Antihyperlipidemic Potential of Siddha Formulation- Pavala Veera Chunnam in High Fat Diet Induced Hyperlipidemic Rats

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Abstract
Background: Hyperlipidemia is a known risk factor for cardiovascular disease (CVD). Statin group of drugs suppress a rate-limiting stage in cholesterol production, yet all statin medications have musculoskeletal adverse effects. As a result of the present interest, traditional siddha sources are being searched for new lipid-lowering medicines with minimal or no side effects. Objective: The main objective of the present investigation is to evaluate the antihyperlipidemic potential of the siddha formulation Pavala Veera Chunnam (PVC) in high fat diet (HFD) fed rats. Methods: HFD mediated obese model was adopted for the induction of hyperlipidemia in the experimental animals. The animals were divided into control, disease control and treatment groups. Rats belongs to treatment groups were administered test drug PVC at doses of 200 and 400 mg/kg/p.o. Results: The data of the present investigation clearly emphasise that the body weight, total cholesterol, HDL, LDL, VLDL, and triglyceride levels of the HFD group demonstrate a significant increase in comparison with normal control rats. Treatment with the siddha formulation PVC at 200 and 400 mg/kg doses results in a significant decrease in the total lipid profile and body weight of the experimental animals. Furthermore, the PVC treatment causes a consistent decrease in the internal organ weight (heart and liver) of the animals. Histological examination of the liver sample confirms the existence of inflammatory changes in HFD treatment, and treatment with PVC reveals a restorative nature in both the dose level. Conclusion: In conclusion, the data of the present study show that the siddha formulation PVC reveals promising antihyperlipidemic activity in HFD-fed rats. Hence PVC type formulations may be considered an alternative drug of choice in the clinical management of hyperlipidemia.
Keywords: Hyperlipidemia, Siddha, Pavala Veera Chunnam, Lipid profile, Body weight, Histopathology.

1. Introduction

Siddha system of medicine is one of the traditional medicine in the world. 4448 diseases are mentioned in Siddha book Agathiyar 2000 published by thanjavur Saraswathi Mahal Library. The Siddha medicines are prepared from herbs, metals, herbometalic, minerals and herbominerals. Hyperlipidemia is a major cause of atherosclerosis [1]. According to studies, the risk of coronary heart disease is favourably connected with low-density lipoprotein cholesterol (LDL-C) levels and negatively correlated with high-density lipoprotein cholesterol (HDL-C) levels [2]. Hyperlipidemia is linked to a higher risk of coronary heart disease in people in their 40s and 50s, even if they have a low risk of heart disease [3]. In India approximately 25 – 30% of urban and 15 – 20% of rural peoples are suffering from hyperlipidemia.

It is widely accepted that elevated levels of low-density lipoprotein cholesterol (LDL-C) are a direct cause of atherosclerotic cardiovascular disease (ASCVD) [4] as well as its significant clinical consequences [5]. Even though many people with hypercholesterolemia and mixed dyslipidemia do not experience any symptoms, the accumulation of

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atherogenic lipoproteins increases the total atherosclerotic burden. This can result in a thrombus, which can then lead to unstable angina, myocardial infarction, or even death, in the event that the atherosclerotic plaque suddenly ruptures [6].

One of the primary risk factors for atherosclerotic cardiovascular and cerebrovascular diseases is dyslipidemia, which can be characterised by either one or a combination of the following symptoms: elevated total cholesterol; high LDL cholesterol; low HDL cholesterol; and elevated triglyceride levels. Specifically, elevated levels of blood lipid profiles are a significant contributor to the prevalence of atherosclerosis, which is widely acknowledged as the primary risk factor for cardiovascular disease, as well as stroke and peripheral vascular disease [7].

