ABSTRACT

INTRODUCTION

We find a verse in praise of the trial drug “Haritaki” which translates as “One who is away from his mother or who has lost his mother can depend upon Haritaki as his mother”. This quotation itself testifies the intensity of usefulness of Haritaki as a drug. This drug has a wide therapeutic range from the diseases of Gastro intestinal tract to Nervous disorders, from Skin ailments to Urinary tract disorders and from Cardiovascular disorders to Geriatrics. It has particularly been postulated that it cures with success the disease conditions emerging out of blocking of micro and macro channels of the body particularly because of over-saturation and over-nutrition, which is a bitter reality of the present day’s affluent society.

SELECTION OF TOPIC

- The very root meaning of the word ‘Panacea’ can be undoubtedly implied to the multifaceted properties possessed by “Haritaki (Terminalia chebula)”.
- Classically mentioned properties of Haritaki as Usna Vritya (hot in potency), having predominance of Kashaya Rasa (Astringent in taste) despite the presence of all the four other Rasas except Lavana. It is mentioned as Yogavahi and Pacaka.
- Mentioned in the disease conditions caused due to over nutrition.
- Anti-hypercholesterolemic effect which was studied in cholesterol induced atherosclerosis in rabbits (Thakur, C. P. et.al., 1988).
- Preliminary clinical observations also indicated the effect of Haritaki as a good and safe anti-hypercholesterolemic drug which was well tolerated to the patients without any adverse effects.
- Can be taken for longer period without involving much cost.
- An easily available drug.
- The diseases of over-nutrition and over-saturation are now a days not confined to only developed countries. Incidences of such disease conditions are alarmingly increasing in developing countries like ours which is the main contributory factor for Ischemic Heart Diseases (IHDs), the greatest importance has been attached to Hyper-cholesterolemia for the causation of IHDs.

AIMS AND OBJECTIVES

1. To clinically evaluate the effect of Haritaki in Hypercholesterolemia.
2. To investigate the lipid lowering effect of the drug in hypercholesterolemic albino rats.
3. To study the acute toxicity of the drug in albino rats.
4. To find out the toleration of the drug to the patients and adverse effects, if any.
5. To standardize the drug Haritaki (Terminalia chebula) before its administration.

PLAN OF WORK

The work was planned and carried out in following stages:

1. Review of literature
II. Drug standardization
   a) Preparation of drug
   b) Microscopic analysis
   c) Quantitative analysis
   d) Thin Layer Chromatography
   e) Solubility and X-ray analysis
   f) Determination of Rasa and its taste threshold

III. Pharmacological study
   a) Toxicity study
   b) Anti-hypercholesterolemic activity study

IV. Clinical study

REVIEW OF LITERATURE

Drug – However, Haritaki has been referred to at lot many places in vedic literature but no particular reference regarding its use was found. But as far as its therapeutic importance is concerned, this drug has been benevolently put to use in Ayurvedic literature right from the time of Samhitā period. All the Samhitās, Nighantus and later Ayurvedic works were reviewed for its every aspect and inferred accordingly. The other up to date description of the drug like that of its botany, chemistery, pharmacognostical, pharmacological studies and its description in other literature were reviewed thoroughly.

Hypercholesterolemia - The emergence of CHD as the leading cause of death has been attributed to certain risk factors of which the greatest importance is attached to Hyperlipidaemia, the condition in which lipids are present in excess in the blood. The literature was reviewed thoroughly for every aspect of the disease.

Medo dosa - Medo roga and Medo dosa have been described to be synonymous to each other. Literally, it means a disease in which Meda Dhātu is deranged. It is only one type of the disease according to Ayurvedic texts, but Ādamala, the commentator on Śārangadhara, has tried to distinguish between two types of Medo roga:

1. Lipid disorders where Meda acts as an aetiological factor in the genesis of other diseases.
2. Adiposity, including its clinical features (Sthaulya).

