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REVIEW ARTICLE

A review on antihyperlipidemic activity of various herbal plants and various experimental animal models

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ABSTRACT

Hyperlipidemia is a disorder of lipid metabolism which is major risk of coronary heart disease. Now day's synthetic drugs have been associated with number of side effects but herbal medicines have lipid lowering and antioxidant activities without any side effects. Some traditionally herbs like: - Terminalia Arjuna (Arjun), Commiphora mukul (Gugglul), Picrorrhiza Kurroa(Kutki), Allium Sativum (Lasuna), etc. are used as Antihyperlipidemic drug as per ayurvedic literature. The review article is undertaken to investigate the herbal Plants for Antihyperlipidemic activity and models use in this investigation. This review is given on the anti- hyperlipidemic activity of the most familiar medicinal plants of medicine.This matter may be helpful for the researchers, academician and preclinician about the potential herbs having anti-hyperlipidemic activity.

Keywords: Hypolipidemic agents, Hypolipidemic medicinal herbs, Animal models, Phytoconstituents.

INTRODUCTION:

Hyperlipidemia is a disorder of lipid metabolism produced by elevation of plasma concentration of the various lipid and lipoprotein fractions, which cause the cardic disease.[1] Hyperlipedemia is define in a simple way by increase serum TC, TG, VLDL, LDL and IDL which are responsible for various complications like: heart attack, premature coronary artery disease, stroke, atherosclerosis, myocardial infarction and pancreatitis.[2] The aim of treatment of hyperlipidemia is to reduce the risk of heart disease or cardiovascular or cerebrovascular disease.[3] Now a day's therapy includes statins and fibrates which correct the blood lipid profile by inhibiting the biosynthesis of cholesterol. The use of synthetic hypolipidemic drugs having various adverse effects like: nausea, vomiting, diarrhea, gastric irritation, hyperuricemia, dry skin and abnormal liver function.[4] The use of indigenous plants as an alternative medicine which is use to increased the desired activity and minimizes the unwanted side effects of synthetic drugs adopted by the world health organization.[5-6] Research work was done on various plants. About 13000 plants have been studied for various pharmacological actions. Hyperlipidemia can be either primary or secondary type, the primary disease may be treated by hypolipidemic drugs, but the secondary type induced by diabetes, hypothyroidism or renal lipid nephrosis that treated by treating the original disease rather than hyperlipidemia.[7] The Present review work is focused on various herbs that possess hypolipidemic effect and different screening models that may be helpful to reducing the risks of Cardiovascular diseases.

CLASSIFICATION OF HYPERLIPIDEMIA[4, 8]

FAMILIAL (PRIMARY)

It caused by specific genetic abnormalities.

ACQUIRED (SECONDARY)

It causes due to other conditions and medications like: diabetes, low thyroid hormone level, Kidney disease and other metabolic disorders. Various medications like: Estrogens, diuretics, β-blockers, glucocorticoids and alcohol produced hyperlipidemia.[8]

SIGNS AND SYMPTOMS OF HYPERLIPIDEMIA[9-10]

1. Xanthoma
2. Xanthelasma of eyelid
3. Chest Pain
4. Abdominal Pain
5. Enlarged Spleen
6. Liver Enlarged
7. Heart attacks
8. Higher rate of obesity and glucose intolerance
9. Pimple like lesions across body
10. Atheromatous plaques in the arteries

CAUSES OF HYPERLIPIDEMIA[4, 11]

1. Medications: -, Glucocorticoids, alcohol, beta blocker, thiazide.
2. Diabetes (type 2)

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3. Pregnancy
4. Kidney disease
5. Environmental and genetic factors
6. High dietary simple carbohydrates
7. Cushing's Syndrome
8. Estrogen therapy
9. Nephrotic Syndrome
10. Hypothyroidism

TREATMENT FOR HYPERLIPIDEMIA[4]

HMG-COA REDUCTASE INHIBITORS (STATINS)

