SCIENTIFIC VALIDATIONS OF ANTI-HYPERLIPIDERMIC ACTIVITY OF ETHANOL EXTRACT OF *ELAECARPUS VARIABILIS*

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI - 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch- IV - PHARMACOLOGY

Submitted by

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Under the Guidance of

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OCTOBER – 2017

CERTIFICATES

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"SCIENTIFIC VALIDATIONS OF ANTI-HYPERLIPIDERMIC ACTIVITY OF ETHANOL EXTRACT OF *ELAECARPUS VARIABILIS* ",** submitted by the student bearing **Reg. No: 261525211** to "**The Tamil Nadu Dr. M.G.R. Medical University – Chennai**", in partial fulfilment for the award of Degree of **Master of Pharmacy** in **Pharmacology** was evaluated by us during the examination held on……..….

Internal Examiner **External Examiner**

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DECLARATION

I do hereby declared that the dissertation **"SCIENTIFIC VALIDATIONS OF ANTI-HYPERLIPIDERMIC ACTIVITY OF ETHANOL EXTRACT OF *ELAECARPUS VARIABILIS*"** submitted to "**The Tamil Nadu Dr.M.G.R Medical University - Chennai",** for the partial fulfilment of the degree of **Master of Pharmacy** in **Pharmacology,** is a bonafide research work has been carried out by me during the academic year 2016-2017, under the guidance and supervision of **Dr. Dr. R. Shanmugasundaram, M. Pharm., PhD.,** Professor, Department of Pharmacology, J.K.K.Nattraja College of Pharmacy, Kumarapalayam.

I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

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Dedicated to Parents,

Teachers&

My Family

ACKNOWLEDGEMENT

ACKNOWLEDGEMENT

I am proud to dedicate my deep sense of gratitude to the founder, (Late) Thiru **J.K.K. Nattaraja Chettiar,** providing the historical institution to study.

My sincere thanks and respectful regards to our reverent Chairperson **Smt. N. Sendamaraai, B.Com.,** and Director **Mr. S. Omm Sharravana, B.Com., LLB.,** J.K.K. Nattraja Educational Institutions, Kumarapalayam for their blessings, encouragement and support at all times.

It is my most pleasant duty to thank our beloved Principal and Professor **Dr. R. Sambathkumar, M. Pharm., PhD.,** of J.K.K.Nattraja College of Pharmacy, Kumarapalayam for ensuring all the facilities were made available to me for the smooth running of this project.

It is most pleasant duty to thank my beloved guide **Mr. R. Shanmuga sundaram, M.Pharm. Ph D,** Assistant Professor, Department of Pharmacology, J.K.K. Nattraja College of Pharmacy, Kumarapalayam, for suggesting solution to problems faced by me and providing in dispensable guidance, tremendous encouragement at each and every step of this dissertation work. Without his critical advice and deep-rooted knowledge, this work would not have been a reality.

Our glorious acknowledgement to our administrative officer **Dr. K. Sengodan, M.B.B.S.**, for encouraging using kind and generous manner to complete this work.

My sincere thanks to **Dr. R. Shanmugasundaram, M.Pharm., Ph.D.,** Vice Principal & HOD, Department of Pharmacology, **Mrs.Dr.C.Kalaiyarasi, M.Pharm., Ph.D., M.Pharm.,** Associate Professor, **Mrs. M. Sudha M.Pharm.,** Lecturer, **Mrs. R. Elavarasi, M.Pharm.,** Lecturer, **Mrs. M. Babykala, M.Pharm.,** Lecturer, Department of Pharmacology for their valuable suggestions during my project work.

My sincere thanks to **Dr. S. Bhama, M. Pharm., Ph.D.,** Associate Professor Department of Pharmaceutics, **Mr. R. Kanagasabai, B.Pharm, M.Tech.,** Assistant Professor, **Mr. K. Jaganathan, M.Pharm.,** Assistant Professor, **Dr. V. Kamalakannan M.Pharm., Ph.D.,** Assistant Professor **Mr. C. Kannan M.Pharm.,** Assistant Professor, **Ms. Manodhini Elakkiya, M.Pharm.,** Lecturer, and **Ms. S.Sivashankari, M.Pharm.,** Lecturer, Department of pharmaceutics for the in valuable help during my project.

My sincere thanks to **Dr.. N. Venkateswaramurthy, M.Pharm.,Ph.D.,** Professor and Head, Department of Pharmacy Practice, **Mrs. K. Krishna Veni, M.Pharm.,** Assistant Professor, **Mr. R. Kameswaran M.Pharm,** Assistant Professor,, **Dr. Taniya Jacob, Pharm.D.,** Lecturer, **Dr. V. Viji Queen, Pharm.D.,** Lecturer, **Mr. C. Sampushparaj,** Lecturer, **Mr. T. Thiyagarajan M.Pharm** Lecturer, and **Ms. C. Sahana, M.Pharm.,** Lecturer, Department of Pharmacy Practice, for their help during my project.

It is my privilege to express deepest sense of gratitude toward **Dr. M. Vijayabaskaran**, **M.Pharm., Ph.D.,** Professor & Head, Department of Pharmaceutical chemistry, **Dr. S. P. Vinoth Kumar M.Pharm., Ph.D.,** Assistant professor, **Mrs. S. Gomathi M.Pharm.,** Lecturer, **Mrs. B. Vasuki, M.Pharm.,** Lecturer and **Mrs. P. Devi, M.Pharm.,** Lecturer, for their valuable suggestions and inspiration.

My sincere thanks to **Dr. V. Sekar, M.Pharm., Ph.D.,** Professor and Head, Department of Analysis, **Dr. I. Caolin Nimila, M.Pharm., Ph.D.,** Assistant Professor, and **Mr.D.kamala kannan M.Pharm.,** Assistant Professor **Ms. V. Devi, M.Pharm.,** Lecturer, Department of Pharmaceutical Analysis for their valuable suggestions.

My sincere thanks to **Dr. Senthilraja, M.Pharm., Ph.D.,** Associate Professor and Head, Department of Pharmacognosy, **Dr. M. Rajkumar, M.Pharm., Ph.D.,** Associate Professor, **Mrs. Meena Prabha M.Pharm.,** Lecturer, Department of Pharmacognosy and **Mrs. P. Seema, M.Pharm.,** Lecturer, Department of Pharmacognosy for their valuable suggestions during my project work.

I greatly acknowledge the help rendered by **Mrs. K. Rani,** Office Superintendent, **Mr. E.Vasanthakumar, MCA,** Assistant Professor, **Miss. M. Venkateswari, M.C.A.,** typist**, Mrs. V. Gandhimathi, M.A., M.L.I.S.,** Librarian, **Mrs. S. Jayakala B.A., B.L.I.S.,** and Asst. Librarian for their co-operation. I owe my thanks to all the technical and non-technical staff members of the institute for their precious assistance and help.

Last, but nevertheless, I am thankful to my lovable parents and all my friends for their co-operation, encouragement and help extended to me throughout my project work.

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CONTENTS

1. INTRODUCTION

Hyperlipidemia or Hyperlipoproteinemia involves abnormally elevated levels of any or all lipids and or lipoproteins in the blood. It is the most common form of dyslipidemia which includes any abnormal lipid levels. Hyperlipidemias are divided into primary and secondary subtypes. Primary hyperlipidemia is usually due to genetic causes (such as a mutation in a receptor protein), while secondary hyperlipidemia arises due to other underlying causes such as diabetes. Lipid and lipoprotein abnormalities are common in the general population, and are regarded as a modifiable risk factor for cardiovascular disease due to their influence on atherosclerosis. In addition, some forms may predispose to acute pancreatits[1, 2].

It is a secondary metabolic dysregulation associated with diabetes, but also represents increased risk factor for development of diabetes[3, 4,5]. Besides the cause effect relationship with diabetes, elevated serum level of triglycerides, cholesterol and LDL are risk factors for the premature development of cardiovascular diseases like atherosclerosis, hypertension, coronary heart diseases etc[6, 7].

Hypercholesterolemia has been found to induce oxidative stress in various organs such as the liver, heart and kidney. Increased plasma lipid levels mainly total cholesterol; triglycerides and LDL along with decrease in HDL are known to cause hyperlipidemia which is core in initiation and progression of atherosclerosis impasse[8].

Hyperlipidemia is deeply involved in the etiology of atherosclerosis. Moreover, results of various studies have revealed that hyperlipidemia is an important risk factor of coronary artery disease. Thus much attention is being given to primary and secondary prevention of hyperlipidemia. As a result, antihyperlipidemic agents having various pharmacological actions are being tested clinically. Hyperlipidemia in many cases in the modern age is caused by over-investigation of alcohol or foods; Attention is also being paid to treatment of patients with hyperlipidemia using strict management and appropriate exercise[9]. Hence the present study is designed to evaluate the Antihyperlipidemic activity using herbal extracts.

is the most common cause of coronary heart disease (CHD) and related mortality. The first observable event in the process of atherosclerosis is the accumulation of plaque (cholesterol from low-density lipoproteins, calcium, and fibrin) in the endothelium of large and medium size arteries.

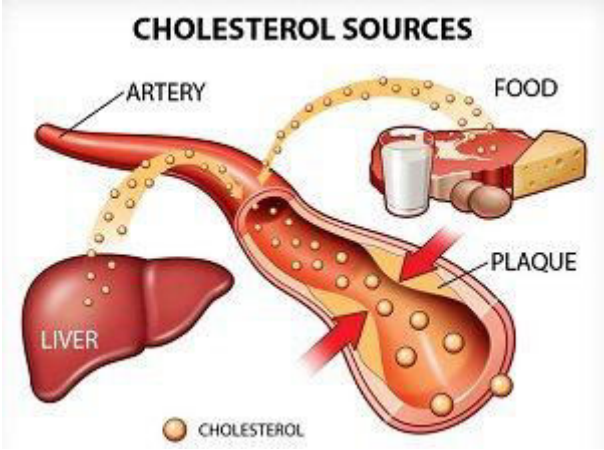

Fig 1. Cholesterol sources

Lipids are classified according to their structure into simple, compound and derived lipids based on the hydrolysis, which result in breaking off the fatty acids, leaving free fatty acids and a glycerol, using up three water molecules. Simple lipids are esters of fatty acids with various types of alcohol. They are distinguished into fats and oils. Compound lipids contain an inorganic or organic group in addition to fatty acids and glycerol. They include phospholipids, glycolipids and lipoproteins. Finally, derived lipids are obtained by hydrolysis of simple and compound lipids. These lipids contain glycerol and other alcohols. The main source of dietary lipids is through the intake of (TG) which can be found as fats or oils.

