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A Study on Anti Dyslipidemia Activity of *Haritaki* and *Madhu* in albino rats treated with high cholesterol diet

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ABSTRACT

Dyslipidemia is a disorder of lipoprotein metabolism, including lipoprotein over production or deficiency. Dyslipidemia may be manifested by elevation of total cholesterol, LDL cholesterol and triglycerides concentration and decrease in HDL cholesterol concentration in the blood i.e. presence of one or more than one abnormal serum lipid concentration. Dyslipidemia has becoming one of the major problems leading to various disorders like obesity, diabetes, atherosclerosis, cerebrovascular diseases, hypertension etc. Dyslipidemia is a condition which shares a lot of similarity in pathogenesis and clinical presentation of *Medoroga*. *Medoroga* is a condition in which there is abnormal and unequal distribution and collection of *Medo Dhatu* in body. In the comprehensive Ayurvedic literature *Medoroga* has been synonymously described as *Sthoulya*, which has been classified under *Ashta Nindita Purusha*. The incidence and the magnitude of the problem are constant rise due to alternation in lifestyle with sedentary habits, overeating and stressful life environmental factors etc. The treatment strategy is to implement lifestyle changes including diet and exercise, weight loss and lipid lowering drugs. In spite of availability of numerous drugs, mankind is still leading miserable life with this disease. Hence Ayurveda emphasizes natural and effective remedies which are cost effective and helpful in prevention of the disease. There are variety of drugs mentioned for *Medodushti* and *Atisthoulya*. *Haritaki* and *Madhu* is one such combination explained in *Samhita*.

Key words: Dyslipidemia*, Medoroga, Haritaki, Madhu.*

INTRODUCTION

Veda is an ancient scientific document from which every science and technology has originated. Ayurveda is *Upaveda* of *Atharvaveda*. The fundaments of Ayurveda give healthy human life. Health is one of the important requirements to achieve *Purusartha Chatushtaya*. *Dhatu Samyata* is the sign of health. Fast foods, lack of exercise, stress, various addictions etc. are some of the factors which contribute greatly to such diseases. These factors generally act by impairing the metabolism of an individual making him prone to series of disorders. Dyslipidemia is one such disorder which is identified as a potential risk factor for multitudes of diseases like cardiovascular diseases, metabolic syndrome and even hypertension. A study conducted by ICMR in India showed 13.9% had hypercholesterolemia, 29.5% had Hyper-triglyceridemia, 72.3% had low HDL-C, 11.8% had high LDL-C levels and 79% had abnormalities in one of the lipid parameters. Urban residents had the highest prevalence of lipid abnormalities compared to rural residents.[1] Ayurveda emphasis on different *Shamana Yogas* for the treatment of *Meda Slesmavikaras*. *Vikrut Meda*

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Slesma can be correlated with pathophysiology of dyslipidemia. There are variety of drugs mentioned for *Medodushti* and *Atisthoulya*. *Haritaki* and *Madhu* is one combination explained in *Samhita*.[2] *Haritaki* is said to be *Pathyatama* in *Agrya Prakarana*. *Madhu* is also a drug advised as a *Nityasevaniyadravya*. Both the drugs are individually *Medohara* due to their inherent qualities. Considering *Medodushti* in parlance with Dyslipidemia the study is planned to experimentally evaluate the Antidyslipidemic activity of *Haritaki* and *Madhu* in albino rets.

OBJECTIVES

To evaluate the Antidyslipidemic effect of *Haritaki* and *Madhu* in Albino rats.

MATERIALS AND METHOD

Study design

It is a randomised experimental trail. The selected albino rats have been grouped into 5 groups with 6 animals in each group. In group 1 only water and normal diet has been administered without Hyperlipidemic diet, whereas group 2 receive only Hyperlipidemic diet. 3, 4 and 5 have received the drug and diet for 27 days as per table. On 28th day, after overnight fasting, the rats had been sacrificed. Blood will be collected from retro-orbital puncture and assigned for biochemical investigation. The liver, kidney and heart excised out from sacrificed animal, weighed and transferred to fixing solution (10% formalin) for Histopathological examinations.

Table 1: Grouping of the animal

Group	No. of rats	Drugs
1	6	Normal diet
2	6	High cholesterol diet
3	6	Atorvastatin with high cholesterol diet.
4	6	*Haritaki* and *Madhu* with high cholesterol diet
5	6	*Madhu* with high cholesterol diet

Drug selection

1. *Haritaki Churna* was purchased from SDM Pharmacy Udupi for the study.
2. *Madhu* was collected from Brahmavara and authentication done in SDM Research Lab.