Drugs: - Atorvastatin, Lovastatin

1. FIBRIC ACID DERIVATIVES

Drugs: - Clofibrate, Fenofibrate

2. BILE ACID SEQUESTRANTS

Drugs: - Colestipol

3. NICOTINIC ACID

Drugs: - Niacin

BIOCHEMICAL ANALYSIS OF SERUM

Serum samples is analysed for TC, HDL and TG levels using standard enzymatic assay kits: Total cholesterol Kit, HDL-Precipitating RGT Kit, Triglyceride Kit. Low density lipoprotein (LDL) and Very low density lipoprotein (VLDL) were calculated according to Friedwald formula. Atherogenic index (A.I) is also calculated as per the formula.[12]

LIPIDS

Lipids describe as a class of fats and fatlike substances in the blood. Various important lipids in the blood are fatty acids, cholesterol, TGLs, and phospholipids.[13]

TRIGLYCERIDES (TGS)

They are esters consisting of a glycerol molecule and synthesized in the liver and adipose tissue to provide a source of stored energy.[13]

LIPOPROTEIN

They are macromolecular complexes that carry hydrophilic plasma lipids. The major lipids of the lipoproteins are cholesterol, TGs, and phospholipids.[13]

SCREENING MODELS[14]

Various animal species use for the screening of potential Antihyperlipidemic drugs. The selection of animal model which can best evaluate this effect is important since marked variations in drug responses have been obserbed with the same drug tested in several species.

Several of the animal models mostly used are following**:**

1. Use of normal hyperlipidemic animal for primary screening: -

a) Leghorn
b) Rat

2. Use of hyperlipidemic Animals: -

a) Weanling Rats
b) Adult Rats
c) Rabbit
d) Birds

3. Intermediate animal models: -

a) Dog
b) Swine

4. Estrogen induced hyperlipidemia in birds

5. Triton induced hyperlipidemia

a) Mice
b) Rat

USE OF NORMAL HYPERLIPIDEMIC ANIMAL FOR PRIMARY SCREENING: -

Normocholesterolemic animals use for preliminary screening has the advantage of rapidity, simplicity and detects inhibitors of the absorption and synthesis of cholesterol.

LEGHORN

In this test take white leghorn, 9-11 weeks of age, for which drug was administered in the diet for four consecutive days. Then on 5th day heart is puncture and collects the blood for analyses. Compounds that lowered serum cholesterol by at least 20% at a dose of 400mg/kg were find vigorous.[14-15]

RAT

The test drug given orally to the normocholesterolemic rat for four consecutive days and on 5th day serum cholesterol analyses.[16]

USE OF HYPERLIPIDEMIC ANIMALS[14]

Hypercholesterolemia is produced in several animal species by including fats and cholesterol in their diets. Drugs that are active against the diet induced hyperlipidema by one or more mechanisms involving inhibition of intestinal absorption of cholesterol, enhancement of cholesterol degradation interference with lipoprotein production and acceleration of the removal of lipoproteins.

WEANLING RATS

The serum cholesterol levels of weanling rats are usually 2-3 times greater than adult levels. This hypercholesterolemia is sensitive to certain types of drugs like thyroxine and may be insensitive to certain inhibitors of cholesterol biosynthesis. In this model take weanling rats, weighing 60-95 gm, maintained on a normocholesterolemic diet supplemented with the test drug clofibrate for a 2-week interval. Serum level is depressed to 75 mg%. The use of weanling rats can provide a rather simple, rapid, and inexpensive means of testing potential hypocholesterolemic agents[14]

RABBIT

a. Cholesterol containing diets: - In this method feeding a diet with a high level of cholesterol and fat progressively elevated the serum cholesterol level so that

at the end of a 2-week period the mean serum cholesterol has increased to 600 mg%. The test drugs are given in diet and administered to the animals.

b. Cholesterol free semisynthetic diet: - In this method investigators have reported that feeding rabbits with saturated fat, without cholesterol, induces a hypercholesterolemia more closely related to the human type. This method is use for the screening of drugs affecting lipid metabolism since plasms cholesterol is endogenously synthesized, and its level is limits of that normally encountered in human hypercholesterolemia.