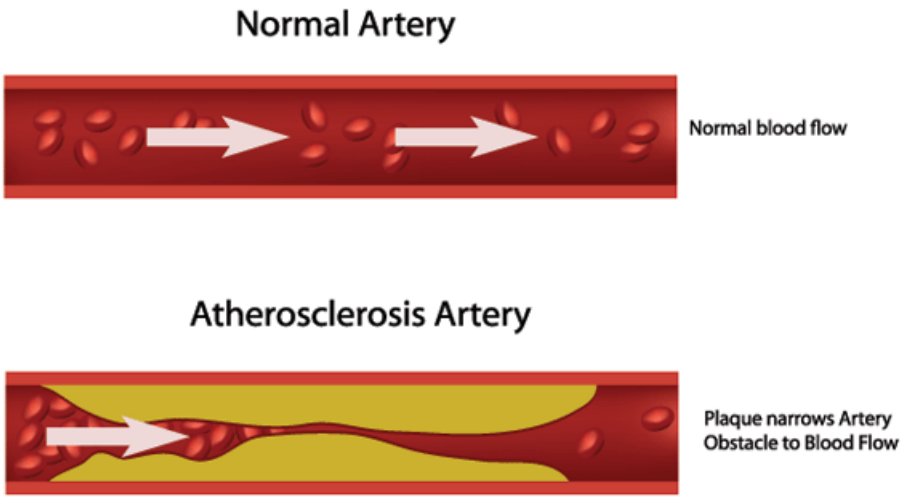

Fig 2. Normal & atherotic artery

Lipids are important in maintaining the structure of cell membrane (cholesterol, phospholipids), steroid hormone synthesis (cholesterol), and energy metabolism (TG and fatty acid).

Pathophysiology

Hypercholesterolemia develops as a consequence of abnormal lipoprotein metabolism, mainly reduction of LDL receptor expression or activity, and consequently diminishing hepatic LDL clearance from the plasma. It is a major predisposing risk factor for the development of atherosclerosis. This mechanism is classically seen in familial hypercholesterolemia and when excess saturated fat or cholesterol is ingested. In addition, excessive production of VLDL by the liver, as seen in familial combined hyperlipidemia and insulin resistance states such as abdominal obesity and Type -II diabetes, can also induce hypercholesterolemia or mixed dyslipidemia.

A current theory for the initiating event in atherogenesis is that apoprotein B-100 containing lipoproteins are retained in the sub endothelial space, by means of a charge-mediated interaction with extracellular matrix and proteoglycans. This allows reactive oxygen species to modify the surface phospholipids and unesterified cholesterol of the small LDL particles. Circulating LDL can also be taken up into macrophages through unregulated scavenger receptors. As a result of LDL oxidation, isoprostanes are formed. Isoprostanes are chemically stable, free radical-catalyzed products of arachidonic acid, and are structural isomers of conventional prostaglandins. Isoprostane levels are increased in atherosclerotic lesions, but they may also be found as F2 isoprostanes in the urine of asymptomatic patients with hypercholesterolemia.

A strong association exists between elevated plasma concentrations of oxidized LDL and CHD. The mechanisms through which oxidized LD promotes atherosclerosis are multiple and include damage to the endothelium, induction of growth factors, and recruitment of macrophages and monocytes. Vasoconstriction in the setting of high levels of oxidized LDL seem to be related to a reduced release of the vasodilator nitric oxide from the damaged endothelial wall as well as increased platelet aggregation and thromboxane release. Smooth muscle proliferation has been linked to the release of cytokines from activated platelets. The state of hypercholesterolemia leads invariably to an excess accumulation of oxidized LDL within the macrophages, thereby transforming them into "foam" cells. The rupture of these cells can lead to further damage of the vessel wall due to the release of oxygen free radicals, oxidized LDL, and intracellular enzymes. This is a metabolically

complex disease of lipid -lipoprotein metabolism and the exact etiology is not fully appreciated. The familial type in schnauzers may involve defects lipoprotein lipase and/or Apoprotein C-II, a required cofactor for lipoprotein lipase activity. This defect causes a failure to breakdown chylomicrons and VLDL, and results in excessive levels of circulating triglycerides. It is the elevated concentration of triglycerides that is responsible for the clinical signs.

Pathways of Lipid Transport

Cholesterol is absorbed from the intestine and transported to the liver by chylomicron reminants, which are taken up by the low density lipoprotein (LDL)-receptor related protein (LRP). Hepatic cholesterol enters the circulation as verylow-density lipoprotein (VLDL) and is metabolized to remnant lipoproteins after lipoprotein lipase removes triglyceride. The remnant lipoproteins are removed by LDL receptors (LDL-R) or further metabolized to LDL and then removed by these receptors. Cholesterol is transported from peripheral cells to the liver by high-density lipoprotein (HDL). Cholesterol is recycled to LDL and VLDL by cholesterol-ester transport protein (CETP) or is taken up in the liver by hepatic lipase. Cholesterol is excreted in bile. The points in the process that are affected by the five primary lipoprotein disorders and familial hypertriglyceridemia (FHTG), Familial combined hyperlipidemia (FCHL), remnant removal disease (RRD, also known as familial dys-beta-lipoproteinemia), Familial hypercholesterolemia (FH), and hypo-alpha-lipoproteinemia shown. The effects of drug therapy can also be understood from these pathways. Statins decrease the synthesis of cholesterol and the secretion of VLDL and increase the activity of LDL receptors. Bile-acid binding resins increase the secretion of bile acids. Nicotinic acid decreases the secretion of VLDL and the formation of LDL and increases the formation of HDL.

Fibrates decrease the secretion of VLDL and increase the activity of lipoprotein lipase, thereby increasing the removal of triglycerides. d. LDL cholesterol: The low density lipoprotein (LDL) cholesterol (sometimes called "bad cholesterol") is a more accurate predictor of CHD than total cholesterol. Where all concentrations are given in mg/dl. Higher LDL cholesterol concentrations have been associated with an increased incidence of CHD in a large number of studies. They have longest plasma half-life, of about 1.5 days. Ideally, LDL cholesterol levels should be less than 100 mg/dl in patients who have had CHD in the past or CHD risk equivalents. People with

levels of 160 mg/dl or higher have a high risk of CHD. Intermediate levels — 130 to 159 mg/dl — predict an intermediate risk of CHD. LDL particles are finally delivered to hepatic and certain extra hepatic tissues for further liposomal degradation to release the cholesterol which can be utilized in cell membrane formation. The LDL cholesterol can only be determined accurately on a blood test after fasting for 12 to 14 hours. e. IDL cholesterol:- These are the lipoproteins obtained when the triglyceride content of VLDL are partially digested in capillaries by the action of extra hepatic lipoprotein lipase and having the diameter of 20-35 nm. f. Triglycerides: Elevated levels of triglycerides are also associated with an increased risk of CHD.

• Normal - less than 150 mg/dl (1.69 mmol/l)

• Borderline high - 150 to 199 mg/dl (1.69 to 2.25 mmol/l)

• High - 200 to 499 mg/dl (2.25 to 5.63 mmol/l)

• Very high - greater than 500 mg/dl (5.65 mmol/l) Triglycerides in mg/dl = Abs T/Abs STD×200 Like LDL cholesterol, triglycerides should only be measured in a blood specimen obtained after fasting for 12 to 14 hours.

This is a group of heterogeneous lipoprotein having low lipid content and is also called as good cholesterol. HDL enhances the removal of cholesterol from the arterial wall. Hence, chances of development of atherosclerotic lesions are more when HDL value falls below normal.

Similar to total cholesterol, the HDL-cholesterol can be measured in blood specimen without fasting.

HDL cholesterol mg/dl = Abs TH/Abs STD×50

Conversion Factors: Cholesterol: mmol/L x 38.7 = mg/dl mg/dl x 0.026 = mmol/L Triglycerides: mmol/L x 885.5 = mg/dl mg/dl x 0.0113 = mmol/L Phospholipids: g/L x 0.01 = mg/dl mg/dl x 10 = g/L Simple blood tests can determine levels of Lipoproteins. Including Total cholesterol, LDL and HDL cholesterol, and triglycerides.

Causes

Hyperlipidemia is caused by lifestyle habits or treatable medical conditions. Lifestyle habits include obesity, sedentary life without exercise, smoking. Medical diseases that may result in Hyperlipidemia are diabetes, kidney disorders, pregnancy, and an under active thyroid gland. Common secondary causes of hypercholesterolemia are hypothyroidism, pregnancy, and Kidney failure. Common secondary causes of hypertriglyceridemia are diabetes, excess alcohol intake, obesity, and certain prescription medications.

Symptoms based diagnosis of Hyperlipidemia

Generally hyperlipidemia condition does not show apparent symptoms and it is discovered and diagnosed during routine examination or evaluation for atherosclerotic cardiovascular disease. However, deposits of cholesterol may be formed under the skin in individuals with familial forms of the disorder or in persons with very high levels of cholesterol in the blood. In individuals with hypertriglyceridemia, several pimple-like lesions may be developed across their bodies. Pancreatitis, a severe inflammation of the pancreas that may be lifethreatening can also be developed due to extremely high levels of triglycerides. For diagnosis of hyperlipidemia, levels of total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides are measured in blood sample. It is important to note that the lipid profile should be measured in all adults 20 years and older, and the measurement should be repeated after every 5 years. Food or beverages may increase triglyceride levels temporarily, so people must fast at least 12 hours before giving their blood samples. Blood tests are carried out to identify the specific disorders, when lipid levels in the blood are very high. Specific disorders may include several hereditary disorders, which produce different lipid abnormalities and have different risks.

