EVALUATION OF ANTIHYPERLIPIDAEMIC AND ANTIOXIDENT ACTIVITY OF ARTOCARPUS HETEROPHYLLUS STEM EXTRACT

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IN

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Submitted by

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MAY – 2017

CERTIFICATE

This is to certify that this dissertation work entitled **"EVALUATION OF ANTIHYPERLIPIDAEMIC AND ANTIOXIDENT ACTIVITY OF ARTOCARPUS HETEROPHYLLUS STEM EXTRACTS"** Constitutes the original work carried out by **Reg.No:261525755**, Under the guidance and supervision of **Prof. P PANNERSELVAM, M. Pharm.,** Professor, Department of Pharmacology, Padmavathi College of Pharmacy and Research Institute, Periyanahalli, Dharmapuri, Tamilnadu – 635 205.

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DECLARATION

I Hereby I declare that this thesis work **"EVALUATION OF ANTIHYPERLIPIDAEMIC AND ANTIOXIDENT ACTIVITY OF ARTOCARPUS HETEROPHYLLUS STEM EXTRACTS",** has been originally carried out by myself under the guidance and supervision of **Prof. P PANNERSELVAM, M. Pharm.,** Professor, Department of Pharmacology, Padmavathi College of Pharmacy and Research Institute, Periyanahalli, Dharmapuri, Tamilnadu – 635 205.This work has not been submitted for any degree at any university.

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"The prime mover, my deepest and sincere gratitude for inspiring and guiding this humble being."

Mr. NISAR P.M

Reg.No: 261525755

EVALUATION CERTIFICATE

This is to certify that dissertation entitled **"EVALUATION OF ANTIHYPERLIPIDAEMIC AND ANTIOXIDENT ACTIVITY OF ARTOCARPUS HETEROPHYLLUS STEM EXTRACTS"** constitutes the original work carried out by **Mr. NISAR P.M Reg.No: 261525755**, under the guidance and supervision of **Prof. Dr. P. PANNERSELVAM, M. Pharm.** Professor, Department of Pharmacology, Padmavathi College of Pharmacy and Research Institute, Periyanahalli, Dharmapuri, Tamilnadu – 635 205, has been evaluated on_____

Evaluators:

1.
2.

DEDICATED TO MY BELOVED FAMILY,

TEACHERS AND FRIENDS

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LIST OF ABBREVATIONS

%	:	Percentage
µl	:	micro liter
CPCSEA	:	Committee For the purpose of care and supervision of experimentation on animals
ANOVA	:	Analysis of Variance
Fig	:	Figure
Tab	:	Table
G	:	Gram
M mole	:	Mille moles
Mg/dl	:	Milligram per deciliter
Min	:	Minutes
ml	:	Mille liter
mm	:	mille meter
Mm	:	Mille molar
SD	:	Standard deviation
Kg	:	Kilogram
SR	:	*Sidarhombifolia*
EESR	:	Ethanol extract of *Sidarhombifolia*
N	:	Normality
NaOH	:	Sodium Hydroxide
TCA	:	Trichloroaceticacid
NaCl	:	Sodium chloride

1. INTRODUCTION

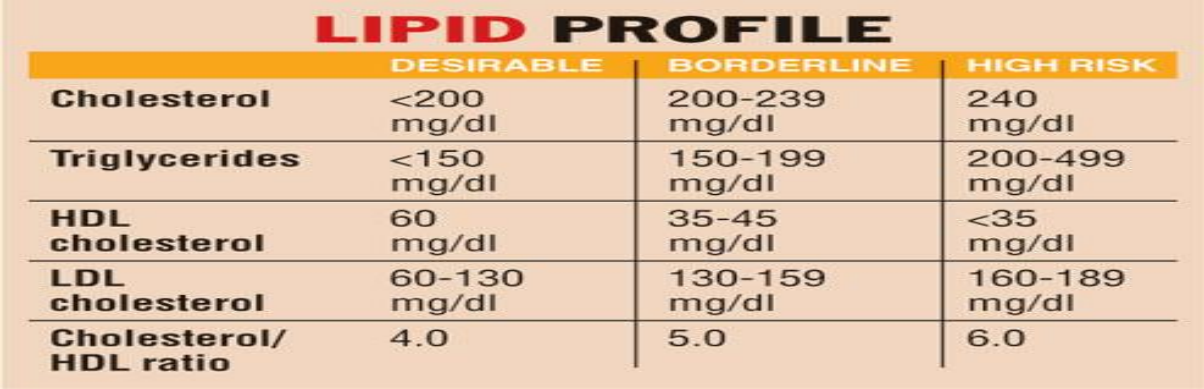
Herbal medicines are the oldest remedies known to mankind. Herbs had been used by all cultures throughout history. In the last few years, there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries. India has a rich heritage of traditional knowledge and is a birth place to several important time-honoured systems of health care like Ayurveda, siddha and homeopathy. India is one of the largest producer of medicinal plants around the globe and is rightly called the "Botanical garden of the World"[1]. The herbal medicines serve the health needs of about 80% of the world's population, especially for millions of people in the vast rural areas of developing countries; more than 65% of the global population uses medicinal plants as a primary health care modality.

It is estimated that three quarter of the population rely on herbal and traditional medicine as a basic for primary health care[2]. Herbal formulations, which have attained widespread acceptability as therapeutic agent in India, includes neo-tropics, anti-diabetics, hepato-protective agents and lipid lowering agents there are many limitations regarding the safety and efficacy of these preparations. Herbal medicines are getting more popularity due to their potent antioxidant activity, minimal side effects and economic variability.

HYPERLIPIDAEMIA

Hyperlipidaemia is characterized by elevated serum total cholesterol, low density, and very low-density lipoprotein and decreased high-density lipoprotein levels[3]. It is also called hyperlipoproteinemia because these fatty substances travel in the blood attached to proteins. This is the only way that these fatty substances can remain dissolved while in circulation. Hyperlipidaemia associated lipid disorders are considered to cause atherosclerotic cardiovascular disease. Among these hypercholesterolemia and hypertriglyceridemia are closely related to ischemic heart disease. Hyperlipidaemia can be either primary or secondary type, the primary disease may be treated by antilipidemic drugs, but the secondary type originating from diabetes, renal lipid nephrosis or hypothyroidism demands the treatment of the original disease rather than hyperlipidaemia.[4]

Figure 1-Lipid profile normal values



LIPID PROFILE

	DESIRABLE	BORDERLINE	HIGH RISK
Cholesterol	<200 mg/dl	200-239 mg/dl	240 mg/dl
Triglycerides	<150 mg/dl	150-199 mg/dl	200-499 mg/dl
HDL cholesterol	60 mg/dl	35-45 mg/dl	<35 mg/dl
LDL cholesterol	60-130 mg/dl	130-159 mg/dl	160-189 mg/dl
Cholesterol/ HDL ratio	4.0	5.0	6.0

Hyperlipidaemia may basically be classified as either familial (also called primary hyperlipidaemia) caused by specific genetic abnormalities, or acquired (also called secondary) when resulting from another underlying disorder that leads to alterations in plasma lipid andlipoprotein metabolism (Chait et al 1990)[5]. Primary hyperlipidaemia may result from defects inthe hepatic uptake and degradation of LDL via the LDLR pathway, commonly caused by mutation in the LDLR gene or in the gene encoding apoB. The most recent gene in which defects cause hyperlipidaemia, is the gene encoding a member of the pro-protein convertase family, PCSK9. Mutations in PCSK9 associated with hypercholesterolemia. PCSK9 normally down regulates the LDLR pathway by causing degradation of LDLR protein and mutation sin PCSK9 result in low plasma LDL levels (Soutar et al 2007)[6]. Also, hyperlipidaemia may be idiopathic without known cause. The most common causes are lifestyle habits or treatable medical conditions. Lifestyle habits include obesity, no physical activity, high dietary fat intakes, and smoking. Medical diseases that may lead to hyperlipidaemia are diabetes, kidney disease, pregnancy, and hypothyroidism (Ahmed et al 1998)[7]. One has a greater chance of developing hyperlipidaemia is old aged a man (45years) or a woman (55), heart diseases or familial history of hyperlipidaemia. Table 1 shows the common causes of secondary hyperlipidaemia.

FAMILIAL (PRIMARY)

Familial hyperlipidaemias are classified according to the Fredrickson classification, which is based on the pattern of lipoproteins on electrophoresis or ultracentrifugation. It was later adopted by the World Health Organization (WHO). It

does not directly account for HDL, and it does not distinguish among the different genes that may be partially responsible for some of these conditions. It remains a popular system of classification, but is considered dated by many. [8]

ACCORDING TO "FREDRICKSON" CLASSIFICATION, THERE ARE FIVE TYPES OF HYPERLIPIDAEMIA

- Type I - Raised cholesterol with high triglyceride levels
- Type II - High cholesterol with normal triglyceride levels
- Type III - Raised cholesterol and triglycerides
- Type IV - Raised triglycerides, atheroma, and raised uric acid
- Type V - Raised triglycerides

ACQUIRED (SECONDARY)

Acquired hyperlipidaemias (also called secondary dyslipoproteinemias) may mimic primary forms ofhyperlipidaemia and can have similar consequences. They may result in increased risk of premature atherosclerosis or, when associated with marked hyper triglyceridemia, may lead to pancreatitis andother complications of the chylomicronemia syndrome. The most common causes of acquired hyperlipidaemia are:

- Diabetes Mellitus
- Use of drugs such as diuretics, beta blockers, and estrogens Other conditions leading to acquired hyperlipidaemia

Include:

- Hypothyroidism
- Renal Failure
- Nephrotic Syndrome
- Alcohol
- Some rare endocrine disorders and metabolic disorders

Causes	Lipid Abnormality		
	↑ LDL-C level	↑ TG level	↓HDL-C level
Diabetes mellitus	√	√	√
Hypothyroidism	√	√	
Nephrotic syndrome	√		
Obstructive liver disease	√		
Obesity or Overweight		√	√
Renal insufficiency		√	
Menopause			√
Puberty (in males)			√
Uremia			√
Anabolic steroids use	√		√
Transplant (bone marrow, heart, kidney, or liver)		√	√
Progestins	√		√
Beta-adrenergic blockers	√	√	√
Thiazides	√		
Bile acid-binding resins		√	
Estrogens		√	
Ticlopidine (Ticlid)		√	
Alcoholism		√	
Cigarette smoking			√

SIGNS AND SYMPTOMS OF HYPERLIPIDAEMIA

Hyperlipidaemia usually has no noticeable symptoms and tends to be discovered during routine examination or evaluation for atherosclerotic cardiovascular disease.[9,10]

1. Xanthoma
2. Xanthelasma of eyelid
3. Chest Pain
4. Abdominal Pain
5. Enlarged Spleen
6. Liver Enlarged
7. High cholesterol or triglyceride levels

8. Heart attacks
9. Higher rate of obesity and glucose intolerance
10. Pimple like lesions across body
11. Atheromatous plaques in the arteries
12. Arcussenilis
13. Xanthomata

CAUSES OF HYPERLIPIDAEMIA[12]

1. Lifestyle habits or treatable medical conditions. Lifestyle contributors include Obesity, not exercising, and smoking
2. Diabetes (type 2)
3. Kidney disease
4. Pregnancy
5. An under active thyroid gland
6. Environmental and genetic factors
7. Alcohol
8. Monoclonal Gammopathy
9. Nephrotic Syndrome
10. Obstructive Jaundice
11. Hypothyroidism
12. Cushing's Syndrome
13. Anorexia Nervosa
14. Medications-
    - Thiazide Diuretics
    - Ciclosporin
    - Glucocorticoids
    - Beta Blockers
    - Retinoic Acid
15. High dietary simple carbohydrates
16. Estrogen therapy
17. Lipoprotein lipase mutations.

PATHOPHYSIOLOGY OF HYPERLIPIDAEMIA[12]

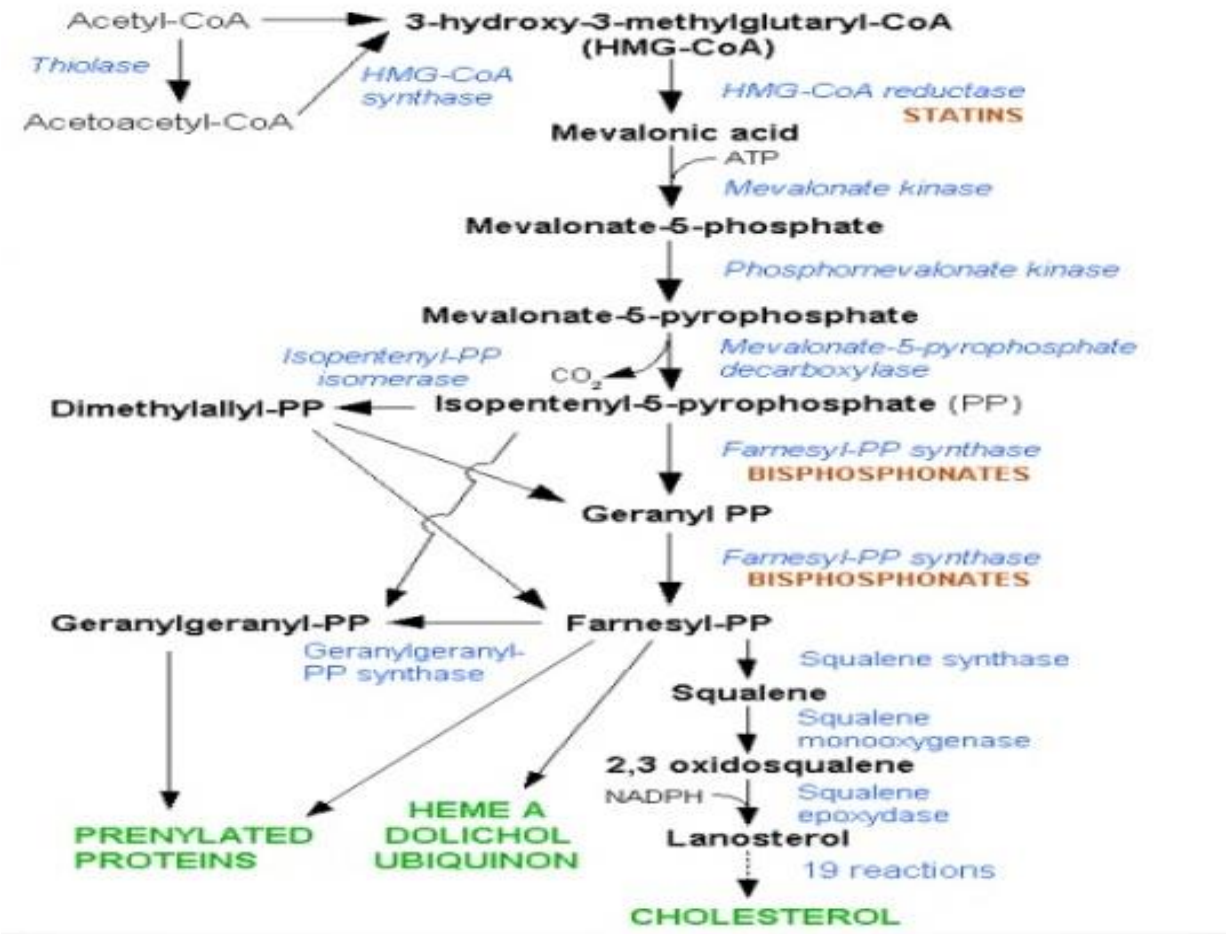
Decreased clearance of triglycerides rich lipoproteins is due to inhibition of lipoprotein lipase and triglyceride lipase. Other factors such as peripheral insulin

resistance, carnitine deficiency, and hyperthyroidism may contribute to lipid abnormalities. In nephrotic syndrome, the decreased circulation of effective plasma albumin's results in increased lipoprotein synthesis to maintain plasma oncotic pressure.

PATHOPHYSIOLOGY OF HYPERCHOLESTEROLEMIA

LDL cholesterol normally circulates in the body for 2.5 days, and subsequently binds to the LDL receptor on the liver cells, undergoes endocytosis, and is digested. LDL is removed, and synthesis of cholesterol by the liver is suppressed in the HMG-CoA reductase pathway. In FH, LDL receptor function is reduced or absent, and LDL circulates for an average duration of 4.5 days, resulting in significantly increased level of LDL cholesterol in the blood with normal levels of other lipoproteins. In mutations of ApoB, reduced binding of LDL particles to the receptor causes the increased level of LDL cholesterol. It is not known how the mutation causes LDL receptor dysfunction in mutations of PCSK9 and ARH.