Dose for Animals: Human dose x 0.018 x 5 / Kg wt

Dose for rats: Human dose x 0.018 x 5 x wt of the rat / 1000 g

Dose of *Haritaki Choorna* - 12g ×0.018×5

= 1.08g / kg

Dose of Madhu = 1ml /100g

Dose of cholesterol = 1ml /100g

Route of drug administration

The test drugs were administered according to the body weight of the animals by oral route with the help of gastric catheter.

Inclusion criteria

Not less than eight week old healthy albino rats of either sexes weighing about 150-250g were selected in random.

Exclusion criteria

Diseased rats, rats under trail for other experiments, pregnant rats and rats below 150g and more than 250g

Parameters studied

Ponderable changes

Body weight, weight of organs like Heart, Liver and kidney were recorded and expressed in terms of relative values.

Clinical chemistry

From the blood collected from the orbital plexuses serum would be separated and analysed for the following parameters in each animal (collected at the end of the study or at the time of sacrificing moribund or intercurrently ill animals. The animals would be subjected to overnight fasting).

Serum Bio-Chemical Parameters

For estimation of bio-chemical parameters, serum was separated from collected blood and requisite

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quantity of serum was fed to the auto analyser which was automatically drawn into the instrument for estimating different parameters. Bio-chemical parameters like Serum Cholesterol, Serum Triglycerides, Serum HDL-cholesterol, Serum LDL-cholesterol, Serum Urea, Serum Creatinine, Serum Glutamic oxaloacetic transaminase(SGOT), Serum glutamic pyruvic transaminase (SGPT) activity, Total Protein, Serum Albumin, Serum Globulin, Serum Alkaline phosphatise activity, Total bilirubin, Direct Bilirubin were estimated.

Statistical Analysis

The data generated was analysed by employing one way ANOVA with Dunnet's multiple 't' test as post hoc test.

Observations and Results

Table 2: Effect of *Haritaki* and *Madhu* on serum cholesterol level.

Groups	Cholesterol (mg/100ml)	% change
Normal control	52.66 ± 4.31	-
Cholesterol control	98.5 ± 5.22**	87.04↑@
Standard	65.66 ± 3.90**	33.34↓#
H+ M	54 ± 4.56**	45.17↓#
M	102.8 ± 10.06	4.36↑#

Data: MEAN ± SEM, **P<0.01, H+M = *Haritaki* +Madhu, Standard = Atorvastatin, M = Madhu. @-compared with normal control, #-compared with cholesterol control

The data shows that due to hyperlipidemic diet there was an increase in serum cholesterol level in cholesterol control group when compared to the normal control group. The observed increase was found to be statistically very significant.

The data shows there was a decrease in serum cholesterol level in standard group and H+M group when compared to the cholesterol control group. The observed decrease was found to be statistically very significant.

Table 3: Effect of *Haritaki* and *Madhu* on Triglyceride level.

Groups	Triglyceride (mg /100ml.)	% change
Normal control	89.5 ± 5.70	-
Cholesterol control	235± 40.70*	162.56↑@
Standard	214.6± 47.55	8.56↓#
H+ M	116.5 ± 29.97	50.42↓#
M	266 ± 43.09	13.19↑#

The data shows that due to hyperlipidemic diet there was an increase in Serum Triglycerides level in cholesterol control group when compared to the normal control group. The observed increase was found to be statistically significant.

The data shows there was a decrease in serum Triglycerides level in standard group and H+M group when compared to the cholesterol control group. The observed decrease was found to be statistically not significant. (Table 3)

Table 4: Effect of *Haritaki* and *Madhu* on HDL cholesterol level.

Groups	HDL Cholesterol (mg/100ml)	% change
Normal control	26.83 ± 3.26	-
Cholesterol control	34.5± 2.81	28.56↑@
Standard	46.33± 4.0	34.28↑#
H+ M	34 ± 4.27	1.44↓#
M	32.2 ± 1.80	6.66↓#

The data shows that due to hyperlipidemic diet there was an increase Serum HDL cholesterol level in cholesterol control group when compared to the

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normal control group. The observed increase was found to be statistically not significant.

The data shows there was an increase in serum HDL cholesterol level in standard group and decrease in H+M group when compared to the cholesterol control group. The observed decrease was found to be statistically not significant.

Table 5: Effect of *Haritaki* and *Madhu* on LDL cholesterol level.

Groups	LDL cholesterol (mg/100ml)	% change
Normal control	17 ± 1.21	-
Cholesterol control	23.5 ± 2.24	38.23↑@
Standard	12.33 ± 1.11**	47.53↓#
H+ M	11.88 ± 2.40**	49.44↓#
M	27.2 ± 3.05	15.74↑#

The data shows that due to hyperlipidemic diet there was an increase serum LDL cholesterol level in cholesterol control group when compared to the normal control group. The observed increase was found to be statistically not significant.The data shows there was a decrease in serum LDL cholesterol level in standard group and H+M group when compared to the cholesterol control group. The observed decrease was found to be statistically very significant

Table 6: Effect of *Haritaki* and *Madhu* on VLDL cholesterol level.