Laboratory Testing

Patients are subjected to fasting for at least 12 hours before collecting the blood sampling. Because, chylomicron clearance can take up to 10 hours. However, a fasted sample is not required for simple cholesterol screening. Laboratory testing of the lipid profile measures total plasma cholesterol, HDL, and triglycerides levels directly. VLDL cholesterol levels are calculated by dividing the triglyceride value by 5. LDL cholesterol is calculated by subtracting HDL cholesterol and VLDL

cholesterol from total cholesterol. When triglycerides are above 400 mg/dl, LDL calculation is inaccurate, and specialized laboratory tests are required.

Types of hyperlipidemia:

Hyperlipidemia may basically be classified as either familial (also called primary) caused by specific genetic abnormalities, or acquired (also called secondary) when resulting from another underlying disorder that leads to alterations in plasma lipid and lipoprotein metabolism. Also, hyperlipidemia may be idiopathic, that is, without known cause.

Diagnosis of hyperlipidemia:

Many hyperlipidemic individuals are detected as a result of screening procedures, either in the course of 'health-screening' or of 'profiling' of patients. Fasting serum TG concentration is generally >1000 mg/dL (>11.2 mmol/L), and sometimes can exceed 10.000 mg/dL (112 mmol/L) (5). Concomitant lipid abnormalities include a modest elevation in serum total cholesterol, with decreases in low density lipoprotein cholesterol (LDL) and high density lipoprotein cholesterol (HDL- c) (6). A full lipid profile including plasma cholesterol, plasma TG and HDL-c should be obtained following an overnight fast (12-14 hours). In routine practice, LDL concentration (mg/dL) is estimated indirectly from the measured levels of TG, HDL-c, and total cholesterol (TC) using the Friedewald equation: LDL = TC – HDL – (TG / 5).When concentrations are expressed in mmol/L, TG is divided by 2.17 instead of others.

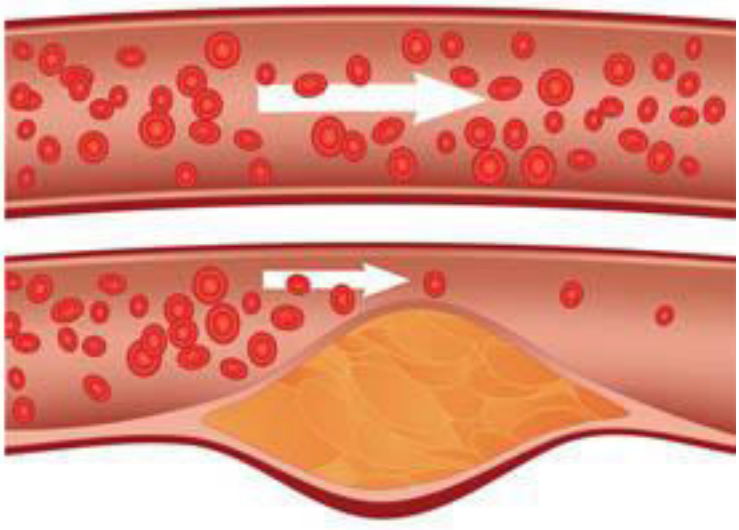

Fig 3. Blockage of arteries

Treatment

The main aim of treatment in the majority of hyperlipidaemic patients is to reduce the risk of developing premature vascular disease (primary prevention) or the occurrence of further vascular events in those with clinical vascular disease (secondary prevention). The non pharmacological treatment of hyperlipdemia depends on life style modification including diet control, weight loss and exercise (8). While drug therapy includes: Statins, Fibrates, Nicotinic acid, Omega-3 fatty acids (fish oils), Ezetimibe (9).

Hyperlipidemia

Definition:

- Abnormally high level of any lipoprotein species.
- Hyperlipoproteinemia (hyperlipidemia) . any type of lipid
- Hyperlipemia (hypertriglycridemia). only TG

Causes:

- 1ry hyperlipidemia → genetic factors.
- 2ry hyperlipidemia → Disease .
- Liver & biliary disease
- Hypothyroidism ↓ (metabolism)
- Obesity – diabetes
- Drug – oral contraceptives
- Alcohol

Clinical consequences :

- Atherosclerosis
- Coronary heart disease
- Acute pancreatitis

Lipoprotein classification :

- 5 classes & lipoprotein

  1- Chylomicron

  Largest lipoprotein

  Transport dietary TGs

2- VLDL

Carry endogenous TGs synthesized in liver to peripheral tissue

3- IDL- intermediate density lipoprrptein. Remnant of VLDL

4- LDL- low density lipoprotein. Bad , the oxidized form of LDL is v. dangerous → ischemic heart disease.HLD- high density lipoprrptein. Good

Important points in the figure :

- Type II a : increased risk of ischemic heart disease .(more dangerous LDL)
- Type II b : VLDL over production w\LDL
- Type III: IDL
- Type IV: VLDL high
- Type V: mixed lipids increase.

Classification of antihyperlipidemia :

1- Fibric acid derivatives (fibrates)

2- Bile acid binding resin

3- Statins . HMG-coA reductase inhibitors

4- Niacin (nicotinic acid)

5- Ezetimibe

1. Fibrates

- Clofibrate (no longer used)
- Fenofibrate (tricor)
- Gemfibrozil (lopid)
- Besafibrate
- Cilorofibrate

Mechanism of action :

- Are ligands for nuclear transcription receptors called peroxisome proliferator activated receptor – alpha (PPAR-a)
- Increase lipoprotein lipase activity
- Increase lipolysis of TGs (VLDL + chylomicrons)

Pharmacological action:

- Increase VLDL clearance.
- Reduce hepatic VLDL production.
- Mainly reduce VLDL , Moderately reduce LDL.

Pharmacokinetics:

- Finofibrate is a prodrug (ester).
- Well absorbed orally.
- Bound to plasma proteins.
- Cross the placenta
- Metabolized in liver (enterohepatic circulation).
- Renal excretion as glucouronides.
- Plasma 1\2 life is 20hr for fenofibrate , 1.5hr for gemfibrozil.
- Absorbtion is enhanced in the presence of food.
- Fenofibrate is more effective than gemfibrozil.

Uses:

- hyper TAG
- Type 3 (dysbetalipoproteinemia)
- Type 4 (hypertriglyceridemia) ↑VLDL.
- Type 5 (elevated VLDL+chylomicrons)

Adverse effect:

- GIT: gastrointestinal upset.
- Myopathy: more common in alcholics.
- Inflammation of the muscles with ↑creatine level.
- Lithiases: increase in gallstone incidence and gallbladder diseases.
- This was a problem seen with clofibrate more than other fibrates . that is why it has been removed from the market.

Drug interaction:

- increase oral anticoagulant (warfarin) activity.
- Fibrates ↑ coagulation, so dose must be reduced when given with anticoagulant.
- Aminotransferase elevation: drug must be stopped .
- Arrhythmias.

Contraindications:

- Hepatic\renal disease.
- Billiary tract disease.
- Combination with statins.

2. Bile-Acid binding (resin)

- Colestipol(colestid).
- Cholestyramine (Questran, Questran light).
- Colesevelam (welcohol).

Chemistry:

- Polymeric cationic exchange resins.

Pharmacokinetics:

- Insoluble in water.
- Not absorbed systemically, not metabolized.
- Excreted unchanged in feces.

Mechanism of action:

- Bind bile acid in the intestine , so prevent their reabsorbtion.
- Increased bile acid clearance causes increased conversion of cholesterol to bile acids.
- Increase the uptake of plasma LDL by the liver (up regulation of LDL receptors).
- Resins have NO effect on patients with homozygous familial hyperlipiemia.

Clinical uses:

- Type 2a (familial hypercholesterolemia).
- Type2b (combined hyperlipidemia).
- VLDL may increase so niacin for example is given to reverse this.
- Pruritis: is incomplete biliary obstruction (cholestasis and bile salt accumulation).
- Sever digitalis toxicity (by ↓ing their absorbtion).

Adverse effect:

1. Constipation, bloating (psyilium seed).
2. reduced absorption of drugs (warfarin, digitalis glycosides, thiazides ,statins, iron salts) . (Thus give it 1hr before or 4-6 hrs after)
3. Interfere with absorption of fat soluble vitamins.
4. Increase serum triglyceride (VLDL)

3. HMG-CoA reductase inhibitors (statins)

Chemistry:

- Structural analogs of HMG-CoA
- (3_hydroxy_3_methyl glutaryl_coenzyme A)

Drugs:

- Rosuvastatin (most imp)
- Atorvastatin
- Simvastatin
- Pravastatin
- Lovastatin
- Fluvastatin (least imp)

Mechanism of action:

- Reversible competitive inhibition of HMG-CoA reductase .
- Inhibit denovo synthesis of cholesterol.
- Up regulation LDL high affinity receptors.
- Small decrease in plasma triglycerides , slight increase in HDL cholesterol.

Pharmacokinetics:

- Prodrugs (lovastatin & simvastatin –GIT)
- Active drugs:

Atorvastatin – Pravastatin – Fluvastatin –Rosuvastatin.

- All are given orally at night.

- All have high first pass effect.
- Excreted mainly in bile.
- 5-20 % is excreted in the urine.
- T½ = 1-3 hrs except Atrovastatin (14 hrs), Rosuvastatin (19 hrs).
- Food enhances absorption except Provastatin.

Clinical uses:

- Treatment of elevated LDL plasma levels: monotherapy or with bile-acid binding resins or ezetimibe or niacin.

Adverse effect:

- Aminotransferase elevation.
- Myopathy (increase in creatine kinase, muscle pain) → medication should be stopped.
- Consequence of myopathy: myoglobinuria & acute renal failure ARF (Rhabdomyolysis).
- Increase warfarin blood level.

Contraindications

- Female → pregnant or lactating.
- Children.
- Severe liver disease.
- Severe kidney disease.
- Combination with cycbsporine – fibrates - azole & itraconazole (antifungal drugs) – erythromycin → (precipitate myositis).