Figure 2 – Biosynthesis of cholesterol



Although atherosclerosis occurs to a certain degree in all people, FH patients may develop accelerated atherosclerosis due to the excess level of LDL. The degree of atherosclerosis approximately depends of the number of LDL receptors still expressed and the functionality of these receptors. In many heterozygous forms of FH, the receptor function is only mildly impaired, and LDL levels will remain relatively low. In the more serious homozygous forms, the receptor is not expressed at all. Some studies of FH cohorts suggest that additional risk factors are generally at play when an FH patient develops atherosclerosis [13,14]. In addition to the classic risk factors such as smoking, high blood pressure, and diabetes, genetic studies have shown that a common abnormality in the prothrombin gene (G20210A) increases the risk of cardiovascular events in patients with FH [15]. Several studies found that a high level of lipoprotein(a) was an additional risk factor for ischemic heart disease[16]. The risk was also found to be higher in patients with a specific genotype of the angiotensin-converting enzyme (ACE).

PATHOPHYSIOLOGY OF HYPERTRIGLYCERIDEMIA

Hypertriglyceridemia may be the result of two processes.

- One process is the overproduction of VLDL by the liver in response to an increase in free fatty acids flowing to this organ.·
- The other process is a defect in the lysis of VLDL triglycerides and chylomicrons by lipoprotein lipase. When lipoprotein lipase activity is deficient, triglycerides cannot be converted, hydrolyzed, or broken down, and the metabolism of chylomicron and VLDL remnants may be delayed, as in type III hyperlipoproteinemia (dysbetalipoproteinemia)[17,18].

POSSIBLE ATHEROGENIC CHANGES ACCOMPANYING HYPERTRIGLYCERIDEMIA

- Plasma triglyceride levels less than 200 mg/dL are classified as normal.

There has been some debate about whether an elevated triglyceride level is an independent risk factor for atherosclerosis. However, it is clearly associated with a number of metabolic or physiologic changes that are risk factors for this disease. These include:

- Low HDL

- Unusually atherogenic forms of LDL Elevated triglycerides often reflect an increase in triglyceride-rich remnant lipoproteins that have atherogenic potential.

DISEASES ASSOCIATED WITH HYPERLIPIDAEMIA

Following are some diseases which are closely associated with hyperlipidaemia in various pathophysiology.

- Atherosclerosis
- Obesity
- Diabetes mellitus
- Renal disorders
- Liver disorders
- Thyroid diseases
- Cushing`s syndrome
- Hepatic lipase deficiency
- Glycogen storage disease

PREVELANCE

Many studies have shown that there is a direct correlation between the incidence of coronary artery disease (CAD) and total low-density lipoprotein (LDL) cholesterol levels. Every year, approximately 1.5 million Americans experience an acute myocardial infarction and one-third of them do not survive. Because of adaption of the new NCEP GUIDELINES many more patients are now candidates for intensive lipid lowering therapy and these guidelines estimates that the number of Americans who qualify for dietary treatment will rise from 52 million to 65 million, and the number who candidates for drug therapy will nearly triple-from 13 million to 36 million.

THE RISK FACTORS FOR HYPERLIPIDAEMIA ARE

1. High fat intake is one of the factor which leads to hypercholesterolemia
2. Type 2 diabetes mellitus
3. Hypothyroidism

4. Chronic renal failure

5. Nephritic syndrome

6. Obesity

7. Alcohol intake

8. Drugs

a. Number of drugs can adversely affect the serum lipid and lipoprotein concentrations.

b. Antihypertensive agents

c. Diuretics

d. Oral contraceptives

e. Corticosteroids- administration of glucocorticoids increases total cholesterol and TG by elevating LDL-C and to less extent VLDL-C

9. Metabolic syndrome

COMPLICATIONS OF HYPERLIPIDAEMIA

- Pancreatitis
- Premature coronary artery disease
- Heart attack
- Stroke
- Atherosclerosis
- Myocardial infarction

PROGNOSIS

Hyperlipidaemia is a condition characterized by an increased amount of fats (lipids) present in the bloodstream. The prognosis (outlook) for the condition varies according to a number of different factors. The prognosis for persons is in direct proportion to their serum cholesterol levels. Persons with hypercholesterolemia are at high risk of dying from heart disease or stroke. Many studies have looked at the relationship between elevated cholesterol levels, increased risk for heart attack and death. In one research investigation of relatively young males who had no known heart disease, cholesterol levels were measured and participants were followed for 6 years. During this time, all heart attacks and deaths that occurred among participants were recorded. As serum cholesterol levels increased, so did the risk of experiencing a fatal heart attack. The risk of a fatal heart attack was approximately five times

higher among persons having cholesterol levels of 300 mg/dL or more compared to those with cholesterol levels below 200 mg/dL. The Framingham Heart Study is an ongoing research effort. Cholesterol levels, smoking habits, heart attack rates, and deaths in the population have been recorded for over 40 years. After 30 years, more than 85% of persons with cholesterol levels of 180 mg/dL or less were still alive; almost a third of those with cholesterol levels greater than 260 mg/dL had died [25-26].

OUTLOOK (PROGNOSIS)

Diet changes, exercise, and medications can lower cholesterol levels for those with the milder form of this disorder, and may significantly delay a heart attack. Men and women with familial percholesterolemia typically are at increased risk of early heart attacks. Risk of death varies among patients with familial hypercholesterolemia. Persons who inherit two copies of the defective gene have a poorer outcome. That type of familial hypercholesterolemia causes early heart attacks and is resistant to treatment.

THE FACTS

The American Heart Association reports that the lipids contained in the bloodstream include cholesterol, triglycerides, cholesterol compounds (esters) and phospholipids. Terms applied to various forms of hyperlipedemia include hypercholesterolemia, hypertriglyceridemia and hyperlipoproteinemia.

TREATMENT FACTORS

The Society for Vascular Surgery notes that treatments for hyperlipidaemia vary according to factors that include heart disease risk, lipid levels and a patient’s overall health.

TREATMENT OPTIONS

Potential treatments for lipid disorders include dietary changes,weight loss, regular exercise, quitting smoking, medications and periodic lipid screenings, reports the U.S. National Library of Medicine.

UNSUCCESSFUL OUTCOMES

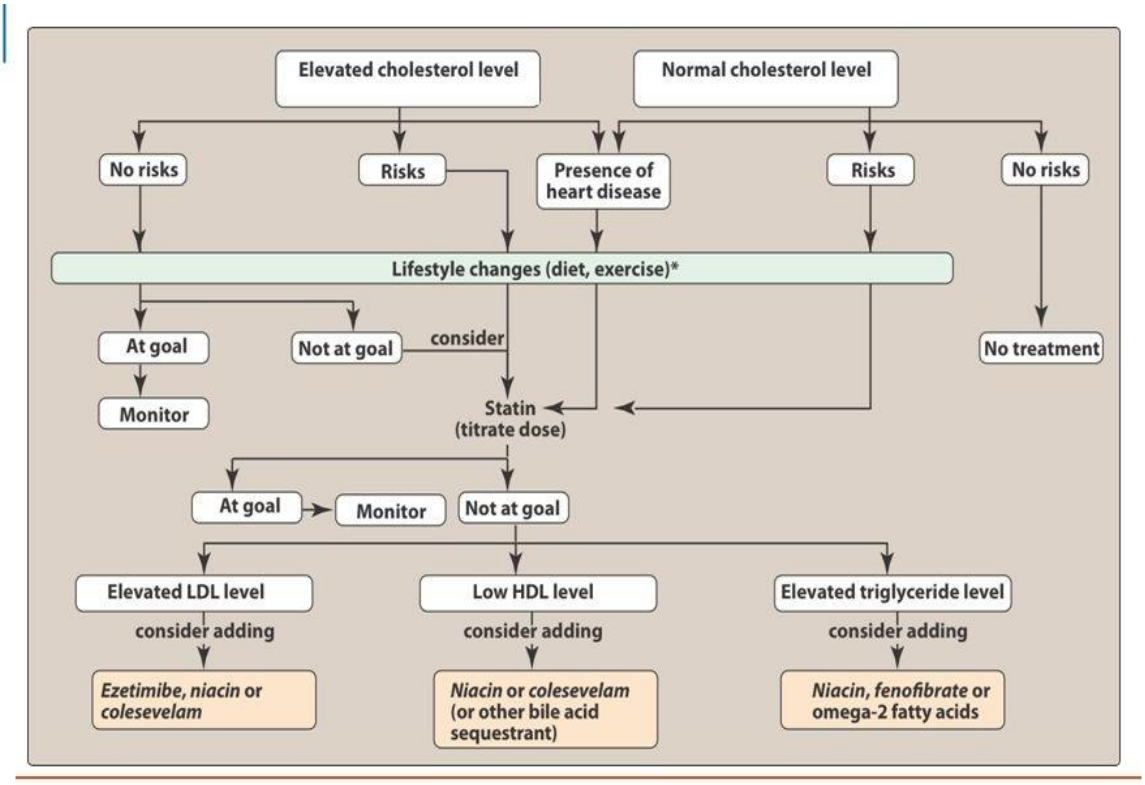
The U.S. National Library of Medicine cites potential outcomes of unsuccessful high cholesterol treatment that include coronary artery disease, hardening of the arteries (atherosclerosis), heart attack, stroke and death. Unsuccessful treatment for high triglycerides can result in pancreatic inflammation (pancreatitis).

TREATMENT FOR HYPERLIPIDAEMIA

HMG-COA REDUCTASE INHIBITORS (STATINS)

Statins (or HMG-CoA reductase inhibitors) are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular diseases (CVD), and statins are therefore used in the prevention of these diseases. Statins have rare but severe adverse effects, particularly muscle damage, and some doctors believe they are overprescribed [19].

Figure 3 –Treatment Guideline of Hyperlipidaemia



Harvey RA. *Lippincott's Illustrated Reviews: Pharmacology*. 5th ed. Baltimore, MD: Lippincott, Williams & Wilkins; 2012.

The approved statins are

- Atorvastatin
- Fluvastatin
- Lovastatin
- Pravastatin
- Rosuvastatin

- Simvastatin
- Pitavastatin

MODE OF ACTION

Statins act by competitively inhibiting HMG-CoA reductase, the first committed enzyme of the HMGCoAreductase pathway. Because statins are similar to HMG-CoA on a molecular level they take the place of HMG-CoA in the enzyme and reduce the rate by which it is able to produce mevalonate, the next molecule in the cascade that eventually produces cholesterol, as well as a number of other compounds. The HMG-CoA reductase pathway is blocked by statins via inhibiting the rate limiting enzyme HMG-CoA reductase**.** This ultimately reduces cholesterol via several mechanisms. Statins block the production of cholesterol in the liver itself. They lower LDL, the "bad" cholesterol, and triglycerides, and have a mild effect in raising HDL, the "good" cholesterol. These drugs are the first line of treatment for most people with high cholesterol. Side effects can include intestinal problems, liver damage, and in a few people,muscle tenderness [20].

FIBRIC ACID DERIVATIVES (FIBRATES)

Fibrates are cholesterol-lowering drugs that are primarily effective in lowering triglycerides and to a lesser extent in increasing HDL-cholesterol levels [21].

Fibrates prescribed commonly are

- Bezafibrate
- Ciprofibrate
- Clofibrate
- Gemfibrozil
- Fenofibrate

MODE OF ACTION

Fibrates are agonists of the PPAR-α receptor in muscle, liver, and other tissues. Activation of PPAR-α signaling results in:

- Increased β-oxidation in the liver
- Decreased hepatic triglyceride secretion
- Increased lipoprotein lipase activity, and thus increased VLDL clearance
- Increased HDL
- Increased clearance of remnant particles

Fibrates activate PPAR (peroxisome proliferatoractivated receptors), especially PPARα. The PPARs are a class of intracellular receptors that modulate carbohydrate and fat metabolism and adipose tissue differentiation. Activating PPARs induces the transcription of a number of genes that facilitate lipid metabolism. Fibrates are structurally and pharmacologically related to the thiazolidinediones, a novel class of anti-diabetic drugs that also act on PPARs (more specifically PPARγ)

BILE ACID SEQUESTRANTS

The bile acid sequestrants are a group of medications used to bind certain components of bile in the gastrointestinal tract. They disrupt the enterohepatic circulation of bile acids by sequestering them and preventing their reabsorption from the gut. In general, they are classified as hypolipidemic agents, although they may be used for purposes other than lowering cholesterol. They are used in the treatment of chronic diarrhea due to bile acid malabsorption. When the statins are not sufficient to lower high cholesterol, these drugs can be added. Their use is often limited by side effects, which are primarily gastrointestinal. They can include nausea, bloating, cramping, and an increase in liver enzymes. Three drugs are members of this class; all are synthetic polymeric resins:

- Cholestyramine
- Colesevelam
- Colestipol

MODE OF ACTION

Bile acid sequestrants are polymeric compounds that serve as ion exchange resins. Bile acid sequestrants exchange anions such as chloride ions for bile acids. By doing so, they bind bile acids and sequester them from enterohepatic circulation. Since bile acid sequesterants are large polymeric structures, they are not well absorbed from the gut into the bloodstream. Thus, bile acid sequestrants, along with any bile acids bound to the drug, are excreted via the feces after passage through the gastrointestinal tract [22].

NICOTINIC ACID FOR HIGH CHOLESTEROL

MODE OF ACTION

Nicotinic acid reduces the production of triglycerides and VLDL (very low-density lipoprotein, which is converted to LDL in the blood). This leads to decreased

LDL ("bad") cholesterol, increased HDL ("good") cholesterol, and lowered triglycerides Nicotinic acid raises HDL cholesterol more than other lipid-lowering medicines. The nicotinic acid form of niacin lowers cholesterol, but other forms of niacin do not. The other forms that do not lower cholesterol include nicotinamide and inositol nicotinate (also called no-flush niacin) [23].

FREE RADICALS

The Free radicals[24] are chemical species which have an unpaired electron (represented as R·). Free radicals are some of the potent chemically active compound that need to pair its single electron, thus it must abstract a second electron from a nearly attaching molecule. This results in the production of yet other free radical and self-reacting steps of reaction sequences. This reactions including free radicals are usually divided by three distinct steps such as initiation phase, propagation phase and termination phase[25].

- **Initiation** reactions are those started for the number of free radicals multiplication. The free radicle generated by stable species reactions.
- **Propagation** reactions are those in which the total number of free radicals remains the same but formation and destruction of free radicle are balanced.
- **Termination** reactions are those reactions resulting total decrease amount of free radicals. However, combination of two or three free radicals to convert stable species, for example: **$2Br^{\cdot} \rightarrow Br_2$**

Free radical generation in human body can start from modern life style habituates such as high fatty meal, alcohol consumption, smoking, environmental pollutants, ozone, ionisation, toxins, carcinogen toxins etc. The vast majority of free radicals originates within the body, an unavoidable enzymatic chemical reaction leading to free radical by product of living system. Under possible condition reactive free radical intermediates are synthesised in living tissues, the biochemical reaction in the body neutralise this free radical formation by the breakdown of compounds via biotransformation via metabolic enzymes. The primary sources of free radicals (such as O_2^- and $HO_2\cdot$) are produced due to the leakages from the electron transport chains in mitochondria, endoplasmic reticulum and chloroplasts.

DANGEORUS ACTION OF THE FREE RADICALS:

These are four species of free radicals destruction [26]:

1. **Lysosomes damages:** Lysosomes are the self-digesting enzyme which present in little space inside cell that stored degenerative enzymes. These enzymes release when the cell wall breakage, digesting their own cell portions and little bit spreads to nearby cell acting a step by step reaction followed destruction of cells.
2. **Oxidation of the fat compounds:** The fatty membranes covered on the cells being the prime target of free radicals attacks, these damaged membranes then lose its ability to transport oxygen, water or nutrients to the cells.
3. **Denaturation of the protein molecules:** Free radicals are attack inside nucleic acid are comprises the genetic code in every cell. The function of nucleic acids is to control physiological cell function, growth and modulation of the damaged tissues.
4. **Cell necrosis:** Damages done to the chromosomes and nucleic acids may induce the growth of unchaped cells in the body, which was the first step in cancer development.