Statin treatment has been proven to be successful in reducing levels of low-density lipoprotein cholesterol (LDL-C) by 20–50%, as well as reducing levels of triglycerides by 10–20% and perhaps generating a rise in blood levels of high density lipoprotein cholesterol (HDL-C) by 5–10% [8,9]. Recently, concerns have been raised over the over-prescribing of statin medicines, in addition to the potential for statin therapy to have significant adverse effects. As a consequence of this, a number of patients have discontinued their statin treatment, which has raised concerns about the possible dangers of using statins for an extended period of time [10].

Siddha Medicine *Pavala veera chunnam* has many pharmacological activities. Nar Pavalam (Corallium Rubrum) has its own Hepatoprotective, Hypolipidemic, Lithotriptic Diuretic, Laxative, Emetic, Anti-bilious, Anti-Phlegmonous [32, 33] properties. Veeram (Hydrargyrum per chloride) has its own Antibiotic, Anti-septic, Alterative, Caustic properties. The bile's of animals such as cow, buffalo, goat, deer, pig, dog, cat, peacock, fish and snake are used as medicine. Bile has got laxative property [34]. This makes the Siddha medical system an excellent example of indigenous therapy as an art form. The tradition of using minerals as a source of medicine dates back to ancient times and continues to play a significant role in India's current healthcare system. Approximately seventy percent of India's rural population is dependent on the country's traditional method of healthcare [11].

Traditional Indian medicine is gaining popularity due to the fact that it is effective treatment for a significant number of chronic ailments. Although conventional allopathic medicine pioneers in several subfields within this industry, it does not necessarily perform better than more traditional methods [12,13]. The use of medications for the rest of a patient's life is a common practise in allopathic therapy, and many people end up becoming dependent on these drugs [14]. The gold standard model of availing statins for managing dyslipidemia can cause undesirable side effects as well as withdrawal symptoms upon long-term exposure. These symptoms might subsequently become problematic if the prescriptions are suddenly stopped. Several case studies make it strongly evident that patients typically have a positive response to traditional treatments, reporting a diminishment in the severity of their symptoms and, in some cases, even a complete disappearance of those symptoms [15,16]. The main objective of the present investigation is to evaluate the antihyperlipidemic potential of the siddha formulation Pavala Veera Chunnam (PVC) in high fat diet (HFD)-fed rats.

2. Materials and Methods

Ingredients of Pavala Veera Chunnam

1. Nar Pavalam (Corallium Rubrum) 1 part (460grams)
2. Purified Veeram (Hydrargyrum per chloride) :1/10 th part (46grams)
3. Velladu Pithu (Goat's Bile) : 50 counts of gall bladder contents

Collection and Authentication of raw drugs

The sources of raw materials such as veeram (Hydrargyrum perchloride) and Nar pavalam (Corallium rubrum) were procured from the authorised traditional medicine shop in Thakkalai, Kanyakumari District, Tamil Nadu, India. Goat bile was procured from the slaughterhouse in the northern zone of Chennai, Tamil Nadu, India. The Nar pavalam (Corallium rubrum) were authenticated by a Geologist and veeram (Hydrargyrum perchloride) were authenticated by a chemist and Goat bile were authenticated by a vetenarian Doctor.

Purification of Raw drugs

Purification of raw drug proceeded with the standardised procedure enlisted by Gunapadam Thathu Jeeva Vaguppu text literature.

1. Nar Pavalam, also known as Corallium Rubrum, is soaked in lemon juice for a period of twenty-four hours, after which it is thoroughly washed with hot water and then dried.
2. The process of purifying veeram (Hydrargyrum per chloride) was carried out in accordance with the standard operating procedure. Camphor that has been mixed in with the coconut water and then placed in a jar made of mud. The pot is then set ablaze for a quarter of an hour after the hydrargyrum per chloride has been wrapped in a cloth and soaked in the pot without coming into contact with the water.