Drug Interactions:

- Simvastatin – lovastatin – atorvastatin one metabolize by CYT P450 3A4.
- Flovastatin – Rosuvastatin one metabolize by CYT P450 2Ca.
- Provastatin by sulfation (drug of choice)
- Erythromycin – ketoconazole – cimatidine – cyclosporine.
- Rifampicine – phenytoin - phenobarbitone

4. Niacin:

- water soluble vitamin (B3)

Pharmacokinetics:

- given orally (2-3 gm/day in divided dose up to 6 gm)
- excreted with urine.
- Given with meals (because it irritates gastrointestinal mucosa).

Mechanism Of Action: (figure)

- Inhibits lipolysis in adipose tissue (due to intracellular lipoprotein lipase inhibition).
- ↓ TG synthesis in the liver.
- VLDL secretion.
- Decrease VLDL and LDL plasma levels.
- Increase HDL cholestrol in plasma.

Clinical Uses:

- familial hyperlipidemia.
- Heterogenous familial hypercholestrolemia (+ resin /statins)
- Most effective in increasing HDL cholesterol.

Adverse effects:

- Cutanuous flushing + warm sensation

(asprin pretreatment {30 min. before dosing } or lbuprofinal)

- GIT disturbance
- hyperuricemia + gout (allopurinol)
- impaired glucose tolerance
- Aminotransferase elevation
- arrhythmia
- hypotension (potentiate the effect of antihypertensive)

Contraindications:

- sever peptic ulcers
- diabetic (if insulin resistance is increased)

5. **Cholesterol absorption inhibitors ((Ezetimibe))**

- inhibits intestinal absorption of dietary and biliary cholesterol in small intestine
- decrease hepatic cholesterol stores
- increase clearance of cholesterol from the blood
- Reduce LDL level
- metabolized in liver (phase 2 , active glucouronide)
- long plasma half life 22hrs. (enterohepatic circulation)
- no effects on fat soluble vit.
- excreted mainly in feces (80 %)
- Daily dose of 10 mg/kg
- synergestic action with statins
- Plasma level: (see table of effects on LDL ,HDL,TG)
- Increased (fibrates)
- reduced (cholestyramin)
- not affected by digoxin or warfarin

Drug combination

Ezetinibe + statins

- Treatment for hypercholesterolemia

Niacin + statins

- Treatment for familial combined hyperlipidemia

Niacin + rosins

- Treatment of familial combined hyperlipidemia
- Familial hypercholesterolemia

(niacin and fibronates are contraindicated by one another)

Resins + statins

- Treatment for familial hypercholesterolemia

Resins + fibrates

- Treatment for familial combined hyperlipidemia
- Increased risk of choliothiasis.

Managing patients with Hyperlipidemia The current National cholesterol education programme (NCEP) guidelines for management of patients are of two types. One is a population-based approach to reduce CHD risk, which includes recommendations to increase exercise and to lower blood cholesterol by dietary recommendations. Use of complex carbohydrates and fiber is recommended. The second is the patient-based approach that focuses on lowering LDL levels as the primary goal of therapy [19]

Need for Natural Hypolipidemic agents

The use of statins in the treatment of Hyperlipidemia causes concern in both patients and physicians about the safety associated with such medications. Muscle toxicity or myopathy, is a common adverse effect of this class of drugs. Myopathy progressing to rhabdomyolysis and renal failure is the most serious side effect associated with all statins either in monotherapy or in combination therapy and appears to be doserelated. As statins therapy is for a long term basis, there may be a risk of chronic toxic effects like carcinogenic, teratogenic and mutagenic over a life time of use. Till date, there are very less natural medications available in the market to treat hyperlipidemia. Therefore it is a need of the day to search for natural medicaments because of their fewer side effects and less expensive as compared with synthetic drugs. So, numerous studies are needed to explore the anti-hyperlipidemic activity of herbs. This may, at least in part, help future studies to screen the newer anti-hyperlipidemic molecules.

Antihyperlipidemic Drugs

Lipids are transported in the blood by being incorporated within lipoproteins. Lipoproteins are macromolecular disc like complexes of lipids and specific proteins called apoproteins. These apoproteins are crucial in the regulation of lipoprotein metabolism (they act as enzymes, cofactors or cell receptor ligands). Distinct classes of lipoproteins are found depending on the variation in lipid and apoprotein composition. Chylomicrons and their remnant contain apoprotein ß48 which is formed in the intestine. Apoprotein ß100 is synthesized in the liver and are found in (VLDL, IDL, LDL and lipoprotein a) Lipoproteins that convey lipids into the artery

wall. Plasma cholesterol and triglyceride are clinically important because they are major treatable risk factors for atherosclerosis and cardiovascular diseases. Hypertriglyceridemia also predispose to acute pancreatitis. ANTIHyperlipidemiC DRUGS Lipids are transported in the blood by being incorporated within lipoproteins. Lipoproteins are macromolecular disc like complexes of lipids and specific proteins called apoproteins. These apoproteins are crucial in the regulation of lipoprotein metabolism (they act as enzymes, cofactors or cell receptor ligands). Distinct classes of lipoproteins are found depending on the variation in lipid and apoprotein composition. Chylomicrons and their remnant contain apoprotein ß48 which is formed in the intestine. Apoprotein ß100 is synthesized in the liver and are found in (VLDL, IDL, LDL and lipoprotein a) Lipoproteins that convey lipids into the artery wall. Plasma cholesterol and triglyceride are clinically important because they are major treatable risk factors for atherosclerosis and cardiovascular diseases. Hypertriglyceridemia also predispose to acute pancreatitis.

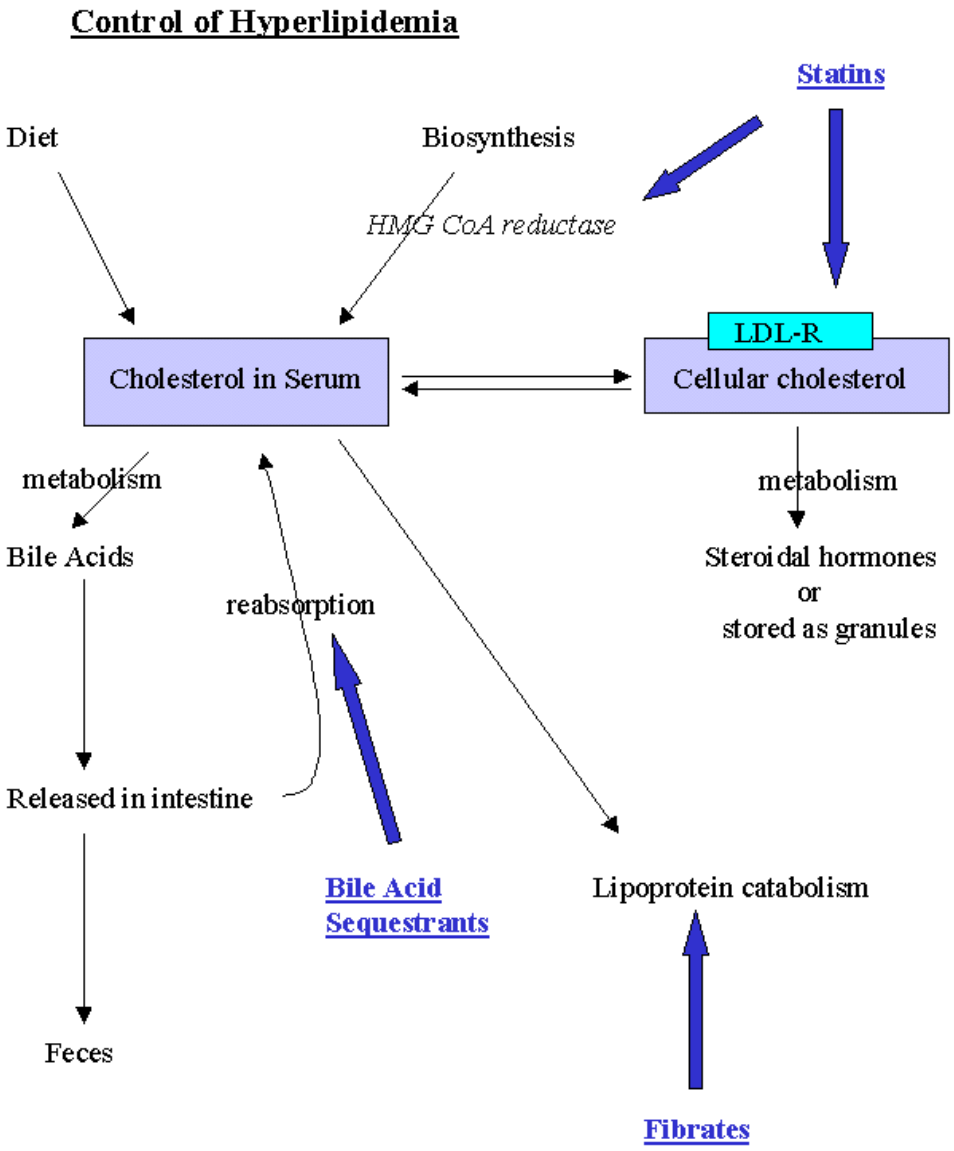

Fig 1. Control of Hyperlipidemia

From over a century, the allopathic industry has been trying to combat degenerative diseases like cardiovascular, metabolic syndromes, cancer, inflammatory disorders, neuro degenerative diseases such as Alzheimer's, Parkinson's, Hodgkin's and other diseases. Though many advances in the diagnosis of diseases have been made, the battle to increase quality of human life and proper treatment of these diseases is still unmet. Till now there is no accurate therapy for many of these diseases without considerable adverse or serious side effects. At present, the only option is a long list of prescription drugs that may alleviate symptoms but slowly eat away body's immunity and quality of life. Hyperlipidemia is one of the greatest risk factors contributing to prevalence and severity of cardiovascular complications like

coronary heart diseases including atherosclerosis. Hyperlipidemia is characterized by elevated serum total cholesterol and low density and very low density lipoprotein cholesterol and decreased high density lipoprotein. Hyperlipidemia associated lipid disorders are considered to cause the atherosclerotic cardiovascular complications. Among these hypercholesterolemia and hypertriglyceridemia are closely related to ischemic heart disease. High plasma level of cholesterol along with generation of reactive oxygen species (ROS) play key role in the development of coronary artery diseases (CAD) and atherosclerosis. Oxidative stress is currently suggested a mechanism underlying hypercholesterolemia

Epidemiologic data reported that around 12 million people die of cardiovascular diseases and cerebral poplexy each year all over world. Therefore, it is very important to pay attention to early stage prevention and control of hyperlipidemia in a comprehensive way. The generally suggested measure for the treatment of hyperlipidemia associated diseases is through restriction of caloric intake or increased caloric expenditure and/or use of lipid lowering drugs. Many allopathic anti-hyperlipidemic drugs are available in the market but the side effects like hyperuricemia, diarrhea, myositis, hepatotoxicity, etc. were reported. Although statins were found to be effective in the lowering of serum low-density lipoprotein (LDL) as well as cholesterol level, they have been found to cause many side effects [8]. As they are basically enzyme inhibitors, so it is likely that they may be inhibiting other critical enzymes in the body. Moreover, statins are ingested on a long term, so there may be a risk of chronic toxic effects such as carcinogenicity, teratogenicity and mutagenicity over a life time of use [9].