EFFECTS OF FREE RADICAL OXIDATION STRESS:

Formation of reactive oxygen species and other synthesised free radicals[65] cause damages to various chemicals and cells also result affect in the toxicity of chemicals, cause ageing of the cells and different age-related disorder, including:

- **Cardiovascular**: Heart Attack, High Blood Pressure, Angina, Stroke, and Atherosclerosis.
- **Lungs** **:** Asthma, Allergies, COPD, Cancer, Chronic Bronchitis
- **Brain** : Alzheimer’s, Parkinson's, Migraine, Insomnia, Lack of Mental Clarity, Depression, Bipolar, Dementia
- **Joints** : Osteoarthritis and Rheumatoid arthritis
- **Eyes** **:** Cataracts, Macular & Retinal Degeneration
- **Skin** : Wrinkles, Acne, Skin Aging, Eczema, Cancer, Psoriasis
- **Immune** **:** Cold and Flu, Autoimmune, HIV, Herpes, Cancer, Ulcerative

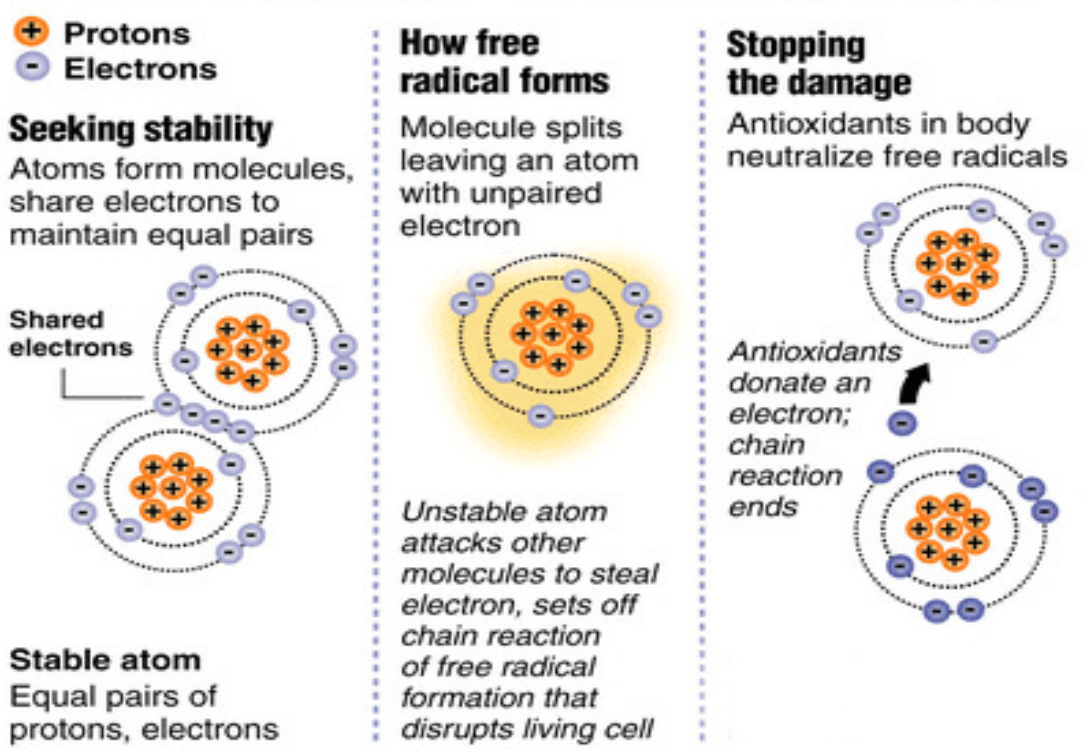
- **Multi organ** **:** Colitis, Chronic Viral Disease, Crohn's, Lupus, Hepatitis Diabetes, Chronic Fatigue, Fibromyalgia, Heavy metal Toxicity, Aging.

SOURCES OF FREE RADICALS:

Free radicals are produced during the various metabolic activities carried out inside our body and also get exposed to free radicals present in the environment. For example:

Exogenous sources: Sunlight, Automobile Exhaust, Cigarette Smoke, Alcohol Consumption, Emotional Stress, Pollutants, UV light, Xenobiotics, Ionising radiation and Exposure to Heavy metals like Mercury, Lead, Cadmium etc

Endogenous sources: Mitochondrial leak**,** Respiratory burstand Enzyme reactions



TYPES OF FREE RADICALS IN THE BODY:

One of the important species of free radicals inside the body is the radical derivatives of oxygen commonly called as reactive oxygen species[27] .These include

oxygen in its triplet state or singlet state, superoxide anion, hydroxyl radical , nitric oxide, peroxynitrite, hypochlorous acid, hydrogen peroxide, alkoxyl radical, and the peroxyl radical. Others are carbon-centered free radical that produced in oxidizing radical of organic compound. Hydrogen-centered radicals produced from reaction the H atoms.

Table 1- Type of Reactive Oxygen Species

Reactive Oxygen Species	
$O_2?^-$	Superoxide radical
?OH	Hydroxyl radical
ROO?	Peroxyl radical
H_2O_2	Hydrogen peroxide
$^1O_2$	Singlet oxygen
NO?	Nitric oxide
$ONOO^-$	Peroxynitrite
HOCl	Hypochlorous acid

ANTIOXIDANTS

The human body also has several natural chemical species or systems for neutralizing free radicals via normal chemical reaction. These agents that neutralize and inhibit the free radical damage, to give or gain an unpaired electrons to get free radicals have attach without produce any harmful effect. Antioxidants are chemical molecule it may be protect about cell necrosis against the action of free radicals. These are the substances produced when body damaged through food consumption or by the environmental exposures of radiation or tobacco smoke by active and passive smokers[28]. This substances are **nutrients** (vitamins and minerals) and **enzymes** (proteins is affect the metabolism in the body). This compound believed to play a vital role for the prevention of the treatment of chronic malignancy, congestive disease, stroke, neurodegenerative disorder (Alzheimer's disease, Parkinsonism) and cataracts. Antioxidant substances include Beta-carotene, Lycopene, Lutein, Selenium and Vitamins A,C,E.

Antioxidants get their name because they prevent oxidation. Oxidation is a reaction in which a molecule loses its electron. The two important formation route of antioxidants are:

- Those get food or food derivatives
- Those synthesised our own body parts.

TYPES OF ANTIOXIDANTS

➢ Antioxidant Nutrients[29]

Antioxidantsconsume by our diet appear to have an importance in trapping free radical generation. Each nutrient have unique by structure and chemical reaction methods.

Vitamin E is a generic word that indicated to all compounds (eight found up to now) have biological action as of the isomer tocopherol. The Alpha-isomer have the heights potency, with action inside tissues. It is a fat-soluble compound safe guard at cell membrane from the free radicle damage. It is also supress the fat cell containing low-density lipoproteins (LDLs or bad cholesterol) from oxidation process.

Vitamin C, also called as ascorbic acid, it is soluble in aqueous vehicle. It neutralise the free radicals in body fluids, such as inside from the cells. Vitamin C react addictive action with vitamin E to reduce the free radicals and regenerates its reduced (stable) form of tocopherol.

Beta-carotene, also a water-soluble vitamin supplement it is the most widely evaluated carotenoids identified still now. It is act as a best quenching agent compared to the singlet oxygen species. Beta-carotene have an excellent in scavenging free radicals at low oxygen concentration.

Selenium is a little tracing compound element but it not survive and form coenzyme at several antioxidant enzymes (example-glutathione peroxidase).

Like this several enzymes and minerals **zinc** and **manganese** are trace elements that form an important part of various type antioxidant enzymes[30].

- **Antioxidant Enzymes**

  The antioxidant enzymes such as **superoxide dismutase** (SOD), **catalase (**CAT) and **glutathione peroxidase** (GPx) act as primary line of the defence in destruction free radicals inside the body.

SOD initially reduced (adds an electron to) as radical superoxide ($O2^-$) subsequently convert a molecule of hydrogen peroxide (H2O2) and molecule of oxygen (O2).

$$2O_{2^-} + 2H \text{ ----SOD--> } H_2O_2 + O_2$$

Catalase &GPx simultaneously work with glutathione is a protein to reduce to convert hydrogen peroxide and subsequent product is the water (H_2O).

$$2H_2O_2 \text{ ---CAT---> } H_2O + O_2$$

H_2O_2 + 2 molecule of glutathione ⟶ oxidized form glutathione + $2H_2O$

- **Other type of Antioxidants**

In addition to enzymes, minerals and vitamins, there are many other nutrients and compounds that have antioxidant properties. Among them is **coenzyme Q10** (CoQ10, or ubiquinone), which is essential to energy production and can also protect the body from destructive free radicals. Also product of DNA metabolism, **uric acid**, has become increasingly recognized as an important antioxidant. Additionally, **phytochemicals** are being investigated for their antioxidant activity and health-promoting potential.

ANTIOXIDANT PROCESS

Antioxidants block the process of oxidation by **neutralizing** free ions and they become oxidized. Thus there is a balance need to replenish among the antioxidant resources. Their work is classified by one of two methods[31]:

- **Chain-breaking** - When a free radical issues or traps an electron, a secondary radical is generated. These compounds then changed around and repeat the same process to the next molecule, generating more unstable products. This reaction continues up to a termination occurs, so the radical is neutralised
- **Preventive** - Antioxidant enzymes like catalase, superoxide-dismutase and glutathione peroxidase supress oxidation reaction by a decreasing the kinetic of chain initiation through scavenging initiating radical, these antioxidants can stabilise oxidation chain from ever setting in motion. It also separate oxidation by stabilizing transition metal radical copper and iron.

The effectiveness of any given antioxidant in the body depends on type of free radical involved, its generation and the target of damage. In certain conditions, an antioxidant may even acted by **pro-oxidant** that generates toxic oxygen species.

A good number of medicinal plants are found mentioned in the ancient classical Ayurvedic texts 'CharakaSamhita'. 'SusrutaSamhita' and 'AstangaHrdayaSamhita'. But many of them still remain to be properly identified[32]. During the process of urbanization the contact with plants in their natural habitat was lost, creating confusion in the correct identity of many plants.

2. LITERATURE REVIEW

1. S. Chackrewarthy, M. I. Thabrew, M. K. B. Weerasuriya, and S. Jayasekera. Evaluation of the hypoglycemic and hypolipidemic effects of an ethylacetate fraction of *Artocarpusheterophyllus* (jak) leaves in streptozotocin-induced diabetic rats. Pharmacogn Mag, 2010 Jul-Sep; 6(23): 186–190.

S.Chackrewarthy et al[34] in his study investigates the hypoglycemic and hypolipidemic effects of an ethylacetate (EA) fraction of the mature leaves of *A. heterophyllus* in a streptozotocin (STZ) induced diabetic rat model. In normoglycemic rats, administration of a single dose (20 mg/kg) of the EA fraction resulted in a significant ($P < 0.05$) reduction in the fasting blood glucose concentration and a significant improvement in glucose tolerance ($P < 0.05$), compared to the controls. In STZ-induced diabetic rats, chronic administration of the EA fraction of *A. heterophyllus* leaves daily for 5 weeks resulted in a significant lowering of serum glucose, cholesterol and triglyceride (TG) levels. Compared to control diabetic rats, the extract-treated rats had 39% less serum glucose, 23% lower serum total cholesterol and 40% lower serum TG levels and 11% higher body weight at the end of the fifth week.

2. E.R.Suchithra and S. Subramanian. Antidiabetic activity of Artocarpusheterophyllus rag extract studied in high fat fed- low dose STZ induced experimental type 2 diabetic rats. Der Pharmacia Lettre, 2014, 6 (3):102-109

Haidy S. Omar et al[34] examined the antioxidative, hypoglycemic, and hypolipidemic activities of Artocarpusheterophyllus (jack fruit) leaf extracts. Various extracts like 70% ethanol n-butanol, water, chloroform, and ethyl acetate extracts are examined. The administration of 70% ethanol extract or n-butanol extract to streptozotocin (STZ)-diabetic rats significantly reduced fasting blood glucose (FBG) from 200 to 56 and 79 mg%, respectively; elevated insulin from 10.8 to 19.5 and 15.1 µU/ml, respectively; decreased lipid peroxides from 7.3 to 5.4 and 5.9 nmol/ml, respectively; decreased %glycosylated hemoglobin A1C (%HbA1C) from 6.8 to 4.5 and 5.0%, respectively; and increased total protein content from 2.5 to 6.3 and 5.7 mg%, respectively. Triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), VLDL-C, and LDL/HDL ratio significantly declined by -37, -19, -

23, -37, and -39%, respectively, in the case of 70% ethanol extract; and by -31, -14, -17, -31, and -25%, respectively, in the case of n-butanol extract; as compared to diabetic rats. HDL-C increased by +37% (70% ethanol extract) and by +11% (n-butanol extract). Both JFEE and JFBE have shown appreciable results in decreasing FBG, lipid peroxides, %HbA1C, TC, LDL-C, and TG levels, and increasing insulin, HDL-C, and protein content.

3.P. Sivagnanasundaram and K. O. L. C. Karunanayake. Phytochemical Screening and Antimicrobial Activity of Artocarpusheterophyllus and Artocarpusaltilis Leaf and Stem Bark Extracts. OUSL Journal, 2015; 9, 1-17.

Venkateswaruluet al[35] in his study used aqueous extract from Artocarpusheterophyllus leaves to evaluated for its hypocholesterolaemic and hypotriglyceridemic activities. The animals were divided into Normal (CG), Triton treated group (T), Triton plus Atorvastatin, Triton plus herb extract 200 mg/kg, Triton plus herb extract 400 mg/kg, treated groups. Oral administration of Artocarpusheterophyllus leaf extract (200 mg/kg and 400 mg/kg) in both groups At 24 hrs after treatment with TRITON WR 1339 caused a significant decrease in serum lipid parameters like Triglycerides (TG), Cholesterol (CH), LDL- cholesterol, Atherogenic index (AI), LDL/HDL Ratio and Total proteins as like in atorvastatin treated groups. The both extract treated groups and atorvastatin treated group bought about a significant increase in HDL-Cholesterol levels.

4.Periyanayagam K*, Karthikeyan V. Wound Healing Activity Of The Leaves Of ArtocarpusHeterophyllus Lam. (Moraceae) On Ex-Vivo Porcine Skin Wound Healing Model. Innovare Journal of Life Science 2013; 1 (1) 28-33.

K Periyanayagam et al[36] *studied the*wound healing activity of the leaves of artocarpusheterophyllus lam. (moraceae) on ex-vivo porcine skin wound healing model and found that that the ethyl acetate extract of the leaves possesses potential wound healing activity.

5. Venkateswarulu .M, Prashanthi.K,GopichandChinta, Sujata .D, Pushpakumari.B, Ranganayakulu.D. Anti-hyperlipidemic activity of the aqueous extract of the

Artocarpusheterophyllus leaves in triton WR-1339 induced hyperlipidemic rats.Drug Invention Today. 2010;2(1),25-28.

P. Sivagnanasundaram et al[37] evaluated the antimicrobial and phytochemical properties of Artocarpusheterophyllus in leaf and stem bark extracts Hexane, dichloromethane and ethanol were used as extraction solvents and test organisms were Escherichia coli, Micrococcus luteus, Aspergillusniger and Trichoderma sp. A disc diffusion test was adopted to test the susceptibility of the selected microbes to the extracts while Minimum inhibitory concentration (MIC) was determined using serial dilution of extracts. Ethanolic stem bark extracts (30mg/ml) of A.heterophyllusexibits significant antibacterial activity against Escherichia coli with 9.50 ± 0.44 inhibition zone radii. Dichloromethane extracts of leaf and stem bark showed lesser antibacterial activity against both of the bacteria with inhibition zones of 3.00 ± 0.34 mm to 5.66 ± 0.16 mm while hexane extracts did not show any antibacterial activity. Antifungal activity on the other hand was not detected in any of the extracts. Phytochemical screening confirmed the presence of phytosterols, anthraquinone, terpenoids, phenols, glycosides, flavonoids and diterpenes.

6. Omar HS, El-Beshbishy HA, Moussa Z, Taha KF, Singab AN. Antioxidant activity of Artocarpusheterophyllus Lam. (Jack Fruit) leaf extracts: remarkable attenuations of hyperglycemia and hyperlipidemia in streptozotocin-diabetic rats.Scientific World Journal. 2011; 5(11):788-800.

E. R. Suchithra et al[38] studied the antidiabetic activity of Artocarpusheterophyllus rag extract studied in high fat fed- low dose STZ induced experimental type 2 diabetic rats" reports that Artocarpusheterophyllus rag possess antibacterial, anti-inflammatory, antioxidant and immune modulatory properties. In the study Diabetic rats were treated with Artocarpusheterophyllus rag extract at a dosage of 300 mg/kg b.w daily for 30 days. Metformin (200 mg/kg. b.w) was used as a reference drug and fasting blood glucose, plasma insulin and HbA1c were theparameters under consideration. The extract supplementation attenuated the elevated levels of glucose, glycosylated hemoglobin, AST, ALT and ALP. The insulin level was improved with an improvement in hepatic glycogen content of insulin resistant diabetic rats. The altered activities of glycogen metabolizing enzymes were normalized upon extract treatment. Also the extract improves insulin sensitivity which

is evident from intraperitoneal insulin tolerance test. The results show that the rags of Artocarpusheterophyllus are non-toxic and possess significant antidiabetic properties.

