-24.11 to -8.96	Yes	***	0.0002

After statical comparison in between Group 1, group 2 was found statical significance P value less than 0.0001, and Group 1, group 3 was found statical significance P value 0.0002.

The result of histopathological studies provided supportive evidence for the hepatoprotective activity of the test drug (*Manjisthadi Yoga*).

Moderate fatty changes, sinusoidal feathery, erosion and necrosis, congestion in portal vein with fibrous tissue proliferation ware found in histopathological examination when given distilled water (group 1).

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Mild fatty changes, mild sinusoidal dilation and congestion was found in histopathological examination when given Test sample - *Manjisthadi yoga* (group 2).

Mild fatty changes, mild sinusoidal dilation and congestion was found in histopathological examination when given Standard drug - Silymarin (group 3).

In the paracetamol group changes observed such as Moderate fatty changes, severe degenerative Sinusoidal feathery, erosion and necrosis were found, congestion in PV with fibrous tissue proliferation. In silymarin group 3 (Standard drug) Toxic changes reduced in most of the rat sections compared to the paracetamol group.

CONCLUSION

The test formulation *Manjisthadi Yoga*, comprising seven important ingredients which are well known for their hepatoprotection activity has been found to have good hepatoprotective activity. In Analytical study showing these characteristics are helpful in determining the quality of formulation. Reversal of these changes by the test formulation and reference standard provide strong evidence for the presence of the hepatoprotective activity in this formulation.

The data obtained during the study clearly establishes that Paracetamol induced hepatotoxicity, based on the analysis of the results - the probable mechanisms postulated for the protective effect seen in the test formulation are:

1. Inhibition of direct bilirubin value
2. Enhance the total protein
3. Inhibition the value of SGPT and SGOT.
4. Mild fatty changes, mild sinusoidal dilation and congestion was fond in histopathological examination

The test formulation is constituted by well-known hepatoprotective ingredients with proven activity as individual drugs. The present study provides strong evidence for the hepatoprotective activity of the individual ingredients. The data generated can be considered as strong basis for the clinical efficacy of this product.

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