Therefore attention is now paid to search natural hypolipidemic agents from plant sources. India, having a rich tradition of folk medicine from centuries, has provided very simple but effective remedies to various ailments using plants and plant derived compounds. Ancient literature mentions many herbal medicines for treating various diseases like Diabetes mellitus, rheumatoid arthritis and cardiovascular diseases. We have also seen an increase in the popularity and use of natural remedies in developed countries, including herbs, herbal medicines, over-the-counter health foods, nutraceuticals and herbal medicinal products. The use of herbal medicines is especially prevalent in primary health care and for many chronic diseases. But unfortunately many potential plants in India lack scientific documentation. Chemical

principles from natural sources have become much simpler and have contributed significantly to the development of new drugs from medicinal plants. The valuable medicinal properties of different plants are due to presence of several constituents i.e. saponins, tannins, alkaloids, phenols, flavonoids, terpenoids etc . The numerous beneficial effects attributed to phenolic products have given rise to a new interest in finding botanical species with high phenolic content and relevant biological activity. The phenolic compounds provide hypolipidemic effect without restricting caloric intake and change in life style. But the amount of polyphenols present in our commonly consumed food is very low. Hence dietary supplements rich in polyphenols are recommended for achieving beneficial results.

Evidences on the cholesterol-lowering properties of medicinal plants have been accumulating and a number of plants have been found to be useful in treatment of hyperlipidemia such as Allium sativum, Commiphora mukul, Boswellia serrata, Emblica officinalis, Garcinia cambogia, Terminalia arjuna, Trigonella foenum-graecum, Ocimum sanctum, Withania somnifera and Zingiber officinale. The present study was aimed to evaluate the selected herbal drugs for their usefulness in the lowering of cholesterol levels and treating cardiovascular complications. Plant selection was done based on the active chemical constituents such as phenols and flavanoids present in them and their antioxidant potential. The selected plants were first screened for their antioxidant activity by using different in-vitro methods. After 4 confirming the antioxidant potential of the extracts.

Elaeocarpus is a genus belonging to family Elaeocarpaceae contain tropical and subtropical evergreen trees and shrubs. It is widely distributed from Madagascar in the west through India, Southeast Asia, Malaysia, Southern China, and Japan, through Australia to New Zealand, Fiji, and Hawaii in the east with its approximately 350 species. The islands of Borneo and New Guinea have the greatest concentration of species1. Some common species with their Occurrence are as follows:

Elaeocarpus aberrans New Guinea

Elaeocarpus acuminatus India. Endangered.

Elaeocarpus amoenus Sri Lanka

Elaeocarpus angustifolius Queensland, Australia.

Elaeocarpus apiculatus China, Indonesia, Malaysia, Philippines

Elaeocarpus blascoi India. Endangered.

Elaeocarpus coorangooloo Queensland (Australia)

Elaeocarpus coriaceus Sri Lanka

Elaeocarpus crassus New Guinea

Elaeocarpus dentatus New Guinea

Elaeocarpus eumundii Australia

Elaeocarpus ganitrus (rudraksh tree) India, South-East Asia, Indonesia, New Guinea, Australia, Guam, and Hawaii

Elaeocarpus gaussenii Southern India. Endangered.

Elaeocarpus grandiflorus India, Indo-China, Malesia

Elaeocarpus hartleyi New Guinea

Elaeocarpus hedyosmus Sri Lanka

Elaeocarpus hookerianus Pokaka. New Zealand.

Elaeocarpus holopetalus New South Wales, Victoria (Australia)

Elaeocarpus williumsianus NSW, Australia

Elaeocarpus variabilis Southern India

Elaeocarpus timikensis New guinea

Elaeocarpus taprobanicus Sri lanka

Elaeocarpus sylvestris Japan, Taiwan, China, Indochina

Elaeocarpus stipularis Indochina, malasia

Elaeocarpus sikkimensis India, Bhutan

Elaeocarpus serratus South asia

Elaeocarpus robustus India, Bangladesh

Elaeocarpus obovatus Australia

Elaeocarpus neobritannicus New Guinea

Elaeocarpus photiniaefolius Ogasawara island

Elaeocarpus montanus Sri lanka

Elaeocarpus miegei New Guinea

Elaeocarpus lanceifolius South Asia

Elaeocarpus kirtonii Australia

2. LITERATURE REVIEW

The comprehensive review of literature is an essential part of any scientific investigation, its main functions are to determine the previous work done, assist in delineation of problem area, provide basis for theoretical framework, and provide an insight into methods and procedures to be used, suggest operational definitions of major concepts and to help for interpretation of findings. Review of literature is directly or indirectly relevant to the objectives of the study.

Singh and Mehta, (1977) reported that Shankhpushpi (C. pluricaulis) possessed significant beneficial effects in patients of anxiety neurosis.

Gupta, et al, (1981) studied the effect of C pluricaulis in patients of thyrotoxicosis and reported that it was more effective with fewer side effects when compared with Diazepam and Neomercazole.

Shukla, (1981) reported that the C pluricaulis had anti-anxiety effect and also it showed reduced plasma cortisol and urinary catecholamines levels.

Dash, et al, (1983) reported that decoction of C pluricaulis showed psychotropic activity in human adults when given orally (50 ml).

Parikh, et al, (1984) studied efficacy of 'Gko 22' containing C microphyllus, Hydrocotylasiatica, Withaniasomnifera, Glycyrrhizaglabra, Saussurealappa, Acoruscalamus, Rauwolfiaserpentina, Myristicafragrans in 17 refractory cases and 22 untreated cases of Schizophrenia. About 50% of patients in both groups showed more than 50% improvement without any prominent side effects after 6 weeks of treatment.

Vaidya and Kulkami, et al. (1991) studied the Ayurvedic formulation 'Jivak' with Shankhpushpi as one of the ingredients. Improvement in appetite, increase in weight and feeling of freshness were observed in treated patients.

Pandit, et al, (1992) used the herbal formulation 'Thyrocap' containing Convolvulus pluricaulis for the treatment of different types of goiter. The treatment showed marked symptomatic as well as biochemical improvement in patients of simple diffuse goiter.

Dandekar, et al, (1992) showed that antiepiletic activity of phenytoin was reduced and there was loss of seizure control following the administration of an ayurvedic preparation containing Shankhpushpi, which could be attributed to pharmacodynamic or pharmacokinetic interaction of drug with phenytion.

Kushwaha and Sharma, (1992) reported the potent anti-depressant activity of Shankhpushpi syrup in patients with depressive illness.

Rajagopalan, (1995) studied the formulation 'Ayushaman-8' containing C pluricaulis, C asiatica, and A calamus. It showed improvement in attention activity level, feed back and in controlling the hyperactivity, aggressiveness etc. in mentally retarded children.

Simonson, (1995) was studied data from several epidemiological expressed that the prevalence of hypertension in patients with DM from 5 to 20 times greater than non diabetic population and associated types-I DM with hypertension not able to find at the time of diagnosis due to renal insufficiency, increase blood pressure which may exacerbate the progression to end-stage renal failure. The incidence of hypertension with DM has related to degree of obesity, increased age and extensive atherosclerosis and it probably includes many patients with essential hypertension. Several other pathophysiological mechanism contribute the genesis and maintenance of hypertension associated with DM.

International Diabetes Mellitus Federation, (2003) was expressed, guide, we have examined and discussed the variety of guidelines already developed in the field of diabetes, and the accessible information on development and implementation of high-quality clinical practice guidelines, both within the diabetes world and elsewhere. This Guide has been prepared for the IDF Clinical Guidelines Task Force at the request of the IDF Executive Board.

Rajappan, et al, (2004) have helps to monitored by communicable diseases surveillance in Kottayam district, Kerala state, India and also 100 diseases are reports for every month. The most frequently reported diseases were acute dysentery, leptospirosis, typhoid and hepatitis. The usage of vaccines for communicable diseases such as childhood diseases, measles diphtheria, tetanus and whooping cough were reported. In this conclusion various communicable diseases occurrence were detected quickly to identify the various diseases and highly successful to take control measures.

Colin Mathers and DejanLoncar, (2005) have expressed updated projections of global mortality from 2002-2030 to burden of diseases which includes data sources, methods and results Non-overweight death rates are reduced at 74% of rate for Other Group II deaths non-overweight death rates reduction at 51% of rate for Other Group

II deaths non-overweight death rates declining at 100% of rate for Other Group II deaths.

Mohan, et al, (2007), have been explained anti diabetic drugs produced age variation based to change of onset of DM to a younger age the recent years and also lasting adverse effects on nation's health and economy. They are identified early risk of individuals using easy screening tools to evaluate Indian Diabetes Risk Score (IDRS) and appropriate lifestyle intervention would greatly helps to preventing or postponing the onset of diabetes to community and the nation as a whole.

Hussain *et al*., (2011) and observed the presence of tannins, steroids, flavonoids, glycosides, saponin, alkaloids, proteins, amino acids and acidic compounds.

Gunjan et al., (2010) has made a review of pharmacognonstical study of *Coccinia indica* and opined that fruit extract has significant anti diabetic properties. Pharmacognonstical studies of *Coccinia indica* done

Sutar et al., (2010) and they detected the alkaloids, carbohydrates, glycosides, flavonoids, tannins and saponins.

