IJPSR (2014), Vol. 5, Issue 8 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 February, 2014; received in revised form, 21 June, 2014; accepted, 15 July, 2014; published 01 August, 2014

HYPERLIPIDEMIA: ITS MANAGEMENT AND INDUCTION

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Keywords:

Hyperlipidemia, Herbal drugs, Animal models

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ABSTRACT: In the present review an attempt has been made to explore and study the various *in vitro* animal models used for the evaluation of hypolipidemic and antihyperlipidemic drugs. Hyperlipidemia has been ranked as one of the greatest risk factors contributing to the prevalence and severity of coronary heart disease. The main aim of treatment in patients with hyperlipidemia is to reduce the risk of the occurrence of cardiovascular or cerebrovascular disease. The present review throws a light on the various herbal drugs used as potential hypolipidemics and antihyperlipidemics. Emphasis has been laid on the study of animal models used in the evaluation and screening of antihyperlipidemic drugs. The review also encompasses the various treatments used for the management of hyperlipidemia.

INTRODUCTION: Human health is one of the most important issues that have been addressed in the past and present. Currently, modern medicine, chemistry, biochemistry and pharmacology are trying to prevent, diagnose, treat and understand the reasons, mechanisms and pathways of disorders in the normal function of human body. Herbal medicine is still the mainstay of about 75-80% of the world population, mainly in the developing countries, for primary health care because of better cultural acceptability, better compatibility with the human body and lesser side effects [1]. There are several areas wherein plant derived drugs are used. Some of them have antiprotozoal activity like quinine from Cinchona, berberine from Berberis, harmaline from Peganum, artemisin from Artemesia.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(8).3152-56

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(8).3152-56

Allicin from garlic is antifingal, ricin from castor is specific immunotoxin against protozoa and liquorice is used in cleansing inflammed stomach. Oleanolic acid, sericic acid, quillia saponins and nimbidine from the seed oil of *Azadirchta indica*, catechin from *Acacia catechu* and lapachol from common teak have antiulcer activity. Colenol from *Coleus forskohli* is a hypotensive drug [2].

Plant products are frequently considered to be less toxic and freer from side effects than synthetic ones. Plants play a major role in the introduction of new therapeutic agents and have received much attention as sources of biologically active substances including antioxidants, hypoglycemics and hypolipidemics. Lipids play an important, but not an exclusive role in development and progression of atherosclerosis. In some persons, lipids will be a major factor, and in some, lipids play a minor role [3].

Hyperlipidemia has been ranked as one of the greatest risk factors contributing to the prevalence and severity of coronary heart disease [4].

The main aim of treatment in patients with hyperlipidemia is to reduce the risk of developing ischemic heart disease or the occurrence of further cardiovascular or cerebrovascular disease. Currently available hypolipidemic drugs have been associated with a number of side effects. The consumption of synthetic drugs leads to hyperuricemia, diarrhoea, nausea, myositis, gastric irritation, flushing, dry skin and abnormal liver function. Many investigators have demonstrated a correlation between raised serum lipids and the incidence of coronary heart disease (CHD) and atherosclerosis. Coronary heart disease (CHD) is the major cause of death in most developed countries and in many developing countries. The clinical complications of CHD lead to substantial disability and are a main source of the rising cost of health [5-8] Age, sex, and personal and family history of cardiovascular disease are nonmodifiable risk factors for CHD. Hypercholesterolemia, hyper-tension and cigarette smoking are the major modifiable risk factors [9-11]. They powerfully influence risk are common in populations and are widely amenable to prevention and treatment. It is well known that atherosclerosis is associated with elevated circulating cholesterol levels [12].

Recently, several herbal drugs have been advocated for their hypolipidaemic action. A list of medicinal plants possessing hypolipidaemic and anti-hyperlipidaemic activity is given in **Table 1**.

Management of hyperlipidemia: Hyperlipidemia, also known as hyperlipoproteinemia or high cholesterol, is a disorder characterized by abnormally high concentrations of lipids (fats) in the blood that are correlated with the development of atherosclerosis, the underlying cause of coronary heart disease (CHD) and stroke. Hyperlipidemia is caused by abnormal lipid and lipoprotein metabolism. Lipids are a group of naturally occurring fatty substances that are present in the blood and tissues of the body. They include cholesterol, cholesterol esters, triglycerides and phospholipids. Lipids are essential dietary constituents because of their important functions [13].

Treatment of hyperlipidemia involves non pharmacological options which includes, diet control, exercise and the pharmacological options which include, the use of lipid-lowering diets and drugs. However, some patients cannot tolerate the adverse effects from these oral drugs. Therefore, improvement in human diet is highly recommended for disease prevention. As a consequence, there continues to be a high demand for new oral antihyperlipidemic drugs. Management of hyper lipidemia without any side effects is still a challenge to the medical system [14].