Formulation of Pavala Veera Chunnam

The Purified hydrargyrum and Corallium rubrum together were pulverised and placed in earthen pot. Incremental addition of goat's bile into the previously powdered raw drug made the consistency in to granules and subjected to drying under sunlight. Subsequently it is covered with another earthen mud plate, the mouth is sealed with seven layers of fabric that has been coated with clay, and it is left to dry. After that, it is incinerated with two hundred and fifty cow dung cakes that are placed in a pit inside of an airtight chamber. After it has been

allowed to cool, it is weighed, then it is powdered, and then it is bottled. Outcome of this standardised procedure yield white coloured finished product with very fine consistency called "*Pavala veera Chunnam*" [17].

Experimental Design

Healthy adult wistar rats procured from Biogen, Bangalore, India, were utilised for ascertain the efficacy of the test formulation PVC. There were 12 hours of light and 12 hours of dark cycle were maintained at the animal house facility. During the whole experiment, all of the experimental animals have free access to pellet meal and RO water. The Institutional Animal Ethical Committee (IAEC) of Sathyabama Institute of Science and Technology in Chennai, Tamil Nadu, India, carefully scrutinised the study protocol looked over the study plan and rendered with the approval number *SU/CLATR/IAEC/XV/166/2020*.

High fat diet induced hyperlipidemia in rats

High fat diet induced hyperlipidemia is a well-recognised model which have been utilised for the present investigation [18,19]. The animals were divided into four groups of six rats each. Group I (Control group) administered with normal saline, while group II received a high-fat diet (HFD) consisting of powdered normal chow, 365 g; lard, 310 g; casein, 250 g; cholesterol, 10 g; vitamin and mineral mix, 60 g; DL methionine, 0.3 g; yeast powder, 0.1 g; and NaCl, 0.1 g. 5.33 kcal/g were found in the high fat diet. The animal will be given HFD for twelve weeks, along with low and high doses of the test medication (PVC). Experimental animals belong to group III (Low dose treatment group) were administered with HFD and treated with 200 mg/kg of PVC, p.o prior to HFD. Group IV (high dose treatment) were administered with HFD and treated with 400 mg/kg of PVC, p.o prior to HFD for twelve weeks' period of time.

Biochemical analysis

Serum samples were analysed for the lipid parameters such as Triglycerides (TGL), LDL, VLDL and HDL as per the standard protocol using mindray auto analyser BS 120 model [20].

Histopathology by simple staining techniques

Liver tissue sample from control and treatment group rats were subjected to simple (H&E) staining techniques for grading the severity index and to elucidate the comparative investigation among different treatment groups with that of the disease control [21].

Statistical analysis

All data were expressed in mean SEM (n=6), and comparisons were done between Control (a) versus Disease control (b) (Group II) and Group II vs Treatment group (c) Group III and IV one-way ANOVA [22] followed by Students T test. Statistic symbols represent significance. *p<0.05, **p<0.01, ***p<0.001.

3. Results

Effect of the siddha formulation Pavala veera chunnam on lipid profile of control and drug treated rats

The data of the present investigation clearly emphasise that the total cholesterol, HDL, LDL, VLDL and triglycerides level of the disease control group demonstrate a significant increase in the lipid profile of the experimental animals. Treatment with the siddha formulation PVC at 200 and 400 mg/kg doses results in a significant decrease in total cholesterol and the related lipid profile of the rats in groups III and IV. As shown in Table 1.

Table 1: Effect of the siddha formulation Pavala veera chunnam on lipid profile of control and drug treated rats Table 1: Effect of the siddha formulation Pavala veera chunnam on lipid profile of control and drug treated rats

Group	Total cholesterol	HDL	LDL	VLDL	TG
Group I- Control	121.7 ± 8.80	53.67 ± 3.35	55.5 ± 5.27	12.5 ± 0.69	34 ± 3.43
Group II- HFD treatment	206.4 ± 2.96*	30.5 ± 2.04*	128.3 ± 1.74*	47.58 ± 2.12*	118.2 ± 2.02*
Group III- HFD + 200 mg/kg PVC	168.7 ± 3.68*	39 ± 2.11*	96.33 ± 3.46*	33.37 ± 1.23*	89.67 ± 2.62*
Group IV- HFD + 400 mg/kg PVC	151.6 ± 4.36*	45.17 ± 1.77*	79 ± 2.97*	27.4 ± 1.31*	62.33 ± 2.76*

Data's represented as mean ± S.E.M. (n=6), comparisons were made between: Control (Group I) Vs Disease control (b) (Group II) and Group II vs Treatment group - Group III & IV. Symbols represent statistical significance: *p<0.05, **p<0.01, ***p<0.001.