Khatun et al., (2012) has studied phytochemical screening and antimicrobial activity of *Coccinia cordifolia* and noticed the presence of compounds like flavonoids, saponins, tannins and terpenoids. The plant shows activity against *Shigella dysenteriae, Escherichia coli* and *Staphylococcus aureus.*

Mahmood et al., (2012) and noticed that aqueous seed extract shows antimicrobial activity against *Pseudomonas multocida, Salmonella typhi* and *L. bulgaricus* and ethanol seed extract showed significant antimicrobial activity against *S. aureus*, *M. luteus*, *E. coli* and *S. epidermidis* and *L. bullgaricus* and petroleum ether extract were effective against

Vasantha et al., (2012) and detected presence of flavonoids and steroids in leaf extract. The flavonoids, tannins, triterpenoids, phenols, steroids, glycosides and cardiac glycosides was detected in the chloroform, methanol and acetone extract but saponin was detected only in methanol and acetone extract.

Experimental studies of anti-hepatotoxic effect of *Trichosanthes tricuspidata* by Vidyasagar (2012) revealed the presence of carbohydrates, proteins, alkaloids, glycosides and flavonoids which shows anti-hepatotoxic effect. In physico-chemical analysis they noticed that drugs were free of impurities like silica, carbonates, phosphates etc.

Poovendran et al., (2011) has performed the antimicrobial assay of *Coccinia grandis* against *E. coli* and noticed that ethanol extract exhibit maximum activity whereas aqueous leaf extract and acetone extract does not show any antimicrobial activity.

Dhiman et al., (2012) has enumerated some important plants of the family Cucurbitaceae plants are: *Momardica charantia*, *Cucurbita pepo*, *Cucurbita andreana*, *Cucurbita ficifolia*, *Cucumis sativus*, *Cucumis melo, Citrullus colocynthis*, *Luffa echinata, Trichosanthes kirilowili, Lagenaria siceraria, Benicasa hispida* etc.

Tamilselvan et al., (2011) noticed that presence of steroids in petroleum leaf extract and detected the compounds like tannins, glycoside, proteins, amino acid, saponins and alkaloids in studied extracts.

Sivaraj et al.,(2011) against some selected bacterial spp. and concluded that the ethanolic leaf extract exhibits maximum activity against *S. aureus*, *B. cereus, E. coli, E .pneumonia* and *S. pyrogens*.

Arawwawala et al., (2011) has noticed antibacterial activity of *Trichosanthes cucumerina* in hot water extract and cold ethanolic extract against *Staphylococcus aureus*, *Streptococcus pyrogenes, Escherichia coli* and *Pseudomonas aeruginosa* and observed that water extract showed significant activity against *S. aureus, S. pyrogenes, E. coli, P. aeruginosa*. The cold water extract has higher antibacterial activity than the hot water extract.

Gopalakrishnan et al., (2012) has performed antimicrobial activity of *Cucumis trigonus* fruits and observed that the petroleum ether and chloroform extracts does not show any activity while the ethanolic extract showed more activity than the benzene and aqueous extracts against *Candida albicans*, *Aspergillus flavans*, *Klebsiella aeruginosa, Pseudomonas aeruginosa* and *Bacillus subtilis*.

Bhattacharya et al., (2010) has evaluated antifungal and antibacterial activity of *Coccinia grandis* and observed that the antifungal activity on *Candida albicans* and *Aspergillus niger* and antibacterial activity was observed on gram positive bacteria like *Bacillus subtilis, Staphylococcus aureus, Escherichia coli* and *Salmonella typhi*.

Ashwini et al., (2012) and noticed that the ethanol and methanol extract has significant antioxidant property. Antimicrobial activity and phytochemical screening of the fruit extracts of *Coccinia indica* was evaluated .

Syed et al., (2009) and reveals that the presence of phytochemicals like alkaloid, steroid, tannins, saponins, phenols, glycosides, and triterpenoids. Petroleum ether extract was the most active and showed considerable antibacterial activity against all tested gram positive and gram negative bacteria. Least activity was in chloroform extract.

Khare et al (2007) noticed that *Trichosanthes tricuspidata* contain Cucurbitacins, it possess anti-tumor, anti-inflammatory, anti- asthmatic, anti-fertility, anti-microbial and anti-hermitic properties.

Shah et al., (2010). The phytochemical study shows bitter fruit contains cucurbitacins B, D, G and H. The leaves contain cucurbitacins B, D, and traces of E. fruit having anti hyperlipidemic, analgesic and anti-inflammatory, diuretic, antioxidant activity.

Deore et al., (2009) were studied *in vitro* antioxidant activity and quantitative estimation of phenolic content of *Lagenaria siceraria*. Phytochemical screening of the crude ethanolic extract of fruit revealed the presence of flavonoids, saponins, glycosides and phenolic compounds which bears antioxidant activity.

Erasto et al., (2009) made HPTLC profile of *Lagenaria siceraria* fruits and noticed that it has high DPPH radical scavenging effect at all concentrations. The ethyl acetate extract shows more activity more activity than rest of the samples.

Pawar et al., (2009) were evaluated central nervous system activity of different leaf extracts of *Lagenaria siceraria.* In their study, three extracts of leaves, petroleum ether, chloroform and methanol were used to study the CNS depressant activity in several animal models. In phytochemical screening the flavonoids, steroid, alkaloid, tannin, and saponin were detected.

Chinyere et al., (2009) The antibacterial activities of *Coccinia grandis* was evaluated and noticed that water extract of leaves and ethanol extract of stem showed high activity against *Shigella boydi* and *Pseudomonas aeruginosa* respectively.

Tomori et al., (2007) were evaluated the antibacterial activity of ethanolic fruit extract of *Lagenaria breviflora*. Tang *et al*., (2010) observed antimicrobial activity of sphingolipids isolated from stems of Cucumber (*Cucumis sativus*). The change in mineral contents in fruit occurs due to infection of rot fungal pathogens in ivy gourd (*Coccinia indica*) which results in reducing the nutritional value.

Modgil et al., (2004) were determined carbohydrate and mineral content of Chyton (*Sechium edule*) and *Lagenaria siceraria.* Both plants were analyzed for their carbohydrate content viz, crude fiber, reducing sugar, non-reducing sugar and different dietary fiber constituents like NDE, ADF, legine, Cellulose and hemicelluloses and minerals.

Hossain et al., (2012) were evaluated anti-inflammatory activity and determination of total flavonoids and tannin contents of *Lagenaria siceraria* root. The phytochemical screening and antimicrobial activity of *Cucurbita pepo* was carried out.

Dewanjee et al., (2007) has studied antimicrobial activity of crude extract from *Coccinia grandis* and noticed that they are active against selected micro-organisms.

Bajpai et al., (2012) has performed HPTLC of *Cucurbita maxima* seed and observed that the presence of steroids, carbohydrates, unsaturated fatty acids and saturated fatty acids in the seed extract.

Chand et al., (2012) noticed the presence of alkaloids, proteins, carbohydrates, flavonoids, glycosides, saponins and tannins in alcohol and water extracts. The nutritive and medicinal property of Cucurbits were recorded and observed that the cultivated cucurbits are the good sources of vitamins and minerals.

Kirtikar et al., (1987) reported that *Diplocyclos palmatus* was distributed throughout India, the annual climber with bright red fruit have high medicinal value.

Gupta et al., (2014) has studied phytochemistry, pharmacology and folklore use of *Diplocyclos palmatus* and noticed the presence of alkaloids, flavonoids, tritrpenoids, saponins, steroids, proteins and resins. The plant has anti-inflammatory properties.

Saboo et al., (2013) were evaluated phytochemical detection and anticancer potential of chloroform root extract of *Trichosanthes tricuspidata*.

Deshpande et al., (2008) were evaluated the ethanolic fruit extract of *Lagenaria siceraria* against the disorders where free radicals play a major role in pathogenesis. The above review reveals that the selected medicinal plants have attracted the attention of workers of pharmacognosy for quite long time. Many investigations in the diverse disciplines have also been undertaken. Pharmacognosy and phytochemistry has also been studied in large measure. But the ethno medicinal uses with Phytochemical.

3. AIM & OBJECTIVE

Productively assess the antihyperlipidemic and antioxidant activity of *Elaeocarpus leaf extract on* elevated fat diet-induced hypercholesterolemia & triton induced hyperlipidaemia models.

1. Collection of literature survey for set up the significance of the study.
2. authenticate of *Elaeocarpus* with the help of botanist.
3. Extract the dried leaf of *Elaeocarpus* *using* suitable solvents.
4. *Invivo* Model
   a. Diet induced
   b.Triton induced hyperlipidemia

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4. PLANT PROFILE

Elaeocarpus is a genus of tropical and subtropical evergreen trees and shrubs. The approximately 350 species are distributed from Madagascar in the west through India, Southeast Asia, southern China, and Japan, through Australia to New Zealand, Fiji, and Hawaii in the east. The islands of Borneo and New Guinea have the greatest concentration of species. These trees are well-known for their attractive, pearl-like fruit which are often colorful. A notable feature of the family is the drooping, often frilly, small clusters of flower. Many species are threatened, in particular by habitat loss.

In Darjeeling and Sikkim areas, the fruit of several species of *Elaeocarpus* is called *bhadrasey* and is used to make pickles and chutney. The seeds of *Elaeocarpus ganitrus* are used to make rudraksha, a type of Hindu prayer beads.