Drug treatment should be reserved for at risk patients with diet resistant hyperlipidaemia. Commonly used drugs include statins (simvastatin, pravastatin), resins (cholecystyramine) and fibrates (gemfibrozil). Less commonly used drugs include nicotinic acid, probucol, clofibrate and colestipol. Fish oils have been advocated for the treatment of increased triglycerides (TG) but were found to raise low density lipoproteins (LDL). The statins have been used for almost a decade and have not produced untoward effects. Furthermore they are more efficacious than existing therapies and have a higher degree of patient acceptability [15].

Therapy should be selected on the basis of the predominant lipoprotein abnormality. Total cholesterol is the most easily measured lipid and reflects LDL. Triglycerides should be measured only following an overnight 14 hour fast and is rarely treated in isolation except at very high levels (> 10mmol/L). Patients with low (< 1mmol/L) HDL cholesterol levels are at increased risk of CHD. Diabetics with elevated TG and cholesterol with reduced HDL are best treated with gemfibrozil. Opinions vary with regard to the threshold for commencing drug therapy. Cholesterol greater than 5.5mmol/L in those with established CHD and greater than 6.5mmol/L in high risk middle-aged men can be justified [16].

Hence, to reduce the amount of side effects caused by these drugs, newer drugs have to be screened. To evaluate the drugs various *in vitro* and *in vivo* methods are used. Evaluation of antihyperlipdemic drugs requires induction of hyperlipdemia in various animals like rats, mice, rabbits etc. induction of hyperlipidemia is done using various animal models which are discussed in this review. Experimental hyperlipdemia can be successfully induced using models discussed below.

TABLE 1: PLANTS WITH HYPOLIPIDAEMIC AND ANTIHYPERLIPDAEMIC ACTIVITY

Sl. No.	Name of Plant	Family	Common/ Indian vernacular names	Plant parts
1	*Aegle marmelos*	Rutaceae	Beal fruit, bilwa	Fruits
2	*Agave veracruz*	Amaryllidaceae	American aloe, barakhawar	Roots, leaves, gum
3	*Allium cepa*	Lilliaceae	Onion, piyaj, palandu	Bulbs
4	*Aloe barbadensis*	Lilliaceae	Ghee kumar, gwarpatha	Leaves
5	*Bambusa arundunacea*	Graminae	Bamboo vamsha	Leaves
6	*Bosswellia serrata*	Burserraceae	Salai guggal	Gum
7	*Brassica vercapitata*	Cruciferae	Cabbage	Oil
8	*Cajanus cajan*	Fabaceae	Red gram	Seeds
9	*Capparis decidua*	Capparaceae	Karli, tint	Leaves, fruits and stems
10	*Capsicum frutescens*	Solanaceae	Chillies	Fruits
11	*Carum capaticum*	Umbelliferae	Jowan, ajowan	Fruits, roots
12	*Celastrus paniculatus*	Celastraceae	Khunjri, kusur	Seed oil, barks, roots and fruits
13	*Curcuma amada*	Zingiberaceae	Mango ginger, haridra	Rhizomes
14	*Cyamopsis tetragonoloba*	Leguminosae	Guar, gwar	Seeds
15	*Emblica officinalis*	Euphorbiaceae	Amla, amlki	Dried fruits, Seeds, leaves
16	*Eugenia cumini*	Myrtaceae	Jamun	Seeds
17	*Inula racemosa*	Compositae	Puskarmul	Roots
18	*Juglans regia*	Juglandaceae	Walnut, akhrot	Kernel, oil
19	*Medicago sativum*	Papilionaceae	Alfalfa	Seeds
20	*Momordica charantia*	Cucurbitaceae	Bitterground,	Fruits
21	*Musa saspientum*	Musaceae	Banana, kela	Roots, Stems, Flowers, Fruits
22	*Nepeta hindostana*	Labiatae	Billiola, badranj boya	Whole plant
23	*Phaseolus aureus*	Fabaceae	Green gram	Seeds
24	*Phaseolus mungo*	Fabaceae	Black gram	Seeds
25	*Picrohiza kurroa*	Scrophulariaceae	Kulki, kataki	Roots
26	*Piper nigrum*	Piperaceae	Golmirch, kalimich	Leaves
27	*Pisum sativum*	Papilionaceae	Gardenpea, matar	Seeds
28	*Pterocarpus marsupium*	Papilionaceae	Indian malabarkino	Gum and leaves
29	*Saussuraea lappa*	Asteraceae	Kustha, Kut	Roots
30	*Terminalia arjuna*	Combretaceae	Arjun	Barks

TABLE 2: DRUGS USED IN DIFFERENT TYPES OF HYPERLIPDEMIA

Hypercholesterolaemia: The statins, pravastatin (Lipostat) and simvastatin (Zocor) are first choice. Alternatives are bile acid resins such as cholecystyramine (Questran).
Mixed hyperlipidaemia: The statins or alternatively fibrates such as (elevated cholesterol and TG) gemfibrozil (Lopid) may be used.
Hypertriglyceridaemia: Use fibrates such as gemfibrozil as first line therapy, (elevated TG) alternatively use the statins.