Groups	VLDL cholesterol (mg/100ml)	% change
Normal control	17.9± 1.14	-
Cholesterol control	46.5 ± 8.21*	159.77↑@
Standard	42.66 ± 9.52	8.25↓#
H+ M	23.4 ± 5.87	49.67↓#
M	53 ± 8.83	13.97↑#

The data shows that due to hyperlipidemic diet there was an increase serum VLDL cholesterol level in cholesterol control group when compared to the normal control group. The observed increase was found to be statistically significant.

The data shows there was a decrease in serum VLDL cholesterol level in standard group and H+M group when compared to the cholesterol control group. The observed decrease was found to be statistically not significant

Table 7: Consolidated statement of biochemical parameters on administration of *Haritaki* and *Madhu*.

Parameters	Compared with normal control	Compared with cholesterol control		
	Cholesterol control	Cholesterol + Standard	Cholesterol + Haritaki + Madhu	Cholesterol + Madhu
Serum cholesterol	SI	SD	SD	SI
Triglyceride	SI	NSD	NSD	NSI
HDL	NSI	NSI	NSD	NSD
LDL	NSI	SD	SD	NSI
VLDL	SI	NSD	NSD	NSI
Serum Urea	SD	NSD	NSD	NSD
Serum Creatinine	SD	NSD	NSD	NSE
B. Sugar	NSI	NSD	NSI	NSD
SGOT Activity	NSI	NSD	NSI	NSI
SGPT	SI	NSD	NSD	NSI

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Activity				
ALP Activity	SI	NSD	NSD	NSD
Total protein	SI	NSD	NSD	NSD
Albumin	NSD	NSD	NSD	NSD
Globulin	SI	NSD	NSD	NSD
Indirect bilirubin	SI	NSE	NSD	NSI
Direct bilirubin	SI	NSD	NSI	NSI
Liver weight	NSD	NSI	NSI	NSI
Heart weight	NSI	SI	NSI	NSI
Kidney weight	SD	SI	NSI	NSI

SD - Significantly decrease, SI - Significantly increase, NSI - NonSignificantly increase, NSD - Non Significantly decrease

DISCUSSION

Any theory or observation emerged from classical and experimental study can only be accepted if there is proper reasoning (*Tarka*) of the observations. According to ancient research methodology, before establishing any theory, *Upanaya* (Discussion) is prior step to *Nigamana* (Conclusion). Discussion is a process of re-examining and forms the base for conclusion. Inspite of detailed literature and experimental study, a theory is accepted only after the proper reasoning of observation. *Acharyas* used their way of experimentation and researches during their period for the upliftment of our science. Charaka says in *Sutrasthana* 10th chapter that those alone are wise who act after investigation. Even he mentioned about testing drugs and food in animals before administering to human. *Sushruta Samhita* has dealt with animal experiment by devoting a separate chapter -*Yogya Vidhi*. It is said that any procedure, which is to be performed on human being, should undergo trial on animals or other things, having similar characteristics. Also in *Kalpasthana* of *Sushruta Samhita* there is similar discussion dealing with the observations of animal experiments. Hence before administering any drug to human it is desirable to experiment the same on lower animals.

Thus for scientific explanation of any phenomena experimentation is necessary. Although the richness and potential of Ayurveda is well known even to common people, it is always considered better to establish such a knowledge based on experimental findings, which is the master key to make such knowledge widespread, to shows its depth of understanding and acceptable to all over the world. There are many concepts in Ayurveda which need detailed scrutiny to assess their utility in the field of science. Among them one concept is *Sthoulya*. *Sthoulya* is the major issue which this era is facing. This is mainly due to our lifestyles and food habits.

Effect of *Haritaki* and *Madhu* on ponderable changes.

In observation it's found that stool of *Haritaki* and *Madhu* group was dry compared to other group. Positive control group stool was unctuous and loose in nature. Weight of positive control group rats was increased compare to *Haritaki* and *Madhu* group. In dissection observed more fat deposition in the omentum of positive control group. In *Haritaki* and *Madhu* group it is significantly reduced. Also more water uptake by the *Haritaki* and *Madhu* group was observed compared to other groups.