The causative factors, pathogenesis and other aspects of the disease were thoroughly reviewed from the Ayurvedic literature and inferences drawn.

DRUG STANDARDIZATION

The drug was collected, authenticated, processed and subjected to standardization on scientific parameters like Microscopic analysis, Quantitative analysis, Thin Layer Chromatography, Solubility and X-ray analysis, Determination of Rasa and its taste threshold.

PHARMACOLOGICAL STUDY

Toxicity study

Results of the acute toxicity studies indicated that the drug sample has shown no toxic effect and is safe up to a loaded daily dose of 3g./kg. in mice. LD₅₀ of the test drug sample Terminalia chebula is very high.
Anti-hypercholesterolemic activity study
Aims and objectives
The aims and objectives of this study were as follows:
1. To develop hypercholesterolemia by cholesterol (500mg/kg) & cholic acid (100mg/kg) oral administration in albino rats.
2. To investigate the lipid lowering effect of Terminalia chebula (95% alcoholic extract) in hypercholesterolemic albino rats.

Material and methods:
Drugs/chemicals:
a. Test drug: Terminalia Chebula (95% alcoholic extract)
Finely powdered crude drug was extracted thrice with 95% ethyl alcohol by maceration. The extract obtained were combined, concentrated and dried under reduced pressure. The dry extract obtained was pulverized to fine powder and used for pharmacological studies.
b. Cholesterol & cholic acid:
Cholesterol & cholic acid purchased from LOBA Chemilab, Mumbai., Cholesterol was determined by enzymatic colorimetric test using Agappe diagnostic kit-Mumbai. Triglycerides were estimated by infinite kit manufactured by Accurex biomedical pvt. Ltd. Mumbai.

Animals:
Healthy Albino rats of Sprague Dawley strain weighing between 130 to 150 g of either sex were purchased from National Toxicology Center, Pune. The animals were housed under 12hrs day & night conditions. The animal had free access to food pellets from Amrut Laboratory (Chakan Oil Mills Ltd.) Sangli, Maharashtra & water ad libitum.

Experimental procedure:
Albino rats were divided into following groups:
Group 1: Received the vehicle coconut oil 10 ml/kg orally once daily for a period of 42 days.
Group 2: Received cholesterol (500 mg/kg) and cholic acid (100 mg/kg) in coconut oil 10 ml/kg orally once daily for a period of 42 days.
Group 3: Received cholesterol (500 mg/kg) and cholic acid (100 mg/kg) in coconut oil 10 ml/kg orally once daily for a period of 42days. Alcoholic extract of Terminalia chebula suspended in Acacia solution (4%) was administered orally once daily for a period of 42 days. The dose of the extract was 500 mg/kg.
Group 4: Received cholesterol (500mg/kg) and cholic acid (100 mg/kg) in coconut oil 10 ml/kg orally once daily for a period of 42days. Alcoholic extract of Terminalia chebula suspended in Acacia solution (4%) was administered orally once daily for a period of 42 days. The dose of the extract was 1gm/kg.

After the end of treatment period of 42 days animals were weighed & lightly anaesthetized with the ether. Blood was collected from heart. The serum was separated & stored at 20° until assayed. Cholesterol and triglycerides levels were estimated.
It is concluded that the alcoholic extract of fruits of Terminalia chebula has significant anti-hypercholesterolemic effect and mild weight reducing effect in rats. None of the animals died or has shown any adverse effect on the drug.

CLINICAL STUDY

Material and method
A. Criteria for selection
   i. Age - Between 20-70 years
   ii. Sex – Either
   iii. Serum cholesterol more than 200 mg/dl (in asymptomatic patients)
   iv. Serum cholesterol more than 200 mg/dl (in the patients of other diseases who were not taking any drug having an anti-hypercholesterolemic effect).