Table 2: Effect of the siddha formulation Pavala veera chunnam on body and internal organs of control and drug treated rats

Group	Initial Body Wt in gms	Final Body Wt in gms	Weight of Heart in gms	Weight of Liver in gms
Group I- Control	207.2 ±2.00	268.2 ±2.12	0.561 ±0.01	4.867 ±0.08
Group II- HFD treatment	206.3 ±2.20	323.2 ±2.57*	0.938 ±0.01*	7.297 ±0.06*
Group III- HFD + 200 mg/kg PVC	203.8 ±1.55	312.3 ±2.67*	0.788 ±0.03*	6.955 ±0.04*
Group IV- HFD + 400 mg/kg PVC	213 ±1.41	297.2 ±2.68*	0.643 ±0.64*	5.59 ±0.07*

Data's represented as mean ± S.E.M. (n=6), comparisons were made between: Control (Group I) Vs Disease control (b) (Group II) and Group II vs Treatment group - Group III & IV. Symbols represent statistical significance: *p<0.05, **p<0.01, ***p<0.001.

Effect of the siddha formulation Pavala veera chunnam on body and internal organs of control and drug treated rats.

Routine body weight profile indicates that there is a prominent increase in the bodyweight of rats subjected to HFD administration as evidenced with pre and post treatment data's. Further data's obtained from gross necropsy procedure depicts significant increase in the internal organ weights of HDF alone treated group in comparison with normal control rats. Treatment with siddha formulation PVC at both the dose of 200 & 400 mg/kg reflects dose dependent decrease in both organ and body weight of the experimental animals. As shown in Table 2.

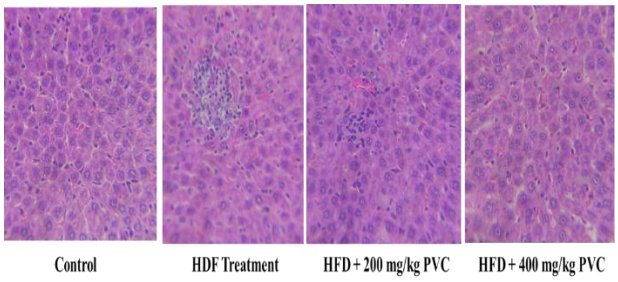

Figure 1:H&E staining of liver sample belongs to control, HFD and PVC treated Rats

4. Discussion

The World Health Organization (WHO) reports that dyslipidemia is a major cause of ischemic heart disease (IHD) and cerebrovascular disease (CVD) [23]. According to the "2020 World Health Statistics report" [24] 41 million people worldwide die of non-communicable diseases (NCDs). 71% of all deaths, i.e., 17.9 million people, die from cardiovascular diseases, twice the number of cancer's deaths and approximately one third of all global deaths.

Marine derivatives also have biological impacts, such as lowering the lipid profile, decreasing blood pressure, fighting tumours, and regulating the immune system. For their high-precision processing and high-value applications, the development and exploitation of marine products is of utmost relevance. Marine bioactive substances will gradually be applied in the food and pharmaceutical industries once a deeper understanding of the relevant studies is achieved. This will lead to further expansion of the areas for their application and make a significant contribution to the improvement of human health. It is common knowledge that the capability of oral therapeutic peptides to penetrate the intestinal epithelial barriers and enter the systemic circulation is a critical factor in determining their level of bioavailability [25]. The Siddha formulation PVC is made up of medicinal components that are produced from minerals (hydrargyrum perchloride) found in marine environments (Corallium Rubrum)