Effect of *Haritaki* and *Madhu* on lipid profile

Administration of hyperlipidemic diet lead to significant elevation in serum total cholesterol, serum triglyceride level, LDLand VLDL cholesterol and decrease in HDL cholesterol. These hyperlipidemic diet induced changes were significantly reversed by the administration of *Haritaki* and *Madhu,* thus providing evidence for its efficacy in reversing the dyslipidaemia induced changes. This can be done by focusing on the mechanisms of action of atorvastatin. Atorvastatin are competitive inhibitors of HMG-CoA reductase, the rate limiting step in cholesterol synthesis. *Haritaki* contains alkaloids phytosterols, saponins, tannins, ellagic acid, gallic acid, chebulinic

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acid, chebugalic acid and corilagin. High amount of saponins, phytosterols, chebulinic acid and corilagin present in *Haritaki* may be responsible for the hypolipidemic effect. Anti-oxidant constituents of *Haritaki* and *Madhu* also prevent the endogenous oxidation of cholesterol resulting in decrease in the concentration of low density lipoprotein and again confirm the hypolipidemic activity. Tannins have been reported to increase faecal bile acid excretion, thereby leading to reduction in cholesterol levels.

As part of biomarkers assessment protein, serum albumin, SGOT, SGPT activity was measured as an index of liver function along with serum bilirubin level, serum urea and creatinine activity was assessed as a measure of kidney function. Disturbance in the tissue integrity especially of liver would get reflected in the form of elevation. The serum SGPT and ALPase activity were found to be significantly elevated due to hyperlipidemic diet. SGOT activity was also elevated but did not reach statistically significant level.

In present study also impaired bile pigment metabolism was seen, but effect was significantly reversed by *Haritaki* and *Madhu* in comparison to positive control. The above effects of hyperlipidemic diet are indicative of impaired liver functions. Most of these parameters were found to be reversed by *Haritaki* and *Madhu* combined group. *Madhu* given alone has no effect. The observed effect may be the result of the reversal of the hyperlipidemic diet induced changes or there may be a hepatoprotective component also.

Serum urea

Generally, Urea is produced from the catabolism of various muscle proteins and amino acids. This urea helps in the metabolism of nitrogen containing compounds, reabsorptionof water, carries nitrogenous waste and helps in the counter-current exchange system. *Haritaki* and *Madhu* show significantly reduced serum urea level compared with positive control group. This is indicative of impact on nitrogen metabolism.

Effect on Serum Creatinine

Generally, creatinine is a break down product of creatinine phosphate in muscle metabolism. Feeding of hyperlipidemic diet per se did not elevate serum creatine level. Effect on serum creatinine and serum urea indicates that this diet did not cause impairment of kidney function. Decrease observed may be due to down regulated metabolism of the serum creatine. This decrease was not affect by *Haritaki* and *Madhu*.

Effect on blood sugar level

Haritaki and *Madhu* show reduced blood sugar level compared with positive control group. This effect was moderate and non-significant. This moderate effect may be useful to improve insulin sensitivity. The magnitude of alpha-glucosidase inhibition by chebulagic acid was greatly affected by its origin. Since this phytochemical is present in *Haritaki* it might have such an enzyme activity inhibitory effect. It may be useful in the treatment of obesity linked diabetes mellitus.

Histological examination

Histological examination of heart, kidney and liver showed that hyperlipidemic diet in the present study did not cause any significant degenerative changes in heart and kidney. However, significant changes were seen in liver in the form of fatty degeneration of the hepatocytes, marked cell depletion and mild to moderate cell infiltration. These degenerative changes were moderately reduced in standard and test drug administered groups.

For any disease line of treatment depends on the basis of their *Samprapti Vighatana*. In the treatment of *Medo Roga* the drug needed to tackle the *Vikruta Meda*, *Prakupita Vayu* and *Tikshna Jatharagni*. Here *Haritaki* has *Kashaya Pradhana Lavana Varjitha Pancharasa*, *Ushnavirya*, *Madhuravipaka*, *Tridoshahara* property, *Ruksha Guna* and *Agnidipana*, *Medhya*, *Rasayana*, *Laghu*, *Anulomaka* in nature[3] and *Madhu* has *Kashaya*, *Madhura Rasa* and *Ruksha*, *Guru Guna*. It is *Kapha*, *Pittahara*, *Chedaka* and also *Yogavahi*.[4] So combination of both *Dravya* fulfils the *Guru Cha Apatarpana* criteria for *Samprapti Vighatana*. Administration of *Haritaki* and *Madhu* tackle the *Prakupita Vayu*, *Tikshna Jathragni* and remove *Prakrupita Meda* by improving the *Medo Dhatvagni*. Ultimately the proper *Upachaya* of *Medo Dhatu* occur and remove the obstruction of *Srotas*.

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CONCLUSION

Dyslipidaemia is one of the major modifiable risk factors for atherosclerosis and its consequences. *Haritaki* and *Madhu* group showed statistically significant reduction in serum T. cholesterol, T.G., LDL, VLDL. In *Haritaki* and *Madhu* group there was reduction in body weight compare to positive control group. There was statistically significant difference between the results of *Haritaki* and *Madhu* group and positive control group. *Haritaki* and *Madhu* is very effective combination to prevent and cure the Dyslipidemia.

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