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Review Article

DIFFERENT CHEMICAL, BIOLOGICAL AND MOLECULAR APPROACHES FOR ANTI-HYPERLIPIDEMIC THERAPY WITH SPECIAL EMPHASIS ON ANTI-HYPERLIPIDEMIC AGENTS OF NATURAL ORIGIN

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ABSTRACT

Elevated levels of serum cholesterol leading to atherosclerosis can cause enhanced risk factors for coronary artery diseases (CAD). Reduction in serum cholesterol levels reduces the risk of CAD, substantially. Medicinal chemists all around the world have been designing, synthesizing, and evaluating a variety of new bioactive molecules for lowering lipid levels. Even so, some patients in the high risk category fail to achieve recommended cholesterol levels and to bring about regression of the already existing atherosclerotic lesions with currently available medications. Thereby, development of novel approaches to battle the world epidemics of hyperlipidemia remains relevant. In addition to existing treatments, some other recent chemical, biological and molecular approaches for the development of novel antihyperlipidemics are discussed herein. But none of these approaches are currently approved for use in humans. Several ongoing agents are in their different stages of clinical trials, in expectation of promising antihyperlipidemic drugs.

Keywords: Antihyperlipidemia, Atherosclerosis, Coronary heart diseases (CHD), Statins and Nonstatins.

INTRODUCTION

In most of the industrialized nations, hyperlipidemia and thereby atherosclerosis is the leading cause of cardiac illness and deaths [1]. About 70% of total cholesterol in the human is synthesized *de novo* and the remaining is supplied by absorption from diet (0.3-0.5 gm/day) [2]. In 1984, it was demonstrated for the first time that there exists a link between serum cholesterol levels and risk to coronary heart disease (CHD) [3]. A 1% drop in serum cholesterol reduces the risk for CHD by 2% [4]. The primary cause of CHD is atherosclerosis, a chronic disease, characterized by the accumulation of lipids and fibrous connective tissue on the arterial wall, resulting in a narrowing of the vessel lumen and ultimately hardening of the vascular system, which may lead to ischemic heart disease, myocardial infarction, and stroke [5].

Hypercholesterolemia is generally, associated with an increase in plasma concentration of LDL and VLDL. Lowering of elevated levels of LDL cholesterol can slow the progression of atherosclerotic lesions. The angiographic studies have established the fact that one of the risk factors for atherosclerotic cardiovascular disease comprises low levels of high-density lipoprotein (HDL) cholesterol concentration and shows an inverse correlation. Another study showed that a 10 mg/dl increases in HDL cholesterol were associated with a 19% decrease in coronary artery disease death and a 12% decrease in all causes of mortality [1,2].

Several other methods are presently practiced to control blood cholesterol levels. These include balance of dietary fats; HMG-CoA reductase inhibitors, bile acids sequester, fibrates, cholesterol absorption inhibitors etc. But no class of drugs is as widely prescribed or as heavily studied as those that inhibit 3-hydroxy- 3-methylglutaryl coenzyme A (HMG-CoA) reductase ("statins") [2]. The reasons for extensive use of statins is their favorable efficacy and safety profiles and their benefit in reducing the risk for cardiovascular events (CVEs) and death in patients with or without established cardiovascular disease (CVD). They are also the recommended first-line treatment for hyperlipidemia and for the prevention of CVD by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) [6]. Pitavastatin calcium is the statin most recently approved by the US Food and Drug Administration and is the seventh statin available in the United States [7].

Although a range of synthetic drugs are available as anti-hyperlipidemic drugs, many of them do not fulfill all requirements and their numerous side effects and potential interference with drug metabolism are common. Thus, the search is on for better medicaments especially from the plant kingdom which might provide a useful source for therapy or alternatively as simple dietary adjuncts to existing therapies [2]. Many such medicinal plants have been studied in this context.

Hyperlipidemia and atherosclerosis

Different stages in progression of atherosclerosis [8].

Different stages of atherosclerosis from the normal, healthy coronary artery (stage I) until the final stage (stage V) leading to its complete blockage resulting in heart attack are described in Fig 1.

Stage I (Normal Artery)

The inner lining of the normal coronary artery is smooth and free of blockages or obstructions.

Stage II (Fatty Streak)

However, with increasing age lipids or fatty substances (cholesterol and triglycerides) are deposited as fatty streaks which are only minimally raised and do not produce any obstruction or symptoms. This is just the beginning of atheroma.

Stage III (Early Atheroma)

Further increase in built up of fatty layers, atheroma, begins to encroach the inner channel which starts interfering with the free blood flow through a coronary artery, thereby exposing the person to more risk of coronary artery disease.

Stage IV (Plaques Formation)

With fibers beginning to grow in the fatty layers of the atheroma, the blockages harden into plaques, which increase the encroachment in the inner channels of the coronary artery.

This encroachment may be up to 50% or more of its diameter and leads to obstruction sufficient to decrease the blood flow of heart muscle, even in the time of its increased need (exercise, emotional stress). This leads to elevation in blood pressure and heart rate.