7. Sanwar Mal Lamba,Kunjbihari Sulakhiya,Parveen Kumar. Anti diabetic,Hypolipidemic and Anti oxidant activities of Hydroethanolic Root Extract of Rhus Mysurensis Heyne in streptozotocin induced Diabetes in Wistar Male Rats.

Sanwar Mal Lamba et al[60] Studied Anti diabetic, Hypolipidemic and Anti oxidant Activities of hyroethanolic root extracts of Rhus mysurensis (HERM) in the treatment of diabetes along with its antioxidant and hypolipidemic effects were studied in streptozotocin induced diabetes in wistar rats. In this study, the antidiabetic,hypolipidemic and anti oxidant activities of hydroethanolic root extract of Rhus mysurensis was evaluated by using STZ induced diabetic rats at a dose of 200mg/kg,400mg/kg and 800mg/kg p.o. daily for 21 days. Blood glucose levels and body weight were monitored at specific time intervals, and different biochemical parameters, serum cholesterol, serum triglyceride, high density lipoprotein, low density lipoprotein were also assessed in the experimental animals.

8. Damayanthi Dalu, Satyavati Dhulipala. Antidiabetic,Antihyperlipidemic and Antioxidant Properties of Root of Ventilago Maderaspatana Gaertn. On Streptozotocin Induced Diabetic Rats.

Damayanthi Dalu et al[61] Studied Antidiabetic,Antihyperlipidemic and Antioxidant Activities of alcoholic root extracts of Ventilago maderaspatana were evaluated for toxicity unto 3000mg kg. In oral glucose tolerance test chloroform extract did not produce significant glucose lowering effect. Alcoholic extract of V.maderaspatana (VMAE and VMHAE) elicited significant glucose tolerance effect. Hence VMAE and VMHAE were screened further by streptozocin induced diabetic model.VMAE and VMHAE significantly lowered blood glucose, triglycerides, total cholesterol, LDL cholesterol, VLDL cholesterol, creatinine, urea and increased HDL cholesterol,serum insulin and liver glycogen levels when compared to standard drug glibenclamide(10mg kg).V.maderaspatana also increased catalase levels and decreased lipid peroxidise and glutathione reductase.VMAE and VMHAE elicited significant dose dependent antidiabetic,antihyperlipidemic and antioxidant

activity.VMHAE at 500 mg kg induced more significant antidiabetic activity than VMAE (500 mg kg) elicited more antihyperlipidemic and antioxidant activity copared to VMHAE(500 mg kg).

9. Prashant R. Verma, Prakash R. Itankar, Sumit K. Arora. Evaluation of antidiabetic antihyperlipidemic and pancreatic regeneration, potential of aerial parts of Clitoria ternatea.

P.R.Verma et al[62], studied Antidiabetic, Antihyperlipidemic and Pancreatic regeneration of ethanol extract of Clitoria ternatea L. Fabaceae. The antidiabetic and antihyperlipidemic potential was evaluated in streptozotocin induced diabetic rats and correlated with its in vitro antioxidant activity. The extract and its fractions were initially screened for acute and sub chronic antidiabetic activity in the dose range of 100-200 mg/kg. The most potent extract and fractions were further evaluated for pancreatic beta cells regeneration activity along with antioxidant and antihyperlipidemic activity. The polyphenolic activity. The most significant pancreatic regeneration activity,antidiabetic and antihyperlipidemic activity and was shown by ethanol extract and butanol soluble fraction at a dose level of 200 mg/kg, while rutin was found to be least potent. In conclusion, pancreatic regeneration studies of ethanol extract treated rats show nesidioblastosis. It is also suggested that the factors causing regeneration are present within the pancreas. The newly generated islets may have formed from the ductal precursor cells and reduced oxidative stress helps in restoration of beta cell function.

10. Pradeep Pal,Ajay Sharma,Mukesh Mehra,Anil Choudhary. Antidiabetic and Antihyperlipidemic activity of ethanolic extract of Artemisia Nilagirica In streptozotocin induced diabetic rats.

Pradeep Pal et al[63], as studied Antidiabetic and Antihyperlipidemic activity of ethanolic extract of Artemisia Nilagirica . Diabetes mellitus is characterized by elevated plasma glucose concentration resulting from insufficient insulin and insulin resistance, or both, leading to metabolic abnormalities in carbohydrates, lipid and protein. The antidiabetic effects of ethanolic extract of leaf were monitored at specific intervals.

3. PLANT PROFILE

Figure 4: Photograph of *Artocarpus heterophyllus*[39]

TAXONOMICAL CLASSIFICATION

Table: 2 – Taxonomical classification of *Artocarpus heterophyllus*[40]

Kigdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Rosales
Family	Moraceae
Genus	Artocarpus
Species	A. heterophyllus

VERNACULAR NAMES

Table: 3 – Vernacular names of *Artocarpus heterophyllus*[41]

LANGUAGES	NAMES
English	Jackfruit
Bengali	Kanthal
Hindi	Kathal, Panas
Malayalam	Chakka
Marathi	Phanas
Tamil	Palaa

Global Distribution: Western Ghats of India, Malaysia and also found in central and eastern Africa, south-eastern Asia, the Caribbean, Florida, Brazil, Australia, Puerto Rico and many Pacific Islands

PLANT DESCRIPTION[42]:

It is a large, evergreen tree, 10-15m in height, indigenous to the evergreen forests at altitude of 450-1,200m and cultivated throughout the hotter parts of India. Stem of this plant is straight rough whereas bark is green or black, 1.25cm thick, exuding milky latex, leaves broad obovate, elliptic, decurrent, glabrous, entire inflorescence solitary axillaries, cauliforous and ramflours on short leafy shoots. Male head is sessile or on short peduncles receptacles, sometimes born on the ultimate twing, Female head are oblong ovoid receptacle, syncarpus, cylindrics. Seeds are separated horny endocarpus enclosed by sub-gelatinous exocarpus (1mm thick) oblong ellipsoid in nature. The sweet yellow sheaths around the seeds are about 3-5 mm thick and have a taste similar to that of pineapple, but milder and less juicy.

USES OF *ARTOCARPUS HETEROPHYLLUS*[43]:

The plant is reported to possess antibacterial, anti-inflammatory, antidiabetic, antioxidant and immune-modulatory properties. *Artocarpus heterophyllus* is an important source of compounds like morin, dihydromorin, cynomacurin, artocarpin, isoartocarpin, cyloartocarpin, artocarpesin, oxydihydroartocarpesin, artocarpetin, norartocarpetin, cycloartinone, betulinic acid, artocarpanone and heterophylol which are useful in fever, boils, wounds, skin diseases, convulsions, diuretic, constipation, ophthalmic disorders and snake bite etc.

It is richly used in folk practices, root is a remedy for skin diseases and asthma and the extract is taken in cases of fever and diarrhoea. The ashes of the leaves, burned together with corn and coconut shells are used alone or mixed with coconut oil to heal ulcers. Mixed with vinegar, the latex promotes healing of abscesses, snakebite and glandular swellings. Heated leaves alone are placed on wounds and the bark is made into poultices. The seed starch is given to relieve biliousness and the roasted seeds are regarded as aphrodisiac. In Chinese medicine the pulp and seeds are considered tonic and nutritious.

1. AIM AND OBJECTIVE

AIM

To successfully evaluate the antihyperlipidaemic and antioxidant activity of *Artocarpus heterophyllus* stem extract on High fat diet-induced hypercholesterolemia and triton induced hyperlipidaemia models.

OBJECTIVE

1. To conduct a literature survey for establishing the relavence of the study.
2. To Collection and authenticate of *Artocarpus heterophyllus* stem.
3. To successfully extract the dried stem of *Artocarpus heterophyllus using* suitable solvents.
4. To evaluate toxicological profile of the extract.
5. To characterize the anti-hyperlipidemic effect as well as antioxidant property of the extract.

5. MATERIALS AND METHODS

PLANT MATERIAL

The fresh bark of *Artocarpus Heterophyllus* used for the present studies were collected from valanchery, kerala in Aug 2016. It was authenticated by Mr.Prabhu kumar, Scientist, aryavaidyasala, kotakkal, kerala

ANIMALS

Wistar rats (150 – 250 g) used for the study were obtained from the animal house of the Department of Pharmacology,Pathmavathy college of pharmacy, Dharmapuri, Tamil Nadu, India. The animals are randomly selected, marked to permit individual identification, and kept in their cages for at least 5 days prior to dosing to allow for acclimatisation to the laboratory conditions. The animals were housed three per cage in a polypropylene cage and maintained in standard laboratory conditions with free access to food and water *ad libitum*[20]. All animal experiments were conducted in compliance with (Organization for Economic Cooperation and Development) OECD Guideline and approved by the Institutional Animal Ethics Committee (SCP/CPCSEA/P11/F150/2016)

CHEMICALS, DRUGS AND INSTRUMENTS

All the major chemicals used in the study like Nitro blue tetrazolium (NBT), Riboflavin, EDTA, Phosphate buffer, DPPH, Triton, are of analytical grade and are procured from imperial chemicals, Coimbatore.

COLLECTION AND AUTHENTICATION OF PLANT

. The fresh bark of *Artocarpus Heterophyllus* used for the present studies were collected from valanchery

The dried bark powder of *Artocarpusheterophyllus*was supplied and authenticated by Mr.Prabhu kumar, Scientist, aryavaidyasala, kotakkal, kerala

The weighed coarse powder was used for the extraction by successive solvent extraction by Soxhlet apparatus using various solvents.

EXTRACTION PROCEDURE[44]

Preparation of *Alcoholic Extract of ArtocarpusHeterophyllus*bark

The bark were initially collected from the plant and rinsed with distilled water and shade dried and then homogenized into fine powder and stored in air tight bottles. A total of 10 g of air dried powder was weighed and was placed in 100 mL of organic solvents (methanol and ethanol) in a conical flask and then kept in a rotary shaker at 190-220 rpm for 24 h. And then it was filtered with the help of muslin cloth and centrifuged at 10 000 rpm for 5 min. The supernatant was collected and the solvent was evaporated by solvent distillation apparatus to make the final volume of one-fourth of the original volume, giving a concentration of 40 mg/mL. It was stored at 40 °C in air tight bottles for further studies.

PHYTOCHEMICAL ANALYSIS[45]

Phytochemicals are biologically active, naturally occurring chemical compounds found in plants, which provide health benefits for humans further than those attributed to macronutrients and micronutrients. Phyto constituents are the contributors of pharmacological activities of a plant. The dried powdered sample is subjected to qualitative tests for identification of various plant constituents.

Test for Carbohydrates

Molisch Test: To the aqueous extract, 1ml of ∝- napthol solution was added and Conc. Sulphuric acid was added along the sides of the test tube. Purple or reddish violet colour at the junction between the two liquids indicates the presence of carbohydrates.

Fehling Test: To the aqueous extract, equal quantities of Fehling A&B were added .Upon heating gently, a brick red precipitate indicates the presence of carbohydrates.

Benedict's test: To 5ml of Benedict reagent, 8 drops of solution under test was added to the aqueous extract and mixed well. Then it was boiled vigorously for 2 minutes and cooled. Red precipitate indicates the presence of carbohydrates.

Test for Proteins

Biuret Test: To the aqueous extract, 1ml of 40%NaOH and 2drops of 1% copper sulphate solution was added. A violet colour indicates the presence of proteins.

Xanthophoretic Test: To the aqueous extract, 1ml of conc. Nitric acid was added. When a white precipitate was formed, it is boiled and cooled. Then 20% of NaOH or ammonia was added. Orange colour indicates the presence of aromatic acids.

Lead acetate Test: To the aqueous extract, 1ml of lead acetate solution was added. A white precipitate indicates the presence of proteins

Test for Amino acids

Ninhydrin Test: 2drops of freshly prepared 0.2% ninhydrin reagent was added to the aqueous extract and heated. Development of blue colour indicates the presence of proteins, peptides or amino acids.

Test for Fats and Oils

Place a thick section of drug on glass slide. Add a drop of Sudan Red III reagent. After two minutes., wash with 50 % alcohol. Mount in glycerin. Observe under microscope. Red globules in the section when viewed under the microscope shows the presence of fats or oils.

Test for Steroids

Liebermann Burchard Test: The aqueous extract was dissolved in 2ml chloroform in dry test tube. 10 drops of acetic anhydride and 2 drops of conc. sulphuric acid were added. The solution becomes red and then blue and finally bluish green in colour indicates the presence of steroids.

Salkowaski Test: The aqueous extract was dissolved in chloroform and equal volume of sulphuric acid was added to it. Bluish red to cherry red colour was observed in chloroform layer, whereas acid layer assumes marked green fluorescence indicates the presence of steroids.

Test for Cardiac glycosides

Keller-killiani Test: Test sample was dissolved in acetic acid containing traces of ferric chloride and transferred to the surface of conc. Sulphuric acid. At the junction, reddish brown colour was formed, which gradually becomes blue indicates the presence of cardiac glycosides.

Test for Saponins

Foam Test: About 1ml of aqueous extract is diluted separately with distilled water to 20ml and shaken in a graduated cylinder for 15 minutes. A1cm layer of foam indicates the presence of saponins.

Test for Flavonoids

Sulphuric Acid Test: On addition of sulphuric acid (66% or 80%) flavons and flavonols dissolves into it and give a deep yellow solution.

Heat the test solution with Zinc and HCl, pink to red colur observation shows the presence of flavonoids.

Test for Alkaloids

Dragendroff's Test: To the aqueous extract, add 1ml of Dragendroff's reagent. An orange red coloured precipitate indicates the presence of alkaloids.

Wagner's Test: To the aqueous extract, add 1ml of Wagner's reagent. Reddish brown coloured precipitate indicates the presence of alkaloids.

Mayer's Test: To the aqueous extract, add 1ml of Mayer's reagent. A dull white coloured precipitate indicates the presence of alkaloids.

Test for Phenolic compounds and Tannins

Small quantities of alcoholic and aqueous extracts in water were tested for the presence of phenolic compounds and tannins with dilute ferric chloride solution (5%), 1% solution of gelatin containing 10% sodium chloride, 10% lead acetate and bromine solutions. The respective observations may be deep blue black colour, white precipitate, white precipitate, decolouration of bromine water showing the presence of tannins and phenolic compounds.

IN VITRO ANTIOXIDANT ACTIVITIES

A. SUPEROXIDE RADICAL SCAVENGING ACTIVITY [46]

Principle:

The superoxide anion radical scavenging activity was determined by nitro blue tetrazolium (NBT) reduction method of Mc Cord and Fridovich (1969). The assay is based on the ability of drug to inhibit the reduction of nitro blue tetrazolium (NBT) by Superoxide, which is generated by the reaction of photo reduction of riboflavin within the system. The superoxide radical thus generated reduce the NBT to a blue colored complex.

Reagents:

- Nitro blue tetrazolium (NBT) - 1.5nm (12.3mg/10ml)
- Riboflavin - 0.12µm (4.5mg/100ml)
- NaCN/EDTA - 0.0015% NaCN in 0.1M EDTA
- Phosphate buffer - 0.06M (pH 7.8)

Procedure:

The reaction mixture contained EDTA (0.1 M), 0.3mM NaCN, Riboflavin (0.12mM), NBT (1.5 n moles), Phosphate buffer (67mM, pH 7.8) and various concentrations of the bark extract in a final volume of 3ml. The tubes were illuminated under incandescent lamp for 15min. The optical density at 560 nm was measured before and after illumination. The inhibition of superoxide radical generation was determined by comparing the absorbance values of the control with that of bark extract and extract. Vitamin C was used as positive control. The concentration of extract required to scavenge 50% superoxide anion (IC_{50} value) was then calculated.

Calculation:

$$\text{\% inhibition} = \frac{OD\,of\,control - OD\,of\,sample}{OD\,of\,control} \times 100$$

B. DPPH RADICAL REDUCING ACTIVITY[47]:

Principle:

It is a rapid and simple method to measure antioxidant capacity. It involves the use of free radical, DPPH (2, 2- Diphenyl - 1- picrylhydrazyl) (Aquino et al, 2001). The odd electron in the DPPH free radical gives a strong absorption maximum at 517nm and is purple in color. The color turns from purple to yellow when the odd electron of DPPH radical becomes paired with hydrogen from a free radical scavenging antioxidant to form the reduced DPPH-H. The resulting decolourisation is stoichiometric with respect to the number of electrons captured.