South Indian Marble Tree is a tree up to 20 m tall. Bark is brownish, warty, wood white to cream. Branchlets are round with fallen leaf scars, warty. Leaves are simple, alternate, spiral, clustered at twig ends. Leaf-stalk is 3 cm long, planoconvex in cross section, purple. Leaves are up to 8 × 5 cm, broad elliptic to elliptic-oblong, tip long-pointed, base narrow, margin toothed, somewhat leathery, hairless, red when young. Midrib and nerves purple; secondary nerves about 7 pairs, forked with glabrous domatia at axils beneath. Flowers are borne in racemes in leaf axils, with purple branches, up to 15 cm long. Flower-stalks are 1 cm long, purple. Flowers are white with frilly petals. Anthers are neither bearded and nor awned. Fruit is ellipsoid, 4 × 3 cm, 1-seeded. South Indian Marble Tree is endemic to the Western Ghats - occasional

Botanical name: Elaeocarpus variabilis

Family: Elaeocarpaceae

Synonmys: Elaeocarpus glandulosus, Elaeocarpus oblongus

Common name: South Indian Marble Tree, Jew's plum

Kannada: bike, bikki, hanaltadi, hanillatade, hennalalade

Malayalam: kattakara, malamkara, malankara

Marathi: kasa

Tamil: malankarai

Fig 4. ***Elaeocarpus variabilis*** **leaf**

Fig 5. ***Elaeocarpus variabilis*** **whole plant-I**

Fig 6. ***Elaeocarpus variabilis*** **whole plant-II**

Fig 7. ***Elaeocarpus variabilis*** **whole plant-III**

Fig 8. *Elaeocarpus variabilis* whole plant-IV

5. MATERIALS AND METHODS

a) Plant collection

The flower part of plant was collected from less rain fall irrigation hills and which authenticated by recognized plant survey office.

b) Extraction procedure by Cold maceration

The 1000g of coarse powder of plants, mixed with 2000ml of solvent in round bottom flask, which kept for 15days and shaken regularly 2 times per day and decanted. The extracts are dried under reduced pressure and stored in a desiccator.

d) Preliminary Phytochemical screening

1. Test for Carbohydrate

Molisch's test

To 2-3 ml of extract, added few drops of α-naphthol solution in alcohol, shake and added concentrated H_2SO_4 from sides of the test tube to form violet ring at the junction of two liquids.

Benedict's test – Test solution was mixed with few drops of Benedict's reagent (alkaline solution containing cupric citrate complex) and boiled in water bath.

2. Test for Proteins

Biuret Test – Test solution was treated with 10% sodium hydroxide solution and two drops of 0.1% copper sulphate solution and observed for the formation of violet/pink color.

3. Test for Free Amino Acids

Ninhydrin Test – Test solution when boiled with 0.2%solution of Ninhydrin, would result in the formation of purple color.

.4. Test for Steroids and Triterpenoids

Liebermann Burchard test - Crude extract was mixed with few drops of acetic anhydride, boiled and cooled. Concentrated sulphuric acid was then added from the sides of the test tube and observed for the formation of a brown ring at the junction of two layers.

5. Test for Glycosides:

Keller Killiani Test – Test solution was treated with few drops of glacial acetic acid and Ferric chloride solution and mixed. Concentrated sulphuric acid was added, andobserved for the formation of two layers.

Bromine water test - Test solution was dissolved in bromine water and observed for the formation of yellow precipitate to show a positive result for the presence of glycosides.

6. Test for Saponins:

Foam Test – Test solution was mixed with water and shaken and observed for the formation of froth, which are stable for15 minutes for a positive result.

7. Test for Alkaloids:

Hager's Test – Test solution was treated with few drops of Hager's reagent (saturated picric acid solution). Formation of yellow precipitate..

8. Test for Flavonoids:

a) Ferric chloride test: Test solution when treated with few drops of Ferric chloride solution would result in the formation of blackish red color.

b) Alkaline Reagent Test: Extracts were treated with few drops of sodium hydroxide solution. Formation of intense yellow colour, which becomes colourless on addition of dilute acid.

c) Lead acetate Test: Extracts were treated with few drops of lead acetate solution. Formation of yellow colour precipitate.

d) Alkaline reagent Test: Test solution when treated with sodium hydroxide solution, shows increase in the intensity of yellow color which would become colorless on addition of few drops of dilute Hydrochloric acid, acetate solution Test – Test solution when treated with few drops of lead acetate (10%) solution.

2.5 Animals: Wistar rats ranges from 150 – 180 gms & Sprague–Dawley rats weighing 200- 250 gms, of either sex were obtained from Central animal house,----------. Animals were maintained under standard laboratory conditions at an ambient temperature of 25°C. Animals had free access to food and water with a natural light and dark cycle. Animals were acclimatized for at least 5 days before behavioral experiments. The study protocol was approved by Institutional Animal Ethics Committee (IAEC) of the college and the experiments were carried out as per CPCSEA guidelines No:----------

Groups:

Group I – Control (Normal saline 1 ml/kg),

Group II – Standard (Imipramine 15 mg/kg),

Group III – EEHC 200 mg/kg ,

Group IV – EEHC 400 mg/kg, Group

High Cholesterol (HC)-Diet

Sprague–Dawley rats weighing 200- 250 gm, were divided into 4 groups of 6 animals each. The animals of all the groups except normal group were given a lipid diet consisting of 2% cholesterol, 1% cholic acid and 2 ml coconut oil with standard pellet diet for 30 days. The first group (Normal control) received normal saline orally for 30 days. The second group (High cholesterol diet (HCD)- positive control) was given High cholesterol diet (HCD) while the third and fourth groups were treated with hydroalcoholic extract of EEHC(200 mg/kg and 400mg/kg, p.o.) respectively, once a day for 30 days. The fifth group was treated with Atorvastatin suspension prepared with 0.5% CMC (10mg/kg; p.o.), once a day for 30 days. After 30 days blood was collected by retro orbital sinus puncture, under mild ether anaesthesia. The collected samples were centrifuged for 10 minutes at 2000 r.p.m. and serum samples so collected were used for various biochemical tests The animals were then sacrificed and the liver collected.

Triton Induced Rat Model

Eight week old adult male albino rats of *Wistar* strain, weighing approximately 150 to 200 g, were acclimatized for 7 days at room temperature (22±2ºC) and humidity of 45-64% in a 12- hour light/dark cycle in a room under hygienic condition. They were given access to water and a commercial diet *ad libitum*. Intraperitoneal (i.p) injections of Triton WR-1339 at a dose of 400 mg/kg body weight. After 72 hours of triton injection received a daily dose of 5% CMC in 5ml/kg body weight for 7 days . At the end of 8th day, rats were fasted overnight and sacrificed by cervical dislocation. Blood was collected, and serums were separated by centrifugation. Liver tissues were excised immediately and rinsed in ice-chilled normal saline, 500mg of the tissues were homogenized in 5.0 ml of 0.1 M Tris–HCl buffer (pH, 7.4). Biochemical estimations were carried out in serum and liver tissues, parameters such as cholesterol, phospholipids, triglycerides, LDL, VLDL and HDL were analyzed.

6. RESULT AND DISCUSSION

Table. No:1: Ethanolic extract of *Elaecarpus variabilis*(EEHC)

Class of compounds	Tests performed	Results
Carbohydrates		EEHC
	Molisch's test Fehling's test	+
Phenols	Phosphomolybdic acid test	+
Flavonoids	Shinoda test Lead acetate test	+
Alkaloids	Wagner's Mayer's Draggendrof's test	+
Glycosides	Legal's test Brontranger's test	+
Saponins	Foam test	-
Sterols	Salkowski's test	+
Amino acids	Ninhydrin test	**+**
Terpenoids	Lieberman Burchardt test	+
Gums and Mucilage	Alcoholic precipitation	**-**

+ =Present
- =Absent

The phytochemical studies results revealed that the Molisch's test no characteristic observation indicated the presence of carbohydrates in both extract. Green color formed indicated the presence of phenols in both extracts. Pink or red coloration of the solution indicated the presence of flavonoids in both. Orange coloration of the spot indicated the presence of alkaloids Yellow or reddish brown precipitation precipitation indicated the presence of alkaloids in both. Pink to red color solution indicates the presence of glycosides in both extract. No layer of foam formation indicates the absence of saponins in both extracts. Pink and red color observed

indicated presence steroids in both extract. Violet precipitation formed in the presence of amino acids in both . Red coloration of the solution formation indicated the presence of terpenoids in both extracts. White color precipitation was not formed indicated the absence of gum and mucilage in both extracts.

Triton Induced Rat Model

Groups	Lipid profile in Serum					
	Cholesterol	**Triglycerides**	**HDL**	**LDL**	**VLDL**	**Phospholipids**
Control	70.28±2.24	65.58±2.11	22.68±1.51	13.12±0.42	12.27±0.32	56±0.45
Triton induced	157.73±2.62	125.58±2.11	25.45±1.24	113.18±3.19	25.12±0.42	66±0.58
Ethanolic extract	109.73±2.31	105.78±2.08	31.67±1.18		21.16±0.4	57±0.67
Aqueous extract	96.12±2.01	95.97±1.43	37.92±1.59	45.7±2.44##	19.19±0.29	53±1.62
Standard (Atrovastatin)	84.33±1.48	84.97±3.394##	40.7±1.12##	34.86±2.51##	16.99±0.68	49.2±0.45
Groups	**Lipid profile in liver**					
	Cholesterol	**Triglycerides**	**HDL**	**LDL**	**VLDL**	**Phospholipids**
Control	62.28±2.24	55.58±2.11	21.68±1.51	13.12±0.42	12.27±0.32	46.2±0.45
Triton induced	147.73±2.62	115.58±2.11	24.45±1.24	106.18±3.19	25.12±0.42	56.1±0.58
Ethanolic extract	99.73±2.31	97.8±2.08	30.67±1.18	73.14±2.1	21.16±0.4	47.2±0.67
Aqueous extract	86.12±2.01	95.97±1.43	36.92±1.59	35.7±2.4	19.19±0.29	43.3±1.62
Standard (Atrovastatin)	74.33±1.48	84.97±3.394##	39.7±1.1	44.86±2.5	16.99±0.68	39.2±0.45

Oral administration of hydroalcoholic extract doses (200 mg/kg and 400mg/kg, p.o.) to Triton induced hyperlipidemic rats, significantly reduced the serum and liver cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C) and VLDL-cholesterol levels. Levels of serum and liver HDL-cholesterol were significantly increased in rats treated with has compared to Triton treated rats

Estimation of serum total cholesterol was done at 15 & 24 hrs after induction of hyperlipidemia by Triton induced hyperlipidemic rats. At 15 hrs normal control rats had Mean ± SEM of serum cholesterol level was 70.28±2.24 and at 24 hrs 78.88 ± 4.10.Where the total cholesterol levels of rats treated with Oral administration of hydroalcoholic extract doses (200 mg/kg and 400mg/kg, p.o.) to Triton induced hyperlipidemic rats, significantly reduced the serum and liver cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C) and VLDL-cholesterol levels. Levels of serum and liver HDL-cholesterol were significantly increased in rats treated with has compared to Triton treated rats

Estimation of serum total cholesterol was done at 15 & 24 hrs after induction of hyperlipidemia by Triton induced hyperlipidemic rats. At 15 hrs normal control rats had Mean ± SEM of serum cholesterol level at 24 hrs 78.88 ± 4.10.Where the total cholesterol levels of rats treated with Triton induced rats had total cholesterol at 15 & 24 hr. It Showed the significantly increases in total cholesterol levels in disease control. On 24 hrs total cholesterol level of rats treated with extract at the dose of 200 mg/kg was 113.9 ± 2.73 Showed significantly decrease in total cholesterol levels as compared to disease control group. While in case of rats treated with of standard drug Atorvastatin Mean ± SEM was found to be 94.3±3.26 at 24 hrs. extract at the dose of 400 mg/kg was Showed potent antihyperlipidemic activity as compared to other extracts.