B. Criteria for exclusion
   i. Age – Below 20 years and above 70 years
   ii. Severe complications of Ischaemic heart diseases, Diabetes mellitus, Rheumatoid arthritis, Obesity and Hypertension
   iii. Any other severe systemic disease
   iv. Non-ambulatory cases

Patients fulfilling the criteria for selection were included under the study after receiving their written consent. They were then randomly divided into treatment and placebo groups irrespective of their age, sex and duration of disease.

C. Withdrawal from the study
   i. Discontinuation of treatment during the trial
   ii. Development of any complication
   iii. Evidence of any inter-current illness which may interrupt the efficacy of the drug

D. Criteria for routine examination and assessment
   Full details of history, physical examination and the data of lab. investigations of the patients were recorded in a specially prepared proforma for the trial. The Ayurvedic methodology for the examination as of Sarīra Prakṛti, Mānasa Prakṛti, Sāra and Srotasa Parīkṣana was also adopted. After the start of treatment, patients were advised to visit after every two weeks interval. During every visit their complete physical examination was done. A score system was observed for the gradation of severity of the symptoms. The mild gradation of a symptom was given the score as 2, moderate as 4 and severe as 6. The effects of drug on various presenting symptoms and bio-chemical investigations were evaluated on the basis of the observations made before and after the course of therapy. The assessment of the results of treatment was done on the basis of reduction in serum cholesterol level after the course of treatment. Dropout patients were not taken into account.

E. Type of study : Single blind
F. Level of study : O.P.D.
G. Period of study : 6 weeks
H. No. of groups : Clinical trial comprised of two groups :
   i) Treatment group
   ii) Placebo group
I. No. of patients : i) 78 patients were studied under treatment group
ii) 75 patients were studied under placebo group

J. Principal drug, placebo and diet
   a) Principal drug: Haritakī (powder)
   b) Placebo: Starch (capsules)
   c) Diet: The whole milk dairy products, egg yolk and meats were replaced with fresh fruits and vegetables along with whole grain products and low fat dairy products.

K. Dose schedule and vehicle
   a) Dose schedule: 1. Treatment group: Haritakī powder in the dose of 9 gms/day in three divided doses after meals.
                   2. Placebo group: Starch capsules in the dose of 2 capsules (500 gms each) thrice daily after meals.
   b) Vehicle: Luke warm water

L. Laboratory Investigations
   i) Urine examination - Routine
   ii) Stool examination - Routine
   iii) Routine blood examination - TLC, DLC, ESR and Hb
   iv) Blood Glucose - Fasting and P.P.
   v) Blood Urea
   vi) Serum Creatinine
   vii) Serum Uric acid
   viii) Lipid Profile - Serum Cholesterol
         - LDL
         - HDL
         - Serum Triglycerides
         - VLDL
         - Serum Total Lipids

Observations and results
Total 153 patients were studied under both the groups of which 78 patients were in the treatment group and 75 patients were in the placebo group. The data of their characteristics, symptoms of disease and lab. investigations and other observations were recorded in the proforma specially prepared for the study and the results were drawn and statistically analyzed.

CONCLUSION
On the basis of the results of present clinical study, animal experiments and the inference drawn about the action of the drug, the following conclusions are drawn:
- Haritakī (Terminalia chebula) brings about a substantial reduction in the increased serum cholesterol level in Hypercholesterolemia and also inhibits the increase of cholesterol level.
- It is effective in the correction of lipid metabolism as a whole and also has a weight reducing property.
It is a well tolerated drug without any adverse effect. Its LD₅₀ is very high and it is safe for the prolonged use.

The diet and lifestyle are the major etiological factors for hypercholesterolemia but they cannot be considered as replacement measures as far as the drug therapy is concerned.

Thus, it can be concluded that Haritaki (Terminalia chebula) is a safe drug, devoid of any toxic effects and possesses appreciable anti-hypercholesterolemic activity. An easily available and economical drug as it is, it can go a long way in maintaining a desirable level of cholesterol and in a way preventing the complications arising out of “CHDs” the name which sends a wave of terror in the minds of the people at large.