Reagents:

- DPPH - 3mg in 25ml methanol (stored in dark bottle)
- Methanol

Procedure:

Freshly prepared DPPH (187 µl) was taken in different test tubes protected from sunlight. To this solution added different concentrations (0, 25, 50, 75,100,150,200µg/ml) of bark extract and fraction-IV. The volume was made up to 1ml with methanol. Keep the tubes in dark and after 20 min absorbance was measured at 515nm. Methanol was used as blank and vitamin C was used as positive control. The concentration of test materials to scavenge 50% DPPH radical (IC_{50} value) was calculated from the graph plotted with % inhibition against concentration.

Calculation:

$$\text{\% inhibition} = \frac{OD\,of\,control - OD\,of\,sample}{OD\,of\,control} \times 100$$

PHARMACOLOGICAL SCREENING

ACUTE TOXICITY STUDY [48,49,50]

Experimental Protocol:

Guideline	:	OECD-423
CPCSEA Ref. No	:	SCP/CPCSEA/P11/F150/2016
Test	:	Limit test
Species	:	*Rattusnorvegicus*
Strain	:	Albino Wistar rats
Number of animals	:	24 animals (6 for each group)
Sex	:	Female
Initial dose	:	5mg/kg
Route of administration	:	Oral
Duration	:	3hr close observation, followed by 14 days observation
Others	:	Body weight, mortality status
Parameters	:	CNS, ANS and behavioural changes
Blood collection	:	Not needed
Sacrifice	:	Not needed

Selection of Test animal

Female adult Wistar rats of 8-12 weeks are selected. Nulliparous and non-pregnant animals were obtained from the centralized animal house of Pathmavathi College of Pharmacy, Dharmapuri. and they are acclimatized for holding 1 week prior to dosing.

Housing and feeding conditions for Experimental Animals

Temperature - As per OECD guideline-420 the temperature of animal house were maintained at $22^0C \pm 3^0C$.

Humidity - The relative humidity of animal room maintained at 50-60% preferably not exceeds 70% (OECD guidelines-420, 2001). Otherwise there may be chances of developing lesions such as ring tail and food consumption may be increased.

Light – The sequence of light used was 12 hrs light and 12 hrs dark.

Caging – Polypropylene cages with solid bottom and walls. The lids are made up of stainless steel grill which is capable to hold both feed and water.

Feeding condition and feed – Sterile laboratory feed (*ad libitum*) and water daily. The feed used were brown coloured chow diet.

Drug administration

Animals are fasted prior to dosing (food but not water should be withheld for overnight).After that animals are weighed and the test substance administered. The healthy rats has been taken and divided into 4 different groups. The test substance is administered in a single dose by oral gavages, using a curved and ball tipped stainless steel feeding needle.

Experimental Design

In this study, 4 groups of 6 rats each were given 5, 50 and 300 and 2000 mg/kg of the decoction (p.o.). After drug administration the food is withheld for 3 hours. The animals are observed continuously for the first 2 hours, then occasionally up to 6 hours and then daily up to 14 days, post treatment to observe for any symptoms of toxicity and mortality. Daily observations on the changes in skin and fur, eyes and mucus membrane (nasal), autonomic effects (salivation, lacrimation, gauntness and piloerection) and central nervous system (gait, tremors and convulsion) were carried out and changes were noted (OECD, 2001).

Table 4 – acute Toxicity study Design

GROUP	Number of Animals	DOSE (mg/kg)
Group 1	6	5
Group 2	6	50
Group 3	6	300
Group 4	6	2000

Clinical observation[51]

All animals were monitored continuously with special attention for 4 hrs after dosing for signs of toxicity. Additional observations are also done for the next 14 days for any other behavioural or clinical signs of toxicity. Weight changes are calculated. At the end of the test animals are weighed. LD_{50} values are established using the formula.

Dose Calculation Equation

$$\mathbf{LD_{50} = higher\ dose - \Sigma\ (a \times b)/n}$$

Where,

a = dose difference

b = animal died

n = No. of animals in each group

$$\mathbf{ED_{50} = \frac{LD_{50}}{10}}$$

ANTIHYPERLIPEDEMIC ACTIVITY

HIGH – CHOLESTEROL DIET MODEL

High fat diet induced hyperlipidemic model Preparation of feed

Method of Blank et el[52] with modification was used to produce high fat diet induced hyperlipidemia.Normal animal food pellets were crushed in mortar and pestle to crush into small pieces and then grinded into fine powder in mixer grinder. The other ingredients i.e. cholesterol l 2% , Cholic acid 1% , sucrose 40% , and coconut oil 10% were added in the mixer grinder in an ascending order of their quantity and mixed well. This dried powder was then mixed with same quantity of water every time to make small balls of feed and later this was stored in self-sealing plastic covers in refrigerator at 2°C to 8°C. The feed for normal group was prepared similarly by grinding only the normal food pellets and then mixing with water without the other excipients.[5,54] This preparation of feed was done once in three days for all the animals. The animals were administered with the high fat diet for 30 days. Check the serum blood cholesterol levels

Study design

Wistar rats weighing 150-180 gm, were divided into 5 groups of 6 animals each.

Group I- served +as normal control and were given only vehicle (distilled water)

Group II- received high fat diet served as hyperlipedemic control

Group III - received atorvastatin 10mg/kg served as standard drug

Group IV- received 200mg/kg AAHP

Group V- received 400mg/kg of AAHP

TRITON INDUCED HYPERLIPIDEMIC RATS[55,56]

30 Wistar rats were randomly divided into 5 groups of 6 each. The first group was given standard pellet diet, water and orally administered with 5% CMC. The II,III,IV,Vgroup animals were injected i.p. with 10% aqueous solution of Triton

100mg /kg body weight. After 72 hours of triton injection, the second group received a daily dose of 5% CMC (p.o) for 7 days. The thirdgroup was administered with the standard Atorvastatin 10mg/kg, p.o. for 7 days, fourth and fifth group was administered a daily dose of AAHP 200 and 400 mg/kg suspended in 5%CMC,p.o., for 7 days, after inducing hyperlipidemia.. Food was withdrawn 10h prior to the blood sampling. The control group animals received the vehicle in the same volume orally.

Group 1: Administered vehicle and served as normal control.

Group 2: Administered Triton X 100 (TR) and served as hyperlipidaemia control.

Group 3: Administered Standard Atorvastatin (10mg/kg), p.o

Group 4: Administered AAHB (200mg/kg), p.o.

Group 5: Administered AAHB (400mg/kg), p.o.

BIOCHEMICAL ANALYSIS OF SERUM

Serum samples were analysed for total cholesterol, High density lipoproteins, Low density lipoproteins and very low density lipoproteins using standard enzymatic assay kit.

Estimation of lipids:

A. Total cholesterol: Cholesterol in serum was estimated by using an Ecoline Diagnostic Kit. Cholesterol and its esters were released from lipoprotein by detergents. Cholesterol esterase hydrolyzes the esters. In the subsequent enzymatic oxidation by cholesterol oxidase, H_2O_2 was formed. This was converted into a coloredquinineimine in a reaction with 4-aminoantipyine and phenol catalyzed by peroxidase. The absorbance of the sample and of the standard was measured against the reagent blank value at 546nm. Cholesterol level in serum was expressed as mg/dL.

B.Triglycerides: Triglycerides level in serum was estimated using Ecoline Diagnostic Kit.

Lipase

Triglycerides ⟶ Glycerol + Fatty acid

GK

Triglycerides ⟶ Glycerol + Fatty acid

GPO

Glycerol-3-phosphate + O_2 ⟶ Dihydroxy-acetone-Phosphate + H_2O_2

$2H_2O_2$ + Aminoantipyrine + 4 chlorophenol ⟶ Chinonimine + $4H_2O$

The absorbance of the sample and of the standard was measured against the reagent blank value at 56nm. Triglyceride level in serum was expressed as mg/dL.

C. HDL cholesterol: The cholesterol was separated from serum after precipitation of LDL cholesterol by phosphotungstic acid precipitating reagent. The supernatant after centrifugation was estimated using Ecoline Diagnostic Kits. The absorbance of the sample and of the standard was measured against the reagent blank value at 546nm. HDL cholesterol level in serum expressed as mg/dL.

D. LDL cholesterol: LDL cholesterol was calculated by using the formula

LDL cholesterol = Total cholesterol – [HDL cholesterol – Triglycerides/5].

LDL cholesterol level in plasma was expressed as mg/dL.

E. VLDL cholesterol: VLDL cholesterol was calculated by using the formula

VLDL cholesterol = Total cholesterol – HDL cholesterol – Triglycerides- LDL.

STASTICAL ANALYSIS[57-59]

Data were statically analysed as mean $\pm$ SEM and expressed as just significant $P<0.05$ and significant $P<0.01$ as the case may be using one way ANOVA followed by Dunnett's multiple comparison test.

6. RESULTS

EXTRACTION OF ARTOCARPUS HETEROPHYLLUS BARK

The percentage yield of the *Artocarpus Heterophyllus* bark was found to be 1.03%w/v.

Table 5 - Extraction of ArtocarpusHeterophyllus Bark

Plant	Part used	Method of Extraction	Solvents	Percentage Yield (%W/V)
ArtocarpusHeterophyllus	Bark	Maceration	Ethanol (95%)	1.03

Preliminary phyto chemical screening

Alcoholic Extract of Artocarpus Heterophyllus bark(AAHB) was subjected various chemical tested as per the standard methods for the identification of the various constituents. The result if this phyto chemical analysis is listed below.

Table 6 - Qualitative phyto chemical screening of AAHB

PLANT CONSTITUENT	INFERENCE
	Ethanol Extract
Carbohydrate	-
Alkaloids	+
Flavonoids	+
Proteins and amino acids	+
Glycosides	-
Fixed oil	+
Terpenoids	+
Volatile oil	-
Tannins	-

"+" Presence,"-" Absence.

II-IN VITROANTIOXIDANT ACTIVITIES:

A. EFFECT OF SUPEROXIDE RADICAL SCAVENGING ACTIVITY:

Superoxide generated in the photo reduction of riboflavin was effectively inhibited by the addition of varying concentrations (0-14μL/ml) of extract table 3. The concentration of the AAHBneeded to scavenge 50% superoxide anion (IC_{50}) was found to be 13 μg/ml (figure 1) Vitamin C which was used as a positive control had an IC_{50} value of 4.5 μg/ml.

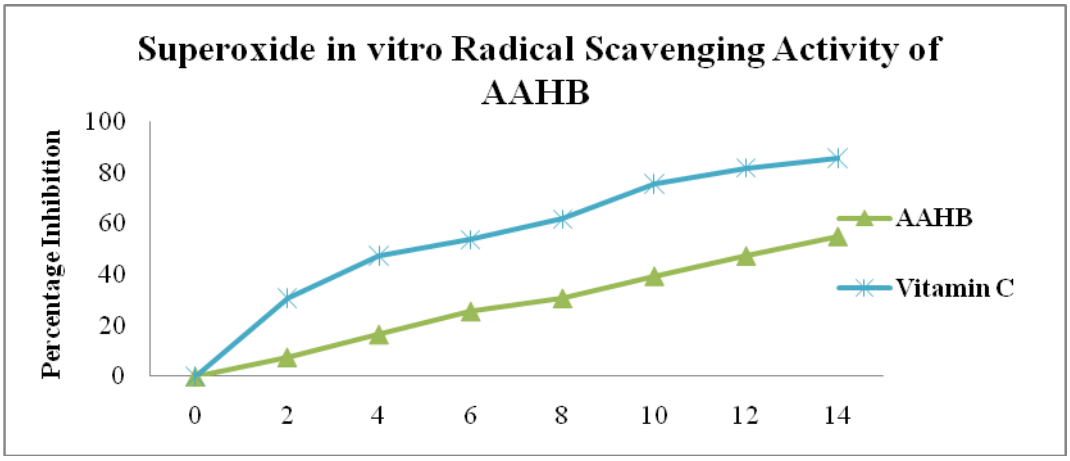
Table 7 - Effect of AAHB on Superoxide *in vitro*Radical Scavenging Activity

Concentration (µg/ml)	**Absorbance**		**Percentage inhibition**	
	AAHB	**Vitamin C**	**AAHB**	**Vitamin C**
0	0.78	0.78	0	0
2	0.72	0.54	7.6	30.76
4	0.65	0.41	16.6	47.43
6	0.58	0.36	25.64	53.84
8	0.54	0.25	30.76	67.94
10	0.47	0.19	39.47	75.64
12	0.41	0.14	47.43	82.05
14	0.35	0.11	55.12	85.89

Results are mean ± SD of three individual experiments

AAHB - *Alcoholic Extract ofArtocarpus Heterophyllus* bark

Figure 5: Effect of AAHB on Superoxide *in vitro*Radical Scavenging Activity



B. EFFECT OF AAHB ON DPPH RADICAL REDUCING ACTIVITY :

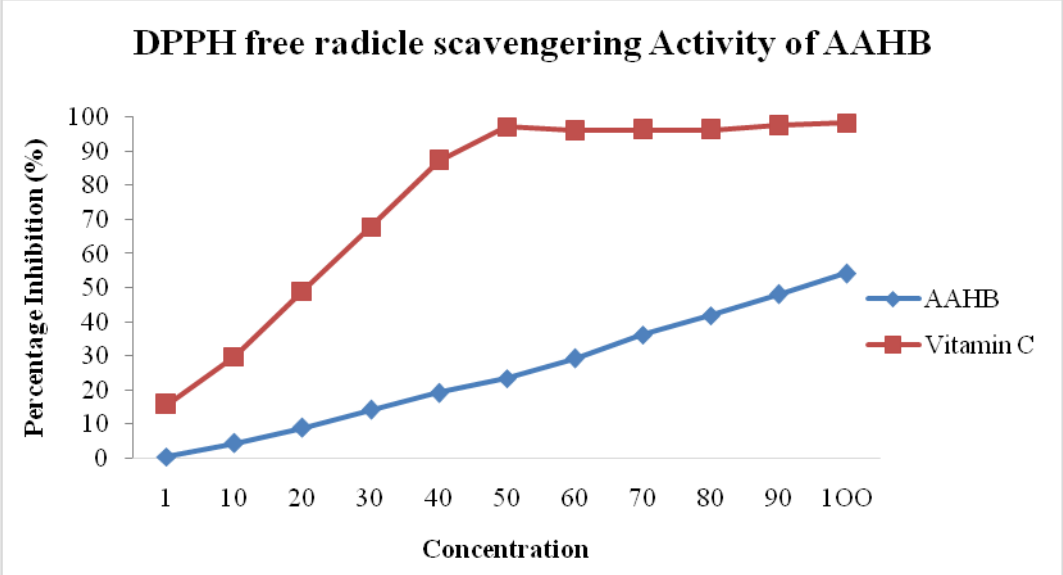
The DPPH radical was effectively scavenged by AAHB. A dose dependent reduction of was observed within the range of concentrations (0-100μg/ml) of Vitamin C which was used as the positive control exhibited an IC_{50} value of 21.6 μg/ml.

Table 8 - Study of *in vitro* DPPH Radical Scavenging Activity

AAHB - *Alcoholic Extract of Artocarpus Heterophyllus* bark

Concentration (µL/ml)	**Absorbance**		**Percentage inhibition**	
	AAHB	**VitaminC**	**AAHB**	**VitaminC**
1	0.694	0.58	0.5	15.8
10	0.676	0.487	4.35	29.9
20	0.640	0.361	9.03	49
30	0.60	0.121	14.2	67.8
40	0.566	0.101	19.2	87.3
50	0.530	0.046	23.4	97.3
60	0.461	0.06	29.2	96.1
70	0.459	0.05	36.3	96.2
80	0.40	0.05	41.9	96.2
90	0.36	0.04	48.13	97.5
1OO	0.327	0.03	54.23	98.3

Figure 6 -DPPH radical reducing activity of AAHB and vitamin C.



Acute Toxicity Study

There was no mortality or signs of toxicity up to the limit dose of 2000 mg/kg in treated rats. All 24 rats were normal throughout the study and survived until the end of the 14-day experiment period. Animal wellness parameters were observed continuously for the first 2 hours, then occasionally up to 6 hours and then daily up to 14 days as per paragraph 24 and 25 of OECD Guideline 423. Experimental observations are recorded systematically for each group. The parameters considered are changes in skin and fur, eyes and mucous membrane and also respiratory and circulatory, autonomic and central nervous system, somatomotor activity and behavioral pattern. Special attention is given for the observations of tremor, convulsion, salivation, diarrhea, lethargy, sleep and coma.