Serum HDL level at 15 hrs normal control rats had Mean ± SEM 24 hrs. where the HDL levels of the rats treated with Triton induced rats at 15 & 24 hrs were , Showed the significantly decreases in HDL levels in disease control. On 24 hrs HDL level of the rat treated with extractwhole plant extract at the dose of 400mg/kg were ,Showed significantly increase in HDL levels as compared to disease control group.

While in case of rats treated with standard drug Atorvastatin Mean ± SEM was found to be 41.1±2.35at 24 hrs.

LDL level at 15 hrs normal control rats had Mean ± SEM of at 24 hrs 24.32 ± 5.01.where the LDL levels at 15 & 24 hrs. Showed the significantly increases in LDL levels in disease control. On 24 hrs LDL level of the rats treated with extract whole plant extract at the dose of 400mg/kg were 48.2±5.4,it Showed significantly decrease in LDL levels as compared to disease control group. While in case of rats treated with standard drug Atorvastatin Mean ± SEM was found to be 49.86±4.21 at 24hrs

VLDL level at 15 hrs normal control rats had Mean ± SEM of was17.39 ±1.04 and at 24 hrs 16.6 ± 0.89.where the VLDL levels of the rats treated with Triton induced rats at 15 & 24 hrs were 33.68± 1.40,35.88 ± 1.94, it Showed the significantly increases in VLDL levels in disease control. On 24 hrs VLDL level of rats treated with extract at the dose of 400mg/kg were 17.52±0.60 Showed significantly decreased in VLDL levels as compared to disease control group. While in case of rats treated with standard drug Atorvastatin Mean ± SEM was found to be 23.5±0.62 at 24 hrs. All the results were shows statistical significant.

The total cholesterol at 15 & 24 hrs were 171.2 ± 2.81, 177.6 ± 3.98. It Showed the significantly increases in total cholesterol levels in disease control. On 24 hrs total cholesterol level of rats treated with extract at the dose of 200 mg/kg was 113.9 ± 2.73 Showed significantly decrease in total cholesterol levels as compared to disease control group. While in case of rats treated with of standard drug Atorvastatin Mean ± SEM was found to be 94.3±3.26 at 24 hrs. extract at the dose of 600 mg/kg was Showed potent antihyperlipidemic activity as compared to other extracts.

Serum HDL level at 15 hrs normal control rats had Mean ± SEM of was 37.7 ±2.39 and at 24 hrs 37.92 ± 2.29 where the HDL levels of the rats treated with Triton induced rats at 15 & 24 hrs were 28.62 ± 2.81, 25.7 ± 2.59, Showed the significantly decreases in HDL levels in disease control. On 24 hrs HDL level of the rat treated with Tephrosia purpurea whole plant extract at the dose of 600mg/kg were 41.7±3.08 ,Showed significantly increase in HDL levels as compared to disease control group. While in case of rats treated with standard drug Atorvastatin Mean ± SEM was found to be 41.1±2.35at 24 hrs.

LDL level at 15 hrs normal control rats had Mean ± SEM of was 25.5 ±5.23 and at 24 hrs 24.32 ± 5.01.where the LDL levels at 15 & 24 hrs were 108.9 ± 5.48,116 ± 6.4Showed the significantly increases in LDL levels in disease control. On 24 hrs LDL level of the rats treated with Tephrosia purpurea whole plant extract at the dose of 600mg/kg were 48.2±5.4,it Showed significantly decrease in LDL levels as compared to disease control group. While in case of rats treated with standard drug Atorvastatin Mean ± SEM was found to be 49.86±4.21 at 24hrs

VLDL level at 15 hrs normal control rats had Mean ± SEM of was17.39 ±1.04 and at 24 hrs 16.6 ± 0.89.where the VLDL levels of the rats treated with Triton induced rats at 15 & 24 hrs were 33.68± 1.40,35.88 ± 1.94, it Showed the significantly increases in VLDL levels in disease control. On 24 hrs VLDL level of rats treated with extract at the dose of 600mg/kg were 17.52±0.60 Showed significantly decreased in VLDL levels as compared to disease control group. While in case of rats treated with standard drug Atorvastatin Mean ± SEM was found to be 23.5±0.62 at 24 hrs. All the results were shows statistical significant.

High diet induced hyperlipidemia

Sample	**Treatment (mg/dl)**				
Serum	Control	HC	HC+ Ethanolic Extract	HC+ Aqueous Extract	HC+ Standard (Atrovastatin)
TC	142.6 ± 2.0	209.0 ± 9.0	169.86±0.98	155.3±0.94	146.6 ± 5.2
TG	128.3 ± 23.0	215.0 ± 8.0	155.0 ± 7.5	132.9 ± 6.5	129.0 ± 7.0
LDL	70.9±0.27	126.±0.63	97.05±0.82	84.51±0.37	74.59±0.56
HDL	44.0 ± 2.4	36.8 ± 4.4b	37.6.0 ± 3.3	41.3±0.56	41.2±0.17
Phospholipids	56±0.45	66.1±0.58	57.2±0.67	63.3±1.62	47.2±0.57

Oral administration of hydroalcoholic extract of (200 mg/kg and 400mg/kg, p.o.) significantly reduced the serum and liver cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C) and VLDL-cholesterol levels but significantly increased serum and liver HDL-cholesterol level as compared with high cholesterol diet (HCD) treated rats.

7. CONCLUSION

The non-ionic detergent, Triton WR-1339, has been widely used to block the uptake of triacyl glycerol-rich lipoproteins from plasma by peripheral tissues in order to produce acute hyperlipidemia in animal models which are often used for a number of objectives, in particular for screening natural or chemical hypolipidemic drugs. With this objective, many medicinal plants have been assessed for their anti-hyperlipidemic activity against Triton WR-1339-induced hyperlipidemia. Schurr et al. demonstrated that on parenteral administration of triton in adult rats maximum blood cholesterol and triglyceride levels were reached at 24 h, followed by a decline to normal values. In our study, this model gave similar plasma lipid profile changes, at 24 h after Triton WR-1339 injection in rats. This result demonstrates the feasibility of using Triton induced hyperlipidemic rats as an experimental model to investigate the hypolipidemic effect of polyherbal extracts. Our study clearly shows that the large increase in serum levels of cholesterol and triglycerides due to Triton WR-1339 injection results mostly from an increase of VLDL secretion by the liver accompanied by a strong reduction of VLDL and LDL catabolism. The reduction of total cholesterol by the hydroalcoholic extract was associated with a decrease of its LDL fraction in serum and liver, which is the target of several hypolipidemic drugs. Report of a study suggests that cholesterol lowering activity of the hydroalcoholic extract of polyherbal formulation could be the result of the rapid catabolism of LDL cholesterol through its hepatic receptors for final elimination in the form of bile acids, as demonstrated Increased level of serum LDL-cholesterol results in increased risk for the development of atherosclerosis. It is well known that HDL-Cholesterol levels have a protective role in coronary artery disease. HDL-cholesterol is reported to have a preventive function against atherogenesis since an independent inverse relationship between blood HDL-C levels and cardiovascular risk incidence has been reported. The hydroalcoholic extract of our polyherbal formulation also increased HDL-cholesterol levels thus exhibiting antihyperlipidemic action. HMG CoA reductase is the rate-limiting enzyme in the cholesterol biosynthetic pathway. It converts HMG CoA to mevalonate. In the present study, HMG CoA reductase activity was indirectly measured in terms of the ratio between HMG CoA and mevalonate. The ratio was found to be inversely proportional to HMG CoA reductase activity, indicating that an increase in the ratio inferred a decrease in the enzyme activity. The hydroalcoholic

extract of polyherbal formulation produced a significant and dose dependent increase in HMG CoA / mevalonate ratio in liver as compared to normal group. Similar results were reported with hydroalcoholic extracts of Nasturtium officinale leaves. Atherosclerotic index (A.I) is believed to be an important risk factor for diagnosis of atherosclerosis. The hydroalcoholic extract of our polyherbal formulation reduced atherogenic index which is one of the most important risk factors of atherosclerotic plaques. Similar results were reported by others when studying the hypolipidemic effect of natural products. Polyherbal extract, Zizyphus jujuba contains Pectin A which has a number of pharmacological properties such as binding bile acid and lowering plasma cholesterol. Z. Jujuba contains saponins which are part of sugar chains which attach themselves to a sterol or triterpene. Saponins are known to form complexes with cholesterol by binding plasma lipids, thereby altering cholesterol metabolism. Capparis decidua contains saponins and tannins which inhibit lipid absorption. Also fibre present in Capparis deciduas has the most pronounced hypocholesterolemic effect which appears to operate through increased fecal excretion of cholesterol as well as bile acids. Thus all these constituents present in our polyherbal extract may be responsible for its hypolipidemic activity.

Thus it can be concluded that hydroalcoholic extract of------- at the dose of 200mg/kg and 400mg/kg; p.o. showed good anti-hyperlipidemic action in Triton WR-1339 and High cholesterol diet induced hyperlipidemia model. The probable mechanism of action of the extract may be inhibition of HMG-CoA reductase enzyme pathway.

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