ADULT RATS

Diet induced hyperlipidemia is useful only for detecting agents which interfering with the absorption degradation and excretion of cholesterol. In this model take male Sprague–Dawley rats weight about 200- 250 gm, were divided into 5 groups of 6 animals each. The animals of all the groups except normal group are given a lipid diet consisting of 2% cholesterol, 1% cholic acid and 2 ml coconut oil with standard pellet diet for 30 days. The first group (Normal control) is receive normal saline orally for 30 days and second group (High cholesterol diet (HCD)-positive control) is given High cholesterol diet while the third and fourth groups are treated with hydroalcoholic extract of herbal formulation (200 mg/kg and 400mg/kg, p.o.) once a day for 30 days. The fifth group is treated with Atorvastatin suspension prepared with 0.5% CMC (10mg/kg; p.o.), once a day for 30 days. After 30 days blood is collected by retro orbital sinus puncture, under mild ether anaesthesia. The collected samples are centrifuged for 10 minutes at 2000 r.p.m. and this sample is used for various biochemical tests. The animals are then sacrificed and the liver collected. Biochemical Analysis of Serum samples are analysed for TG, TC, LDL and HDL levels using standard enzymatic assay kits.[14]

BIRDS

In this test take white leghorn, 9-11 weeks of age, for which drug was administered in the diet for four consecutive days. Then on 5th day heart is puncture and collects the blood for analyses. Compounds that lowered serum cholesterol by at least 20% at a dose of 400mg/kg were considered active.[15]

VARIOUS DIETARY REGIMENS:

Table 1: Various Dietary Regimens for induce Hyperlipidemia.

S. No.	Standard rat diet supplemented	Serum Cholesterol (mg %)	Time	References
1.	Cholesterol (1%) to weanling rats	96	28 days	14
2.	Saturated fatty acids and saturated triglycerides	150	2 months	14
3.	Cholesterol, sodium cholate, and thiouracil	1100	28 days	17
4.	Cholesterol, fat, and cholic acid to weanling rats	436	2 weeks	18
5.	Cholesterol (1%) and oxbile extract (0.5%)	245	28 days	14

INTERMEDIATE ANIMAL MODELS

DOG

Hypercholesteromemia, which leads to the development of atherosclerosis, is produced in dogs by feeding diets containing cholesterol, bile acids, and possibly the thyroid inhibitor thiouracil. We produced hypercholesterolemia in four-month old dogs, maintain on a diet containing cholesterol (5%) and thiouracil (0.6 gm/day). At the end of one month marked hypercholesterolemia (1000 mg%, 5 times higher than the control value is developed.[14]

SWINE AND PRIMATES

Hypercholesterolemia is produced in swine by feeding diets supplemented with butter, egg yolk, and saturated fats. It is shown that the combination of unsaturated fat with cholesterol in the diet produced the greatest degree of typical atheromatosis and the highest levels of cholesterol in the tissues. Similarly, hypercholesterolemia has been produced in primates by feeding experimental diet containing cholesterol and butter. Total serum-cholesterol levels of 300-600 mg% developed in 1-3 months. The animal models can be employed for assessment of hypocholesterolemic agents and their effects on the atherosclerotic process.[14]

ESTROGEN INDUCED HYPERCHOLESTEROLEMIA IN BIRDS

The administration of depot estrogens to hens and cockerels induces a hyperlipidemia which development of atherosclerotic. Blood cholesterol levels rise tenfold over control levels (908 mg% vs. 133 mg %) within 1 week following a single injection of depot β-estradiol in the chicken. This hyperlipidemia is endogenous and not dependent on the presence of dietary fat. Thus it seems that cholesterol biosynthesis inhibitors could be detected using this system. Thyroxine, an agent that can accelerate metabolic degradation of cholesterol and that promotes the removal of serum phospholipids, is the most active agent in reversing the estrogen hypercholesterolemia. Agents which inhibit intestinal cholesterol absorption, such as sitosterol and amide derivatives of linoleic acid

are inactive. The method is simple and rapid and is suitable for hypocholesterolemic screening of thyromimetic agents.[14]