Cholesterol-diet induced atherosclerosis in rabbits and other species: Rabbits are known to be susceptible to hypercholesterolemia and arteriosclerosis after excessive cholesterol feeding. Therefore, this approach has been chosen by many authors to study the effect of potential anti-arteriosclerotic drugs.

Several modifications of the method have also been done in which different experimental animals are used like Cockerels, turkeys, pigeons, Japanese sea quails, rats, mice, hamster, guinea pigs, chimpanzee, the baboon and the rhesus macacus.

Hereditary hypercholesterolemia in rats: A strain of genetically hypercholesterolemic rats (RICO) is used to induce experimental hyper-lipidemia. In contrast to Zucker-rats, these animals are normotriglyceridemic and non-obese. The hypercholesterolemia of the RICO rat is related to a decreased rate of catabolism of chylomicrons and LDL, but more specifically to an excessive production of these two types of lipoproteins. This strain has been proposed to study hypolipidemic drugs, particularly those designed to decrease the plasma concentrations of chylomicrons and LDL.

Hereditary hyperlipemia in rabbits: A strain of rabbits with hereditary hyperlipemia (WHHL rabbit) has been used by several scientists to study development of atherosclerosis, as well as for histological and functional changes of the aorta.

At the age of 10–14 months homozygous animals exhibit an atheromatous plaque, distributed heterogeneously over the luminal surface of the aorta. Serum cholesterol is increased up to 400–600 mg/dl. The increased levels of LDL have been studied in detail using this model.

Transgenic animals: Several transgenic animals as disease model were created during the last decade, mice, rats and rabbits. The widely used model is the Apo E knockout mouse originally created by Nubuyo Maeda, University of North Carolina, Chapell Hill, NC. These Apo E knockout mice have spontaneously elevated plasma cholesterol levels, and develop atherosclerosis even on regular chow within 3–4 months.

The time dependent progression of atherosclerosis leads to lesions similar in histopathology to those observed in humans. This animal model is used as background for atherosclerosis research and target validation.

Triton-induced hyperlipidemia: The systemic administration of the surfactant Triton WR 1 339 (isooctyl-polyoxyethylene phenol) to mice or rats results in a biphasic elevation of plasma cholesterol and triglycerides. In this method, Male Sprague Dawley or Wistar rats weighing 200–350 g are starved for 18 h and then injected intravenously with 200 mg/kg. Serum cholesterol levels increase sharply 2–3 times after 24 h.

Fructose induced hypertriglyceridemia in rats: In this method the rats are switched from a diet low in carbohydrates and high in protein to a high intake of fructose and develop an acute hypertriglyceridemia. Compounds are tested for inhibition of this phenomenon [17].

Cyclosporin A-induced Hyperlipidemia: Cyclosporin A (CsA) is an immunosuppressant drug widely used in organ transplant recipients and patients with auto-immune disorders.

Long-term treatment with CsA is associated with hyperlipidemia and an increased risk of atherosclerosis [18].

TABLE 3: ANIMAL MODELS FOR HYPERLIPIDEMIA

Animal model	Type of animal used
Cholesterol-diet induced atherosclerosis in rabbits and other species	Rabbits, Cockerels, turkeys, pigeons, Japanese sea quails, rats, mice, hamster, guinea pigs, chimpanzee, the baboon and the rhesus macacus.
Hereditary hypercholesterolemia in rats	Rats
Hereditary hyperlipemia in rabbits	Rabbits
Transgenic animals	Mice
Triton-induced hyperlipidemia	Rats
Fructose induced hypertriglyceridemia in rats	Rats
Cyclosporin A-Induced Hyperlipidemia	Rats and mice

CONCLUSION: This review gives an insight of the frequently used animal models used for the evaluation of hypolipidemic and antihyperlipidemic drugs. Most of the herbal drugs lack scientific and pharmacological data in relation with the animal activity. Therefore, more emphasis should be given on the evaluation of the drugs for their safe use. This article focuses on the *in vitro* methods of evaluation. Out of the methods explored, the high fat diet induced model is most frequently used.

ACKNOWLEDGEMENT: The authors are thankful to MMU, Mullana for their unflinching support throughout the writing of this paper. We deeply acknowledge timely support and valuable suggestions from the Rayat and Bahra College of Pharmacy, Kharar.

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How to cite this article:
Kaushik V, Shivali and Saini V: Hyperlipidemia: Its management and induction. Int J Pharm Sci Res 2014; 5(8): 3152-56.doi: 10.13040/ IJPSR.0975-8232.5(8).3152-56