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Review article

Lipid lowering agents of natural origin: An account of some promising chemotypes☆

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ABSTRACT

The role of natural products in the drug development and discovery has been phenomenal. There has been an enormous interest in exploring all possible natural sources to identify structures exhibiting pronounced hypolipidemic activity albeit with no toxicity. The present review describes the profile of some interesting naturally occurring compounds and their derivatives as potential hypolipidemic agents. Some of the interesting natural chemotypes that can control the increased levels of plasma lipids and discussed in this review are compactin, lovastatin, guggulesterone, berberine, lupeol, phytol, polyprenol, aegeline, 4-hydroxyisoleucine, α-asarone, resveratrol, esculeoside A, swertiamarin, rutin, saucerneol B, curcumin and a clerodane diterpene.

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1. Introduction

Past two decades have witnessed an explosion of knowledge in almost all the fields of science and medicine. Developments in one medical arena often have a significant impact on other disciplines. Still the unwavering search for the chemotherapeutic solutions for the various life threatening diseases seems never ending. With time, the way we live has drastically changed giving rise to long queued ailments that generations ago would have been exceptions. During the last century, asbestosis, syphilis and other malicious ailments [1,2] were referred to as lifestyle diseases that more often resulted in a slow and painful death. But today, the term is associated with illnesses and syndromes resulting from the myriad of practices related to our work and lifestyle. In the modern day life "Bad food habits and lack of exercise are the culprits" which give rise to disorders in the plasma lipid profile termed as dyslipidemia.

Dyslipidemia is a metabolic disorder which manifests itself as one or more of the following: elevated total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels or as decreased high density lipoprotein cholesterol (HDL-C) levels. This metabolic syndrome if left unchecked leads to atherosclerosis [3] and other associated complications including the development of ischemic diseases in people of all age groups [4]. The threat is visible in the form of cardiovascular (CVD), coronary heart diseases (CHD) and cerebrovascular events, that currently are the common cause of morbidity and mortality worldwide [5–7].

In the recent past decades death rate due to CVD are gradually falling in most of the developed countries due to preventive measures. On contrary, the burden of disease has risen sharply in middle-income and low-income countries where about 80% of the cases are reported [8,9]. Together CVD and CHD continue to be the leading cause of death [10]. They are more prevalent than any other non-communicable disease worldwide. The prevalence and the socio economic burden of dyslipidemia makes the cholesterol lowering and atherosclerotic drugs the top selling drugs in the world.

Global Industry Analysts, Inc. (GIA) released a report on dyslipidemia therapeutics market which estimated that global market for dyslipidemia therapeutics is going to exceed $28 billion by the year 2015. Apparently the large aging population of hypercholesterolemia patients is providing the required thrust to the growth of *anti*-dyslipidemic drug market.

2. Definition of the problem: understanding dyslipidemia

Solution to a problem comes with understanding the aspects of the problem which created it, in other words to unfold a knot it should be known that how it was tied. Biomedical studies unfolded the various aspects of dyslipidemia, which together gave birth to a small problem, now developed with time into the biggest epidemic in terms of the population affected by it. The problem starts slowly with disturbed lipid profile and ends with a sudden death. The five major components of plasma lipoproteins are (i) Chylomicrons which carry dietary triglyceride and other fats to the liver and other tissues in the body, (ii) very low density lipoprotein (VLDL) known as the "very bad" cholesterol, that circulate through the blood giving up their triglycerides to fat and muscle tissue until the VLDL remnants are modified and converted into LDL, (iii) Intermediate density lipoprotein (IDL) that circulate and transport cholesterol and triglyceride fats throughout the body. IDLs have the ability to promote plaque formation in the blood vessels [11], (iv) Low density lipoprotein (LDL) referred to as "bad cholesterol" because they can also transport cholesterol into the artery wall, where they are retained by arterial proteoglycans and attract macrophages that engulf the LDL molecules and start the initiation of plaques, paving way for atherosclerosis progression. Over a period of time plaque ruptures and subsequent thrombosis results in the acute clinical complications of myocardial infarction and stroke, (v) High density lipoprotein (HDL) is the smallest of the all lipoprotein particles that mediate the reverse transport of cholesterol from peripheral tissues to the liver for clearance. High HDL levels are associated with low body cholesterol and decreased risk of atherosclerosis and associated CVD's thus they are considered as "good cholesterol".

The lifecycle of lipoprotein involves the three main stages of generation, their metabolism and transportation within the body. The pathways responsible for them are exogenous, the endogenous, and the reverse cholesterol transport pathway (Fig. 1) [12]. In the exogenous (dietary) lipid pathway the remnants of chylomicrons are "repackaged" into other lipoproteins, and in the endogenous pathway liver is involved in synthesizing the lipoproteins. The reverse cholesterol transport is responsible for the reverse movement of cholesterol efflux from the blood circulation to the liver. The removal of cholesterol from plasma is triggered off with the involvement of key lipoprotein HDL which acts in conjunction with the cholesterol esterifying enzymes like lecithin cholesterol acyltransferase (LCAT). LCAT converts free cholesterol to cholesteryl ester, thereby increasing the hydrophobic characteristics of cholesterol [13].

3. Currently used drugs

Present chemotherapeutic treatment of dyslipidemia comprises of various classes of compounds which chiefly include statins, fibrates, niacin, cholesterol absorption inhibitors and bile acid sequestrants. The goal of these lipid modifying drugs is to lower the LDL (bad cholesterol) and increase HDL (good cholesterol) to the recommended level. The chemical structures of the currently used pharmaceuticals are depicted in Fig. 2.

Statins, considered to be the first line treatment for dyslipidemia, have been proven to significantly reduce CVD mortality in hypercholesterolemic patients [14] (see Fig. 3). They represent one of the most important class of antihyperlipidemic drugs, exemplified by atorvastatin (**1,** trade name 'lipitor'), fluvastatin (**2,** trade name 'lescol') and rosuvastatin (**3,** trade name 'crestor') which are all well known inhibitors of HMG-CoA reductase (HMGR) [15]. Statin chemotherapy suffer with adverse side effects like muscular