TRITON WR 1339 (ISO OCTYL POLY OXY ETHYLENE PHENOL) INDUCED HYPER LIPIDEMIA MODEL

This method is used for detecting compounds which interfering the synthesis and excretion of cholesterol**.** The use of Triton WR 1339 induced hyperlipidaemia through accelerated hepatic cholesterol synthesis is suggested for test. In this model take Male prague–Dawley rats with weight about 200- 250 gm, are divided into 5 groups of 6 animals each. The first group (Normal control) is received normal saline orally for one week. The second group (Triton positive control) is received Triton WR-1339 dissolved in 0.9% saline (400 mg/kg bodyweight) by i.p. route. The third and fourth groups are treated with hydroalcoholic extract of polyherbal formulation (200 mg/kg and 400mg/kg, p.o.) once a day for one week. The fifth group is treated with Atorvastatin suspension prepared with 0.5% CMC (10mg/kg, p.o.), once a day for one week. On the 7th day, the animals are fasted for 18 hrs (had only access to water) and 400 mg/kg Triton WR 1339 is injected (i.p), to all the four groups of rats immediately after drug administration. On the 8th day, blood is collected by retro-orbital sinus puncture, under mild ether anaesthesia. The collected blood samples are centrifuged for 10 minutes at 2000 r.p.m. and serum samples are used for various biochemical tests.[19]

Table 2: List of herbal medicinal plants of categories 1st and 2nd

S. No.	PLANT NAME	FAMILY	PART USED	ACTIVE CONSTITUENTS	REF NO
1.	Achyranthus aspera	Amarantaceae	Whole Part	Achyranthine, Achyranthol	21
2.	Bauginia purpurea	Caesalpiniaceae	Leaf	Bio-flavanoids	22
3.	Cinnamomum tamala	Lauraceae	Leaf	Eugenol, Methyl eugenol, Volatile oil	23
4.	Terminalia arjuna	Combretaceae	Bark	Arjunolic acid	24
5.	Solanum melongena	Solanaceae	ripe fruits	Solanine, Solanosterol	25
6.	Sapindus emarginatus	Sapindaceae	Pericarp	Saponins, Steroidal sapogenin	26
7.	Gymnema sylvestre	Asclepiadaceae	Leaf	Gymnemic acid	27
8.	Garcinia cambogia	Guttiferae/ Clusiaceae	Peel of matured fruits	L-hydroxy citric acid	28
9.	Commiphora mukul	Burseraceae	Resin	Guggul sterol	29
10.	Cissus quandrangularis	Vitaceae	Stem	Anabolic phytosterol	30

THE HERBAL MEDICINES ARE CATEGORIZED INTO 4 TYPES[20]

Category 1: Native herbal medicines
Category 2: Herbal medicines in Ayurved and Siddha
Category 3: Modified herbal medicines
Category 4: Imported herbal products

1. Bauhinia purpurea

It belongs to family caesalpiniaceae. The Leaf part of Bauhinia purpurea is used for eye diseases skin diseases, to relieve constipation and menorrhagia. The root Part is used for reducing excess body weight.[4] The study was done on anti-hyperlipidemic activity of ethanol extract of unripe pods and leaves of Bauhinia purpurea in cholesterol high fat diet (CHFD) induced hyperlipidemic rat models.The treatment of hyperlipidemic rat with ethanol extract of unripe pods and leaves of Bauhinia purpurea at dose of 300mg/kg p.o for one month along with cholesterol diet shown significantly decrease in seurm total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels.[22]

2. Achyranthes aspera

It belongs to family Amarantaceae. The whole part of Achyranthes aspera is apply for obesity, haemorrhoids, leucorrhoea, oligomenorrhoea, gastric ulcers, syphilitic ulcers, regulating menstruation and dental caries. The root Part is used for reducing excess body weight.[4]The study was done on anti-hyperlipidemic activity of alcoholic extract of A. aspera, in triton induced hyperlipidemic rats. The treatment of hyperlipidemic rat with alcoholic extract of achyranthes aspera at the dose 100 mg/kg for 30 days showed significantly decrease in seurm TC, TG, LDL and VLDL levels.[21]

3. Cissus quadrangularis

It belongs to family Vitaceae. The Stem part of cissus quandrangularis is used for epistaxis, anorexia, fracture of bones, worm infestations, bleeding piles, eczema, gastric ulcers, anaemia and to regulate menstruation. It is a rich source of calcium, phosphorus and magnesium.[9]The study was a randomized and doubleblind design involving 123 overweight and obese persons (47.2% male; 52.8% female; ages 19-50). All participants received two daily doses of the formulation and remained on a normal or calorie-controlled diet for 8 weeks. At the end of the trial period, significant net reductions in weight as well as in fasting blood sugar level, TC, LDL and TG.[24]