Table9 - Changes in wellness parameters observed for*ArtocarpusHeterophyllus* Bark Extract treatedwistar rats.

Sl no	Response	Group1(5mg/kg)		Group 2 (50mg/kg)		Group 3 (300mg/kg)		Group 4 (2000mg/kg)	
		Before	After	Before	After	Before	After	Before	After
1	**Alertness**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
2	**Grooming**	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
3	**Anxiety**	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
4	**Roaming**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
5	**Tremor**	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
6	**Convulsion**	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
7	**Depression**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
8	**Gripping strength**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
9	**Scratching**	Present	Present	Present	Present	Present	Present	Present	Present
10	**Defecation**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal

11	**Writhing**	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
12	**Pupils**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
13	**Urination**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
14	**Salivation**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
15	**Skin and fur**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
16	**Lacrimation**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
17	**Pilo erection**	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
18	**Nail status**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
19	**Gauntness**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
21	**Diarrhoea**	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
22	**Sleep**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
23	**Coma**	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
24	**Lethargy**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal

25	**Mucous membrane**	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal

Effect of AAHP on lipid profile in high fat diet induced model

In high fat diet induce model, oral administration of AAHP (200 mg/kg and 400mg/kg, p.o.) significantly reduced the serum totalcholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C), VLDL-cholesterol levels but significantly increased serum HDL-cholesterol level as compared with positive control group. This study shows serum lipid parameters in animals were significantly reduced ($p<0.001$,) by fourteen days treatment with AAHP at dose levels 200 mg/kg and 400 mg/kg, when compared with control group. 400 mg/kg of AAHP group animals has shown very significant ($p<0.001$) compared with control group

ANTHYPERLIPEDEMIC ACTIVITY

Table 10 -Effect of AAHB *on*Lipid Profile in high-cholesterol diet induced hyperlipidaemia

GROUP	Total Cholesterol (mg/dl)	HDL (mg/dl)	Triglycerides (mg/dl)	VLDL mg/dl)	LDL (mg/dl)
Control	82.1±3.79	42.12±1.34	68.89±2.12	12.79±0.42	26.39±3.55
Positive control	146.72±2.5	34.19±2.82	142.18±3.80	25.83±0.75	64.35±2.82
Atorvastatin 10mg/kg	87.92±1.76	46.34±2.02	99.1±2.35***	20.53±0.64	21.23±2.42**
200mg/kg AAHP	108.42±2.35	40.81±2.40	116.02±2.10**	23.5±0.42	44.73±2.33
400mg/kg AAHP	92.35±1.63**	43.49±2.18***	101.06±2.89	20.6±0.60	28.59±2.02**

Values were mean **±**sd (n=6). Values are statistically significant at *P<0.05 and more significant at **P<0.01,***P<0.001 Vshyperlipidemic control using one way ANOVA followed by Dunnet's test.

Table 11 – Effect of AAHB on Total Cholesterol in high cholesterol diet induced hyperlipidaemia

GROUP	TOTAL CHOLESTEROL (mg/dl)
Control	82.1±3.79
Toxic control	146.72±2.5
Standard (Atorvastatin 10mg/kg)	87.92±1.76
AAHB(200mg/kg)	108.42±2.35
AAHB(400mg/kg)	92.35±1.63**

AAHB - *Alcoholic Extract ofArtocarpusHeterophyllus*bark

Figure 7- Effect of AAHB on Total Cholesterol in high cholesterol diet induced hyperlipidaemia

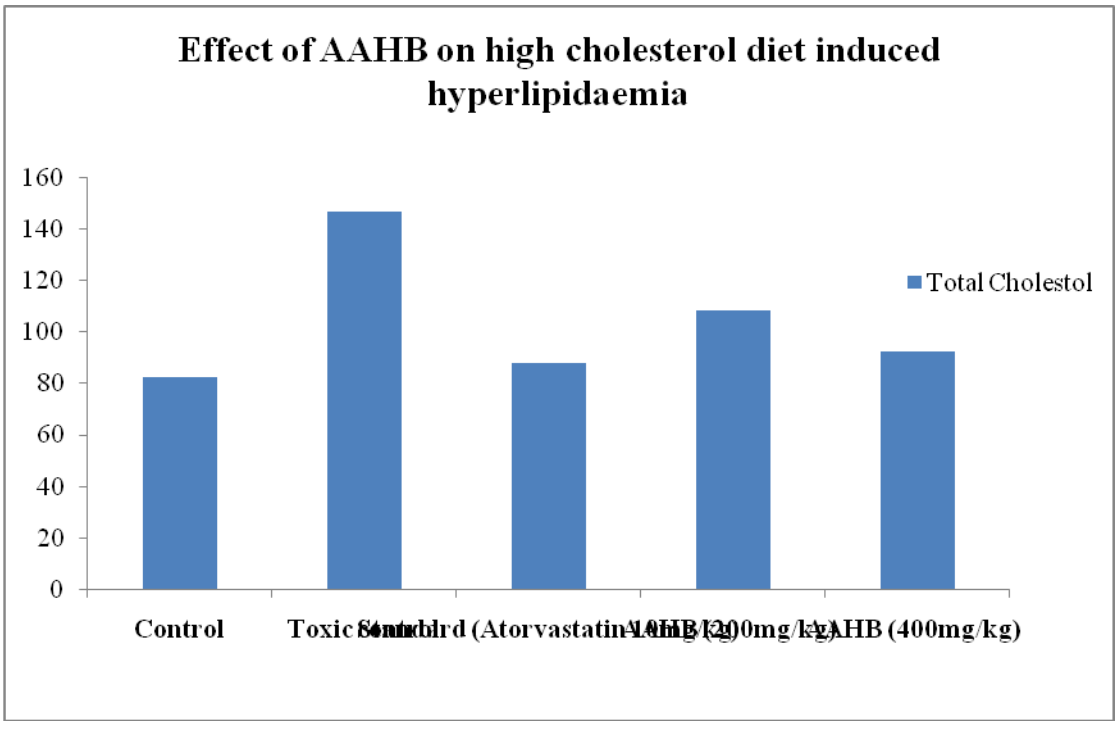


Table 12- Effect of AAHB on HDL in high cholesterol diet induced hyperlipidaemia

GROUP	HDL (mg/dl)
Control	42.12±1.34
Toxic control	34.19±2.82
Standard (Atorvastatin 10mg/kg)	46.34±2.02
AAHB(200mg/kg)	40.81±2.40
AAHB(400mg/kg)	43.49±2.18***

AAHB - *Alcoholic Extract ofArtocarpus Heterophyllus* bark

Figure 8 - Effect of AAHB on HDL in high cholesterol diet induced hyperlipidaemia

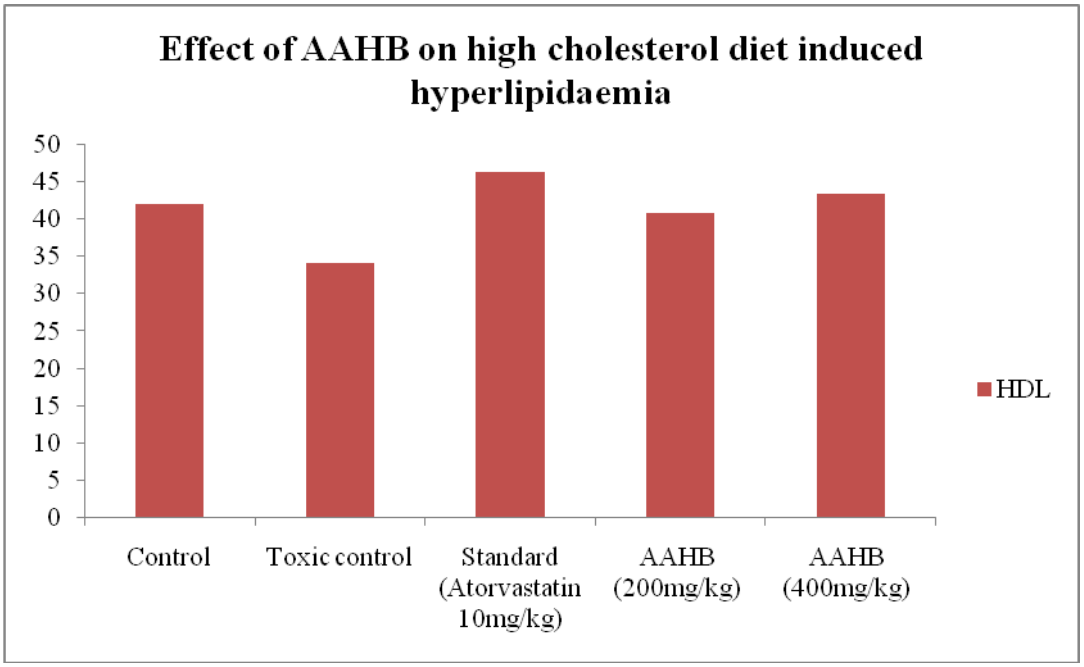


Table13 - Effect of AAHB on Triglycerides in high cholesterol diet induced hyperlipidaemia

GROUP	TRIGLYCERIDES (mg/dl)
Control	68.89±2.12
Toxic control	142.18±3.80
Standard **(Atorvastatin 10mg/kg)**	99.1±2.35***
AAHB(200mg/kg)	116.02±2.10**
AAHB(400mg/kg)	101.06±2.89

AAHB - *Alcoholic Extract ofArtocarpusHeterophyllus*bark

Figure 9 - Effect of AAHB on Triglycerides in high cholesterol diet induced hyperlipidaemia

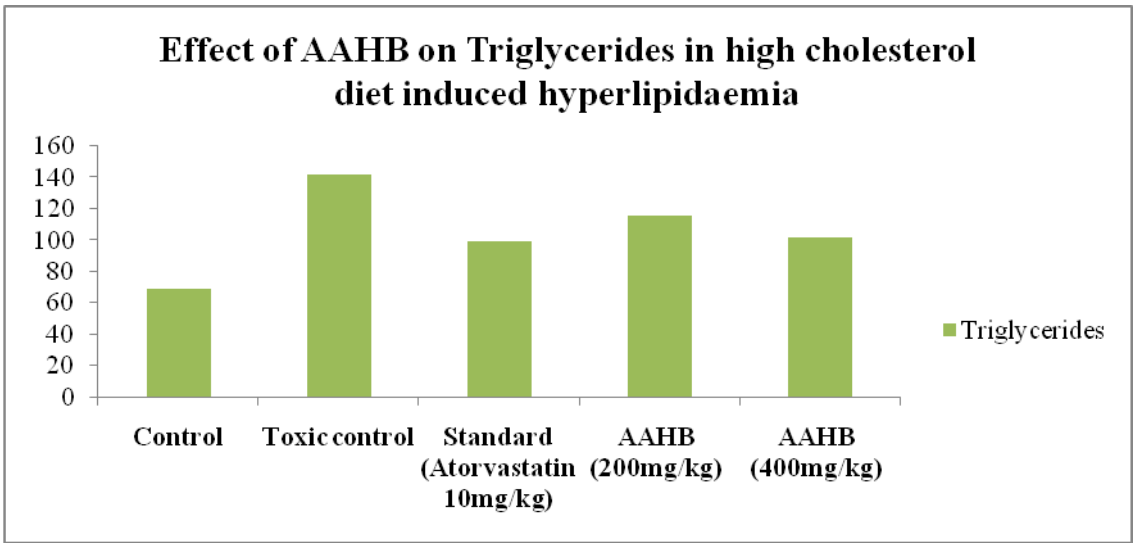


Table14 - Effect of AAHB on LDL in high cholesterol diet induced hyperlipidaemia

GROUP	LDL (mg/dl)
Control	26.39±3.55
Toxic control	64.35±2.82
Standard **(Atorvastatin 10mg/kg)**	21.23±2.42**
AAHB(200mg/kg)	44.73±2.33
AAHB(400mg/kg)	28.59±2.02**

AAHB - *Alcoholic Extract ofArtocarpusHeterophyllus*bark

Figure10 - Effect of AAHB on LDLin high cholesterol diet induced hyperlipidaemia

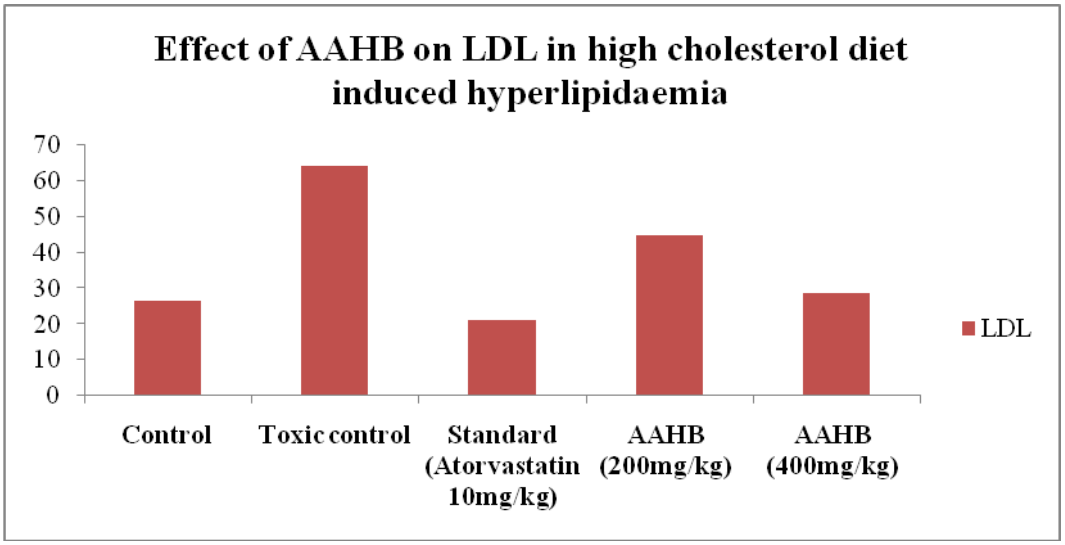
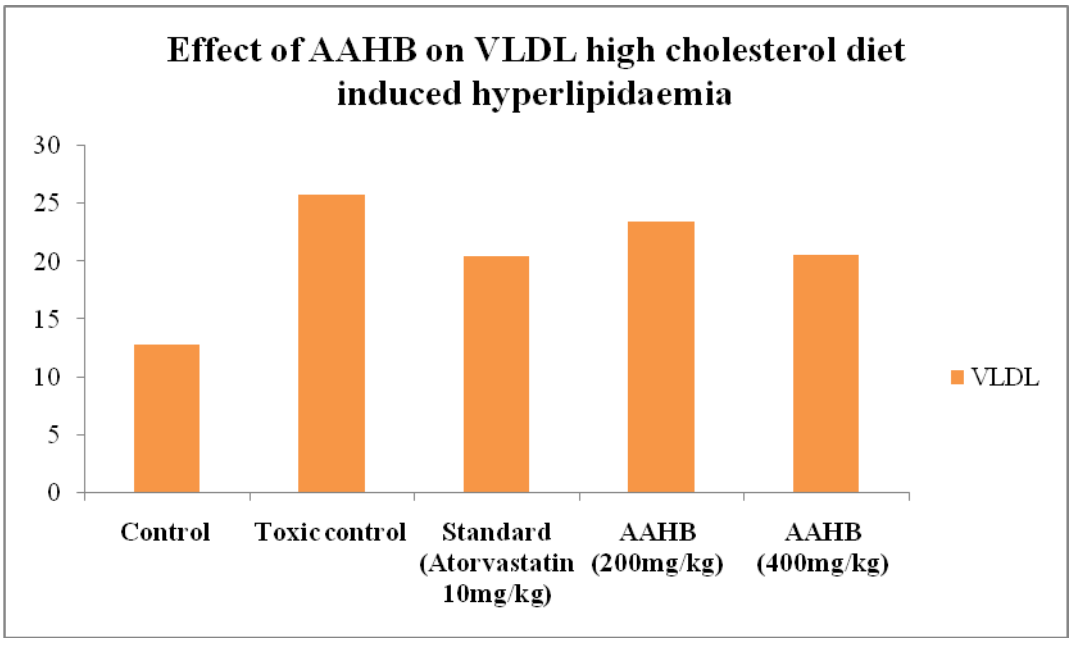


Table15 - Effect of AAHB on VLDL in high cholesterol diet induced hyperlipidaemia

GROUP	VLDL (mg/dl)
Control	12.79±0.42
Toxic control	25.83±0.75
Standard **(Atorvastatin 10mg/kg)**	20.53±0.64
AAHB(200mg/kg)	23.5±0.42
AAHB(400mg/kg)	20.6±0.60

AAHB - *Alcoholic Extract of Artocarpus Heterophyllus* bark

Figure11 -Effect of AAHB on VLDL in high cholesterol diet induced hyperlipidaemia



Effect of *Alcoholic Extract ofArtocarpusHeterophyllus*bark on lipid profile in Triton inducedhyperlipidemia

In triton induced study results shows serum lipid paremeters in animals were significantly reduced ($p<0.01$,) by seven days treatment with AAHP at dose levels 200 mg/kg and 400 mg/kg, when compared with control group 400 mg/kg of AAHP group animals has shown significant ($p<0.001$) compared with control group. At this time, an increased level of HDL was also observed.