It has been observed that an HFD-fed hyperlipidemic rat model is an appropriate in vivo model for evaluating antihyperlipidemic medicines [26]. A rise in plasma total cholesterol and low-density lipoprotein cholesterol can be attributed to a diet rich in fat. Atherosclerosis can be predicted by having high total cholesterol and, more crucially, LDL cholesterol levels [27]. Routine body weight profile indicates that there is a prominent increase in the bodyweight of rats subjected to HFD administration as evidenced with pre and post treatment data's. Data from a gross necropsy process shows that the rats treated with HDF alone had significantly larger internal organ weights than the normal control rats. Dose-dependent reductions in organ and body weight were observed in mice treated with the siddha formulation PVC at 200 and 400 mg/kg.

It has been determined that the lipoprotein LDL-cholesterol, or LDL-c, is the primary risk factor for atherosclerosis (AS) and coronary heart disease (CHD) [28]. Additionally, it has been discovered that elevated circulating levels of free fatty acids (FFA) and triglycerides (TG) have a significant influence on the development of both atherosclerosis and coronary heart disease [29]. Therefore, controlling the dysregulation of lipid metabolism and bringing down the increased levels of serum TC, TG, and LDL-c are believed to be extremely advantageous for the treatment of cardiovascular disease as well as the prevention of cardiovascular disease [30]. The findings of the current study clearly signify that the disease control group demonstrates a significant increase in the total cholesterol, HDL, LDL, and VLDL levels, as well as the triglyceride levels, whereas the lipid profiles of the experimental animals show no such significant increase. The treatment of the rats in groups III and IV with the siddha formulation PVC at dosages of 200 and 400 mg/kg results in a considerable reduction in total cholesterol as well as the related lipid profile of the rats.

The animals that consume HFD have been shown to experience systemic and hepatic inflammation, activation of hepatic NF-B, and an increase in insulin resistance [34]. According to the findings of our research, an HFD not only considerably raised the lipid profile but also altered the architecture of the liver parenchyma [31]. A histological examination of the liver that belonged to group I rats revealed typical hexagonal hepatic lobules together with

Histopathology of H&E-stained Liver samples of control and drug treated rats.

Histological examination of the liver belongs to group I rats reveals normal hexagonal hepatic lobules along with regular radiated hepatic cords. The sample belongs to HFD group (II) and showcases an increased number of Kuppfer cells with numerous migrations of inflammatory cells. Mild, discrete cytoplasmic vacuoles and rare foamy cytoplasm were observed in group III rats (Low dose PVC treatment). No major signs of nodular degeneration, cirrhosis and fibrosis were observed in animals receiving a high dose of PVC treatment. As shown in Figure1.

regular radiating hepatic cords. The sample is from the HFD group (II), and it has a much higher number of Kuppfer cells along with various migrations of inflammatory cell populations. Vacuoles in the cytoplasm of group III rats were mild and discrete, and foamy cytoplasm was detected very infrequently (low-dose PVC treatment). When animals were given a high dose of PVC therapy, there were no substantial symptoms of nodular degeneration, cirrhosis, or fibrosis found in their livers.

5. Conclusion

Hyperlipidemia has a crucial role in the onset and progression of atherosclerosis and coronary heart disease. There are a variety of risks associated with the use of synthetic lipid-lowering medications, despite the fact that they are effective in treating hyperlipidemia. Therefore, the current interest has prompted the hunt for new lipid-lowering medicines that come from natural sources and have minimal adverse effects.In conclusion, the data of the present study show that the siddha formulation Pavala Veera Chunnam reveals promising antihyperlipidemic activity in HFD-fed rats. Hence PVC type formulations may be considered an alternative drug of choice in the clinical management of hyperlipidemia.

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Conflict of Interests

Declared none

PVC- Pavala Veera Chunnam
LDL-C - Low-Density Lipoprotein Cholesterol
HDL-C - High-Density Lipoprotein Cholesterol
ASCVD - Atherosclerotic Cardiovascular Disease
HFD- High Fat Diet

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