4. Commiphora mukkul

It belongs to family Burseraceae. The Resin part of Commiphora mukkul is used for inflammatory swellings arthritis, urticaria, and obesity. The Guggul an extract from the resin of this tree, at a dose of 50 mg guggul in a randomized, double-blind and placebo prohibited trial in general practice including 43 men and women, age 27-70. It decreased the low density lipoprotein cholesterol (LDL) by 12.5%, triglycerides by 12.0%, and the total cholesterol level by 11.7% and the total cholesterol/high density lipoprotein (HDL) cholesterol ratio by 11.1%.[21]

5. Garcinia cambogia

It belongs to family Guttiferae/ Clusiaceae. The Peel of matured fruits part of Garcinia cambogia is used for obesity and cooking recepies. The study was done on anti-hyperlipidemic activity of Crude ethanolic extracts of G.cambogia (bitter kola) seeds of Garcinia cambogia in adult male rats models.The treatment of hyperlipidemic rat with Crude ethanolic extracts of G.cambogia (bitter kola) seeds shown significantly decrease in seurm total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels in a high-fat diet (HFD)-induced obesity mouse model.[22]

6. Gymnema sylvestre

It belongs to family Asclepiadaceae. The Leaf part of Gymnema sylvestre is used for treating diabetes mellitus, obesity and insect bites. The study was done on anti-hyperlipidemic activity of leaf extract in cholesterol high fat diet (CHFD) induced hyperlipidemic rat models.The treatment of hyperlipidemic rat with leaf extract at 25-100 mg/kg dose along with cholesterol diet shown significantly decrease in serum triglyceride (TG), total cholesterol (TC), very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL).[25]

7. Terminalia arjuna

It belongs to family Combretaceae. The bark part of Terminalia arjuna is used for diabetes, heart diseases, leucorrhoea and lowering of cholesterol. The study was done on anti-hyperlipidemic activity of the 50% ethanol extract of bark of T. arjuna in cholesterol high fat diet induced hyperlipidemic rat models. The treatment of hyperlipidemic rat with the 50% v/v ethanol bark extract at the dose of 40mg/kg body weight along with cholesterol diet shown significantly decrease in seurm total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels while HDL cholesterol increased in experimental group.[28]

8. Solanum melongena

It belongs to family Solanaceae. The ripe fruits part of Solanum melongena is used for worm infestations, insomnia and used for liver enlargement. The study was done on anti-hyperlipidemic activity of Flavonoids extracted from the fruits of S. melongena at a dose of 1mg/100g BW/day showed significant hypolipidemic action in normal and cholesterol fed rats. The fresh, ripe fruits of Solanum melongena and Solanum gilo was significantly reduced serum total cholesterol by 65.40% and 52.69% respectively, triglyceride by 47.7 and 27%, LDL cholesterol by 85 and 83% respectively.[29]

9. Sapindus emarginatus

It belongs to family Sapindaceae. The Pericarp part of sapindus emarginatus is used for diarrhoea, epilepsy, hyperlipidemia, menstrual irregularities, scorpion bite, abscess, arthritis and swelling. It has detergent and cleansing properties. The study was done on anti-hyperlipidemic activity of Sapindus emarginatus in Triton induced hyperlipidemic in rats.[36] The treatment of hyperlipidemic rat with Steroidal saponin present in this plant at the dose of 100 and 200mg/kg shown significantly decrease the levels of serum TG, TC, LDL, and VLDL and significant increase in the level of serum HDL.[30]

10. Cinnamomum tamala

It belongs to family Lauraceae. The Leaf part of Cinnamomum tamala is used for bronchial asthma, cough, aphthous ulcers and oligospermia It has aromatic, carminative, digestive and lipid lowering actions.[37] The study was done on anti-hyperlipidemic activity of Aqueous and ethanolic extracts of leaves of Cinnamomum tamala in cholesterol high fat diet induced hyperlipidemic rat models.The treatment of hyperlipidemic rat with aqueous and ethanol extract of leaves of Cinnamomum tamala in doses of 400mg/kg /day p.o. each for 10 days with cholesterol diet shows significantly decrease in serum levels of total cholesterol, triglyceride, LDLC, VLDL-C and Atherogenic index whereas significant increases in the level of HDL-C.[20]

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