TRITON INDUCED HYPERLIPIDEMIA MODEL

Table 16 -EFFECT OF AAHBON LIPID PROFILE TRITON INDUCED HYPERLIPIDEMIA

GROUP	Total Cholesterol (mg/dl)	HDL (mg/dl)	Triglycerides (mg/dl)	VLDL (mg/dl)	LDL (mg/dl)
Control	82.63±0.20	42.70±0.69	67.23±0.78	14.04±0.50	26.09±0.95
Positive control	145.16±2.25	31.04±2.33	127.56±2.54	27.31±0.99	66.99±1.93
Standard (Atorvastatin 10mg/kg)	86.40±0.91***	45.40±0.70	76.07±0.53	18.75±0.34**	22.74±0.59
AAHP (200mg/kg)	108.56±0.94	39.12±0.52	96.15±0.62*	23.88±0.5	38.35±0.61
AAHP (400mg/kg)	91.36±1.72***	42.79±0.91**	82.18±0.86	20.5±0.94	25.09±0.73**

Values were mean **±**sd (n=6). Values are statistically significant at *P<0.05 and more significant at **P<0.01,***P<0.001 Vshyperlipidemic control using one way ANOVA followed by Dunnet's test

Table 17 – Effect of AAHB on Total Cholesterol in Triton induced Hyperlipidaemia

GROUP	TOTAL CHOLESTEROL (mg/dl)
Control	82.63±0.20
Toxic control	145.16±2.25
Standard **(Atorvastatin 10mg/kg)**	86.40±0.91***
AAHB (200mg/kg)	108.56±0.94
AAHB (400mg/kg)	91.36±1.72***

AAHB - *Alcoholic Extract ofArtocarpusHeterophyllus*bark

Figure: 12 - Effect of AAHB on Total Cholesterol in Triton induced Hyperlipidaemia

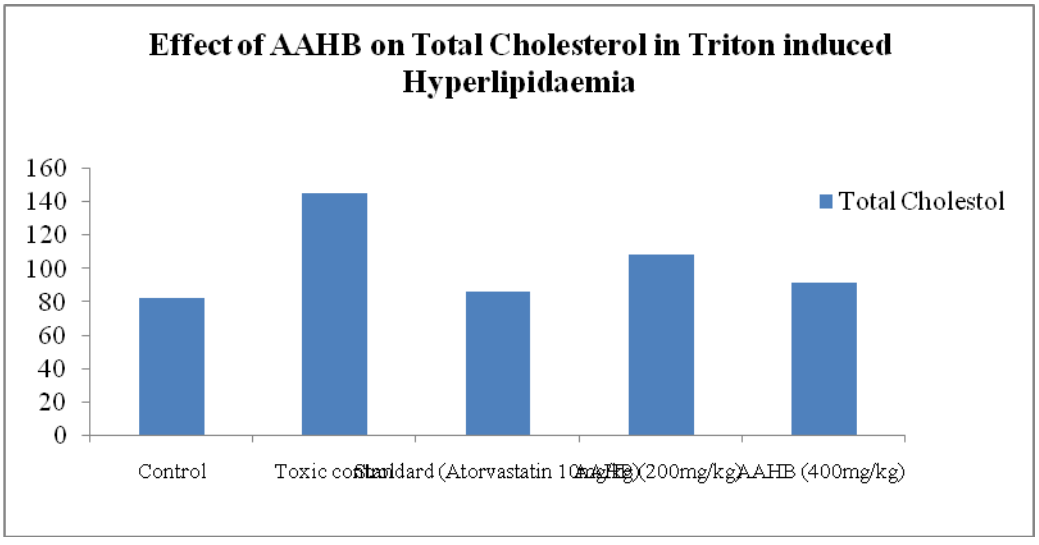


Table 18 - Effect of AAHB on HDL in Triton induced Hyperlipidaemia

GROUP	HDL (mg/dl)
Control	42.70±0.69
Toxic control	31.04±2.33
Standard (Atorvastatin 10mg/kg)	45.40±0.70
AAHP (200mg/kg)	39.12±0.52
AAHP (400mg/kg)	42.79±0.91**

AAHB - *Alcoholic Extract ofArtocarpusHeterophyllus*bark

Figure 13 - Effect of AAHB on Total Cholesterol in Triton induced Hyperlipidaemia

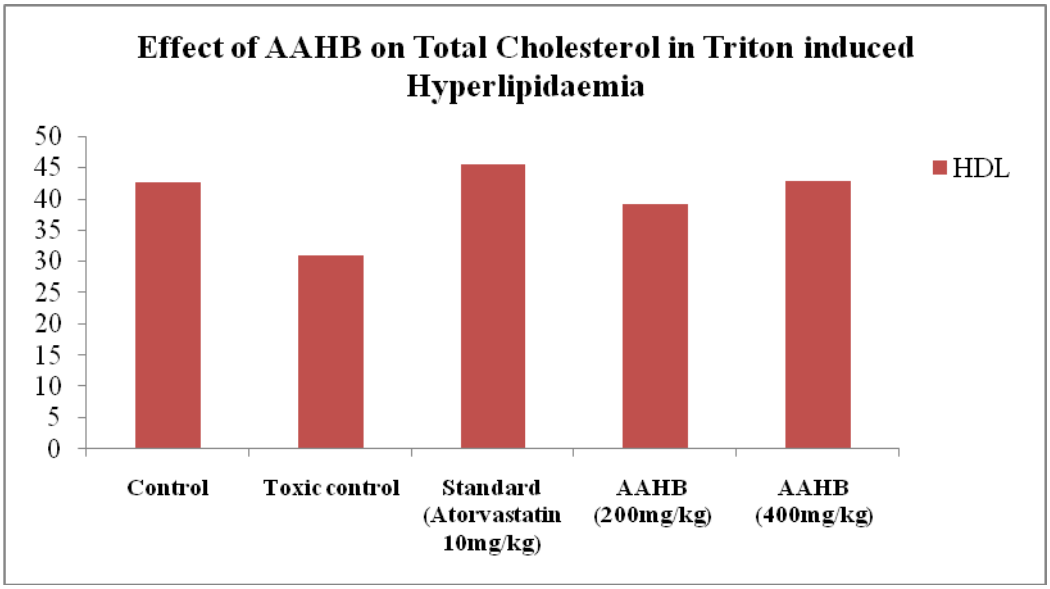


Table19 - Effect of AAHB on Triglycerides in Triton induced Hyperlipidaemia

GROUP	TRIGLYCERIDES (mg/dl)
Control	67.23±0.78
Toxic control	127.56±2.54
Standard **(Atorvastatin 10mg/kg)**	76.07±0.53
AAHB(200mg/kg)	96.15±0.62*
AAHB(400mg/kg)	82.18±0.86

AAHB - *Alcoholic Extract ofArtocarpusHeterophyllus*bark

Figure14 - Effect of AAHB on Triglycerides in Triton induced Hyperlipidaemia

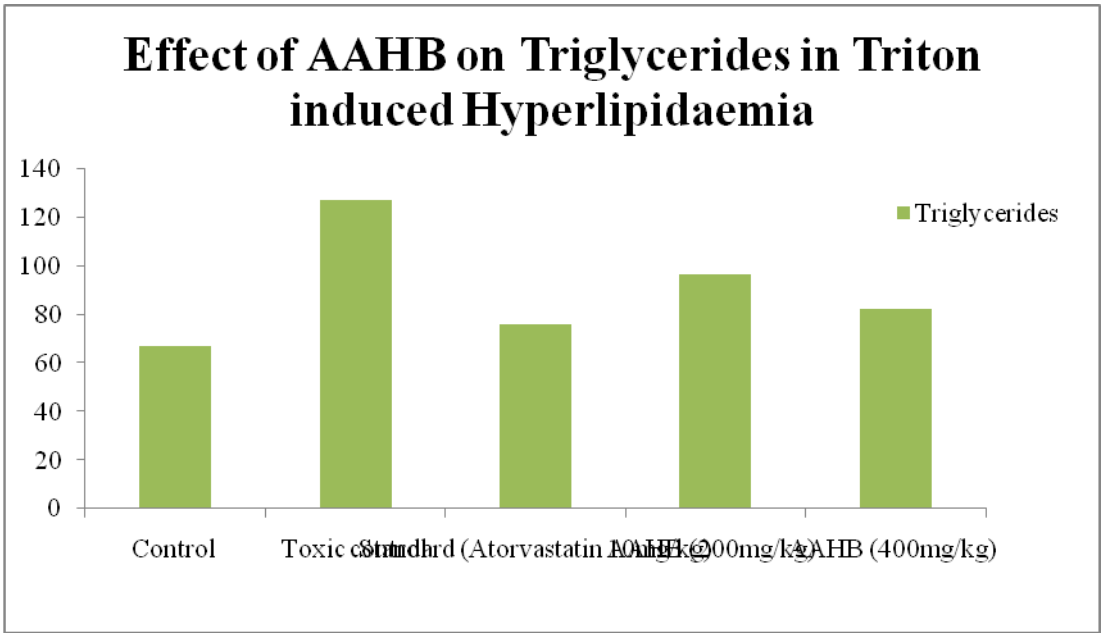


Table 20 - Effect of AAHB on LDL in Triton induced Hyperlipidaemia

GROUP	LDL (mg/dl)
Control	26.09±0.95
Toxic control	66.99±1.93
Standard **(Atorvastatin 10mg/kg)**	22.74±0.59
AAHP (200mg/kg)	38.35±0.61
AAHP (400mg/kg)	25.09±0.73**

AAHB - *Alcoholic Extract of Artocarpus Heterophyllus* bark

Figure 15 - Effect of AAHB on Total Cholesterol in Triton induced Hyperlipidaemia

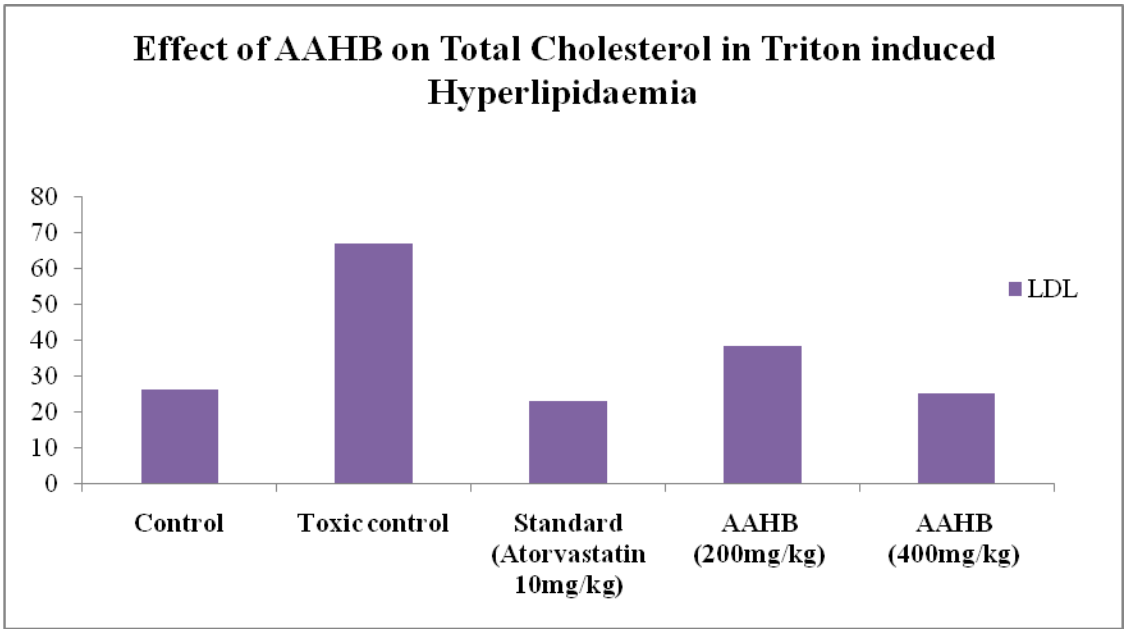
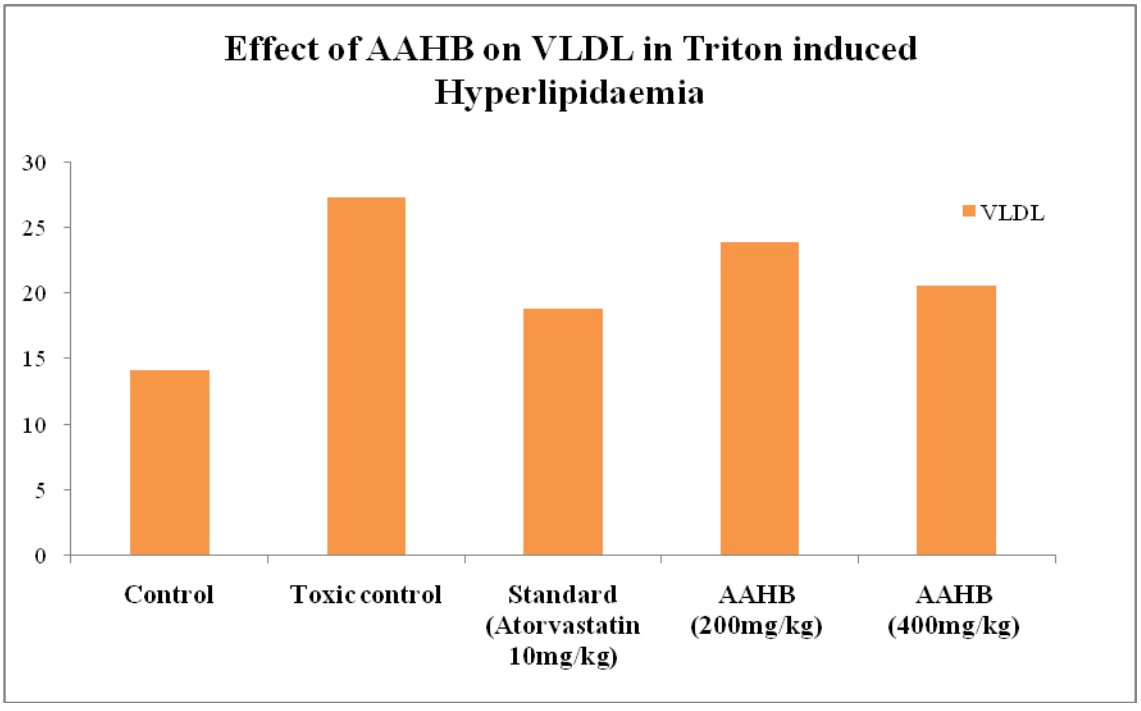


Table 21 - Effect of AAHB on VLDL in Triton induced Hyperlipidaemia

GROUP	VLDL (mg/dl)
Control	14.04±0.50
Toxic control	27.31±0.99
Standard **(Atorvastatin 10mg/kg)**	18.75±0.34**
AAHP (200mg/kg)	23.88±0.5
AAHP (400mg/kg)	20.5±0.94

AAHB - *Alcoholic Extract ofArtocarpusHeterophyllus*bark

Figure 16 - Effect of AAHB on VLDL in Triton induced Hyperlipidaemia



7. DISCUSSION

Artocarpus heterophyllus is a large, evergreen tree found generally in Western Ghats of India, Malaysia and also found in central and eastern Africa, south-eastern Asia, the Caribbean, Florida, Brazil, Australia, Puerto Rico and many Pacific Islands. Different parts of the plant, studied revealed antibacterial, anti-inflammatory, antidiabetic, antioxidant and immune modulatory properties.

The antioxidant screening shows that that it showed reducing power to DPPH radicals. But the efficiency showed is far below from Vitamin C. Considering super oxide radical scavenging studies, ethanolic extract shows similar percentage of inhibition comparing the standard drug.

Accute phase toxicological studies reports no mortality or signs of toxicity up to the limit dose of 2000 mg/kg in treated rats. All 24 rats were normal throughout the study and survived until the end of the 14-day experiment period.

The preliminary phytochemical screening of plant bark extracts indicate in presence of flavonoid, alkaloid, tannins, terpenoids and glycosides may accounts antioxidant and anti-hyprelipidaemic potential.

The presences of various phyto-constituents like alkaloids, flavonoids, terpenoids, phytosterols, saponinsetc, were responsible for the specified pharmacological effects. Alcoholic extracts shows more number of phytoconstituents..

Oral administration of ethanolic bark extracts significantly reduced the cholesterol, triglycerides, low density lipoproteins, very low density lipoproteins and significantly increased the HDL – cholesterol level as compared with high cholesterol diet induced hyperlipidemic animals. The results were significant with the p value ($p<0.001$).

Triton WR 1339 is the non-ionic detergent, induces acute hyperlipidemiaby raising cholesterol levels raise 2-3 times within 24 hours of administration.. The mechanism of the Triton induced hypercholesterolemia is thought to be due to increased hepatic synthesis of cholesterol through the ability of Triton to interfere with the uptake of plasma lipids by the tissue.

In triton induced study results shows serum lipid paremeters in animals were significantly reduced ($p<0.01$,) by seven days treatment with AAHP at dose levels 200 mg/kg and 400 mg/kg, when compared with control group 400 mg/kg of AAHP group animals has shown significant ($p<0.001$) compared with control group. At this time, an increased level of HDL was also observed.

8. CONCLUSION

The preliminary phytochemical screening revealed the presence of sterols, flavonoids, polyphenolics and fixed oil in ethanolic extract and sterols, proteins, polyphenolics, pectin's in the aqueous extract.

The results indicates that the extract possess anti-oxidant properties, but when compared with a standard marketed drug, in superoxide radical scavenging activity studies the percentage inhibition shown by the extract was far less comparing standard drug and in DPPH radical reducing studies we observed a similar percentage inhibition to that of standard drug.

Ethanolic extract showed decreased blood lipids in hyperlipidemic rats when compared to normal and standard groups The bark extracts shows a decreased in the TC, TG, and LDL and an increase in HDL in biphasic model of the Triton induced hyperlipidaemia rats, Diet induced hyperlipidemic rats and also in Normocholesteremic rats.

The present study concludes that the extracts of *Artocarpusheterophyllus* bark possess significant anti-oxidant and anti-hyperlipidemic activity.

9. BIBLIOGRAPHY

1. M. Umadevi, K.P Sampath Kumar, DebjitBhowmik, S. Duraivel, Traditionally Used Anticancer Herbs In
   India. Journal of Medicinal Plants Studies, Vol.1, 2013, 5674.
2. Yogayata S Pathare, Vijay D Wagh. Herbal Medicines and Nutritional supplements used in the treatment of Glaucoma: A Review. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2012 Volume 3 Issue 1. 331-339
3. Balamurugan G and Shantha A. (2010). Effect of Erythrinavariegata seed extract on hyperlipidemia elicited by high fat diet in wistar rats. J Pharm Bioallied Sci. 2(4): 350–355.
4. PourushBadal, RajendramaniBadal, DiyaVadiya et al. (2011).Hypolipidemic activity of Petroselinumcripsum Plant in Triton-Wr 1339 Induced Hyperlipidemic Rats. Herbal Tech Industry.10-15.
5. A Chaith,Bierman, J J Albers, Low Density lipoprotein receptor activity in cultured human skin fibroblast. Mechanism of insulin-induced Stimulation. J clin Investigation.1979,641309 19
6. Anne K Soutar* and Rossi P Naoumova.Mechanisms of Disease: genetic causes of familial hypercholesterolemia. NATURE CLINICAL PRACTICE CARDIOVASCULAR MEDICINE.VOL 4 NO 4. 2007.214-225
7. Ahmed SM, Clasen MD, Donnelly. MD (1998): Management of Dyslipidemia in Adults. Amer, Family Physician; 57:1-16.
8. Kishor Jain S, Kathivarin MK, Rahul S, chamanalJ.The biology and chemistry of hyperlipidemia. Bioorganic And Medicinal Chemistry, 2007, 15, 4674-4699.
9. Bhatnagar D, Soran H, Durrington PN. Hypercholesterolaemia and its management. BMJ, 2008, 337, 993
10. Grundy SM; Balady GJ, Criqui MH. Primary prevention of coronary heart disease: guidance from Framingham: a statement for healthcare professionals from the AHA Task Force on Risk Reduction. American Heart Association. Circulation, 1998, 97(18), 1876–87.
11. K.Harikumar, S. Abdul Althaf, B. Kishore kumar, M. Ramunaik, CH. Suvarna. A Review on Hyperlipidemic. INTERNATIONAL JOURNAL OF NOVEL

TRENDS IN PHARMACEUTICAL SCIENCES. VOLUME 3 | NUMBER 4 | OCT | 2013. 59-71.

12. Hopkins PN et al., Coronary artery disease risk in familial combined hyperlipidemia and familial hypertriglyceridemia: a case-control comparison from the National Heart, Lung, and Blood Institute Family Heart Study. Circulation, 2003, 108, 519-523.
13. Veerkamp MJ, Graaf J, Bredie SJH, Hendriks JCM, Demacker PNM, Stalenhoef AFH. Diagnosis of familial combined hyperlipidemia based on lipid phenotype expression in 32 families: results of a 5- year follow-up study. Arterioscler. Thromb. Vasc. Biol, 2002, 22, 274-282.
14. Suviolahti E, Lilja HE, Pajukanta P. Unraveling the complex genetics of familial combined hyperlipidemia. Ann. Med, 2006, 38, 337-351.
15. Garcia-Otin AL, Civeira F, Peinado-Onsurbe J, Gonzalvo C, Llobera M, Pocovi M. Acquired lipoprotein lipase deficiency associated with chronic urticaria, A new etiology for type I hyperlipoproteinemia. Eur. J. Endocrinol, 1999, 141, 502-505.
16. Hoffmann MM et al., Detection of mutations in the apolipoprotein CII gene by denaturing gradient gel electrophoresis, Identification of the splice site variant apolipoprotein CII-Hamburg in a patient with severe hypertriglyceridemia. Clin. Chem, 1998, 44, 1388-1396.
17. Kwong LK et al., Mutations in exon 3 of the lipoprotein lipase gene segregating in a family with hypertriglyceridemia, pancreatitis, and non-insulindependent diabetes. J. Clin. Invest. 1993;92: 203- 211.
18. ap TS, Jenq SF, Wu YC, Chiu CY, Cheng HM. Mutations in the lipoprotein lipase gene as a cause of hypertriglyceridemia and pancreatitis in Taiwan. Pancreas, 2003, 27, 122-126.
19. Ray KK, Seshasai SR, Erqou S. Statins and all-cause mortality in high-risk primary prevention: a metaanalysis of 11 randomized controlled trials involving 65,229 participants. Arch Intern Med, 2010, 170(12), 1024–31.
20. Lewington S, Whitlock G, Clarke R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet, 2007, 370(9602), 1829–39.

21. Abourbih S, Filion KB, Joseph L, Schiffrin EL, Rinfret S, Poirier P, Pilote L, Genest J, Eisenberg MJ. Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. Am J Med, 2009, 122(10), 962.e1–962.
22. Wong NN. Colesevelam: a new bile acid sequestrant. Heart disease, 2001, 3(1), 63–70.
23. Bhatt et al., Effects of antioxidant vitamins along with atorvastatin and atorvastatin–niacin combination on diet-induced hypercholesterolemia in rats. Int J PhysiolPathophysiolPharmacol, 2010, 2(1), 57-63.
24. Herrling T, Jung K and Fuchs J (2008). The role of melanin as protector against free radicals in skin and its role as free radical indicator in hair. *SpectrochimicaActa Part A: Molecular &BiomolecularSpectroscopy*69(5):1429-35.
25. Halliwell B (2012). Free radicals and antioxidants: updating a personal view. *Nutrition Reviews* 70(5):257-65.Morrison R, Boyd RN and Boyd RK(1992). *Organic Chemistry* 6th ed. Benjamin Cummings.
26. Morrison R, Boyd RN and Boyd RK(1992). *Organic Chemistry* 6th ed. Benjamin Cummings
27. Dillard C J, Litov R E, Savin W M, Dumelin E E and Tappel A L (1978). Effects of exercise, vitamin E, and ozone on pulmonary function and lipid peroxidation. *Journal of Applied Physiology***45**: 927.
28. Goldfarb A H (1999). Nutritional antioxidants as therapeutic and preventive modalities in exercise-induced muscle damage. *Canadian Journal of Applied Physiology* 2**4**: 249-266.
29. Singh B, Singh MP and Dey AC (1980). Indian medicinal plants used in Ayurvedic preparations. *Materiamedica***10:** 200-202.
30. KarlssonJ(1997). Exercise, muscle metabolism and the antioxidant defense. *World Review of Nutrition and Dietectics***82**:81-100.
31. Harman D (1956).Aging: a theory based on free radical and radiation chemistry. *Journal of Gerontology* 11 (3): 298–300

32. Kaczmarski M, Wojicicki J, Samochowiee L, Dutkiewicz T and Sych Z (1999). The influence of exogenous antioxidants and physical exercise on some parameters associated with production and removal of free radicals.*Pharmazie*54: 303-306.

33. S. Chackrewarthy, M. I. Thabrew, M. K. B. Weerasuriya, and S. Jayasekera. Evaluation of the hypoglycemic and hypolipidemic effects of an ethylacetate fraction of *Artocarpusheterophyllus* (jak) leaves in streptozotocin-induced diabetic rats. Pharmacogn Mag, 2010 Jul-Sep; 6(23): 186–190.

34. E. R. Suchithra and S. Subramanian. Antidiabetic activity of Artocarpusheterophyllus rag extract studied in high fat fed- low dose STZ induced experimental type 2 diabetic rats. Der Pharmacia Lettre, 2014, 6 (3):102-109

35. P. Sivagnanasundaram and K. O. L. C. Karunanayake. Phytochemical Screening and Antimicrobial Activity of Artocarpusheterophyllus and Artocarpusaltilis Leaf and Stem Bark Extracts. OUSL Journal, 2015; 9, 1-17.

36. Periyanayagam K*, Karthikeyan V. Wound Healing Activity Of The Leaves Of ArtocarpusHeterophyllus Lam. (Moraceae) On Ex-Vivo Porcine Skin Wound Healing Model. Innovare Journal of Life Science 2013; 1 (1) 28-33.

37. Venkateswarulu .M, Prashanthi.K,GopichandChinta, Sujata .D, Pushpakumari.B, Ranganayakulu.D. Anti-hyperlipidemic activity of the aqueous extract of the Artocarpusheterophyllus leaves in triton WR-1339 induced hyperlipidemic rats.Drug Invention Today. 2010;2(1),25-28.

38. Omar HS, El-Beshbishy HA, Moussa Z, Taha KF, Singab AN. Antioxidant activity of Artocarpusheterophyllus Lam. (Jack Fruit) leaf extracts: remarkable attenuations of hyperglycemia and hyperlipidemia in streptozotocin-diabetic rats.Scientific World Journal. 2011; 5(11):788-800.

39. https://www.google.co.in/search?q=ARTOcarpus+heterophyllus+PLANT+PROFILE+PDF&newwindow=1&source=lnms&tbm=isch&sa=X&ved=0ahUKEwjm0_HhpvPSAhVPv5QKHcTcAUwQ_AUICCgB&biw=1366&bih=638#imgrc=03i8iFVSWOtjSM:

40. https://www.itis.gov/servlet/SingleRpt/SingleRpt?search_topic=TSN&search_value=184183#null
41. http://www.flowersofindia.net/catalog/slides/Jackfruit.html
42. Gunasena, H.P.M. 1993. Documentary Survey on Artocarpusheterophyllus(Jackfruit) in Sri Lanka. Monograph Number 2. Forestry/Fuelwood Research and Development (F/FRED) Project, Winrock International, Arlington, Virginia
43. Thaman, R.R., and I. Ali. 1993. Agroforestry on smallholder sugar-cane farms in Fiji. In: Clarke, W.C., and R.R. Thaman (eds.). Agroforestry in the Pacific Islands: Systems for Sustainability. United Nations University Press, Tokyo
44. Kokate CK., Purohit AP., Gokhale SB.,Pharmacognosy, NiraliPrakashan, Pune, 2006, 35, p 106-107.
45. Adeniyi SA., Orjiekwe CL., Ehiagbonare JE., Arimah BD., Preliminary phytochemical analysis and insecticidal activity of ethanolic extract of four tropical plants (Vernoniaamygdalina, Sidaacuta, Ocimumgratissimum and Telfariaoccidentalis) against beans weevil (Acanthscelidesobtectus), Int J Physical Sci, .02010, 5(6), p 753-762.
46. SiddurajuP,becker k(2007).Antioxidant and free radical scavengeringactivityes of processed cow pig(cassia histula) seeds. Food Chemistry 101,10-19
47. Brands Williams W,Cuvellie ME(1995),Uses of free radical method to evaluate antioxidant activity . Lebensmittelwissenchant and technologies-28, 25-30
48. Organization for Economic Cooperation and Development (OECD). 2001. Guideline For Testing Of Chemicals 423: Acute Oral Toxicity – Acute Toxic Class Method.
49. Organization for Economic Cooperation and Development (OECD). 2002. Guidelines for the Testing of Chemicals /Section 4,Health Effects Test No. 423, Acute Oral toxicity - Acute Toxic Class Method
50. Organization for Economic Cooperation and Development (OECD). 2008. Guidelines For The Testing Of Chemicals 407: Repeated Dose 28-Day Oral Toxicity Study in Rodents.
51. Shawn Tomy, UjwalaTk, Sandra Celine, C Senthil Kumar, Sam Johnson UdayaChander J. Toxicological evaluation of Diakure, An antidiabeticpolyherbal formulation. International Journal of Phytomedicine,2016:8(1)127-137
52. Sumitra Singh, Surendra Kr. Sharma and Rajinder Mann Antihyperlipidemic

activity of suaedamaritima (l.) Dumortier aerial parts in hypercholesterolemic rats. Journal of Pharmacy Research 2012,5(3),1400-1402 ISSN: 0974-6943

53. Grundy SM. Cholesterol and coronary heart disease: a new era. J Am Med Assoc. 1986;256:2849-2858.Durrington P. Dyslipidaemia. Lancet; PMID 12957096. 2003;(362):717-31.
54. Kaesancini AY and Krauss RM. Cardiovascular disease and hyperlipidemia: Current topics of lipid dynamics. 1994; 5:249-251.
55. Usharani et al. World Journal of Pharmacy and Pharmaceutical Sciences 10. Brahma SrinivasaRaoDesu and CH. Saileela Anti-hyperlipidemic activity of methanolic extract of rhinacanthusnasutus,international journal of research in pharmacy and chemistry IJRPC 2013, 3(3) ISSN: 22312781.
56. Mukesh SS and MB. Antihyperlipidemic activity of *Salaciachinensis* root extracts in triton induced and atherogenic diet-induced hyperlipidemic rats. Indian J Pharmacol.2012;44(1):88–9
57. Dunnett, C.W., 1955. A multiple comparison procedure for comparing several treatments with a control. J. Am. Stat. Assoc. 50, 1096–1121.
58. 83. Dunnett, C.W., 1964. New tables for multiple comparisons with a control. Biometrics 20, 482–492
59. 84. Cochran, W.G., 1957. Analysis of covariance: its nature and uses. Biometrics 13, 261–278.
60. Sanwar Mal Lamba,Kunjbihari Sulakhiya,Parveen Kumar. Anti diabetic,Hypolipidemic and Anti oxidant activities of Hydroethanolic Root Extract of Rhus Mysurensis Heyne in streptozotocin induced Diabetes in Wistar Male Rats.
61. Damayanthi Dalu, Satyavati Dhulipala. Antidiabetic,Antihyperlipidemic and Antioxidant Properties of Root of Ventilago Maderaspatana Gaertn. On Streptozotocin Induced Diabetic Rats.
62. Prashant R. Verma, Prakash R. Itankar, Sumit K. Arora. Evaluation of antidiabetic antihyperlipidemic and pancreatic regeneration, potential of aerial parts of Clitoria ternatea.
63. Pradeep Pal,Ajay Sharma,Mukesh Mehra,Anil Choudhary. Antidiabetic and Antihyperlipidemic activity of ethanolic extract of Artemisia Nilagirica In streptozotocin induced diabetic rats.