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Review on Statins: Future Perspective.

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ABSTRACT

Statins are used widely for the treatment of hypercholesterolemia [5]. They inhibit HMG-CoA reductase competitively; reduce LDL levels more than other cholesterol-lowering drugs, and decrease triglyceride levels in hypertriglyceridemic patients. In this review current status of statins, structure and their role and applications is briefly discussed.

Keywords: Statins, lovastatin, Bioconversions of statins

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INTRODUCTION

Recent research in medicine has demonstrated that high levels of cholesterol in blood can lead to atherosclerosis, heart attacks, and strokes [7]. Statins is a group of drugs primarily used in lowering blood cholesterol by 20 to 60 percent. The inhibition of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase, the essential enzyme in cholesterol biosynthesis by statins was a breakthrough in the prevention of hypercholesterolemia and related diseases [14]. All natural statins have a common molecular structure, a hexahydro-naphthalene system and a hydroxy-lactone, but they differ from each other due to side chains and a methyl group around the ring. HMG-COA and statins have in common structural motif β-hydroxy-δ-lactone loop [Fig.1] which aids for its competitive inhibition of cholesterol biosynthesis pathway.

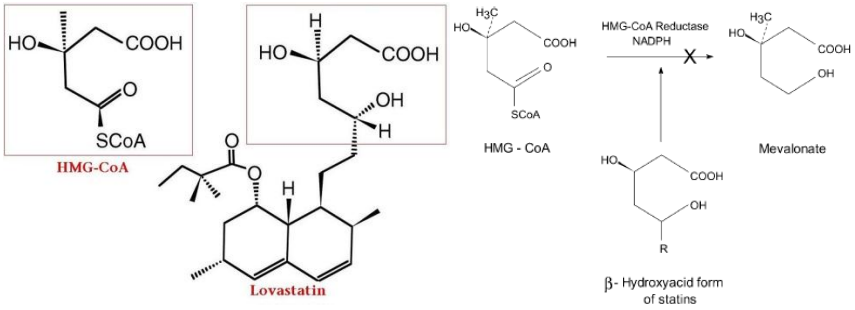
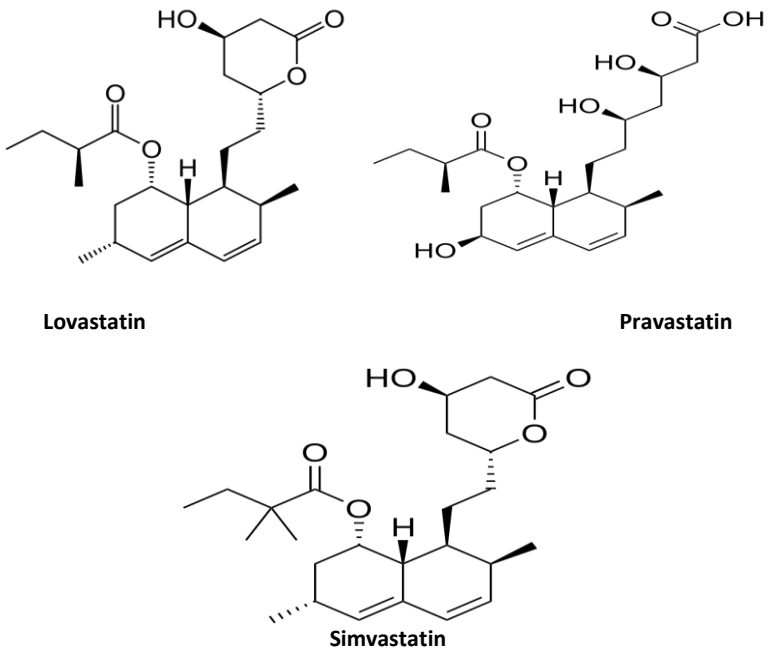


Figure 1: a)Structural similarity of HMG-CoA and Lovastatin b) Structural analogy between HMG-CoA and the β-hydroxyacid form of statins and mechanism of inhibition.

The statins differ with respect to their ring structure and substituent's. These differences in structure affect the pharmacological properties of the statins. The statins are basically classified as natural statins and synthetic statins. Natural statins have been discovered in fungal broths [4].Lovastatin and pravastatin are natural statins of fungal origin .These are of very similar chemical structure. They possess a common main polyketide portion, a hydroxyhexahydro naphthalene ring system, to which different side chains are linked at C8 (R1) and C6 (R2). Lovastatin contains a methylbutyric side chain (R1) and a 6-α methyl group (R2), which is lacking in mevastatin. Pravastatin has the β-hydroxylactone in the 6-hydroxy sodium salt form and is the C6-hydroxy analogue of mevastatin [11]. Simvastatin is derivative of lovastatin where 8-acyl moiety is 2, 2-dimethylbutryl. The structures of these statins are elucidated Fig. 2 a,b,c below.



Lovastatin **Pravastatin**

Simvastatin

Figure 2: a, b, c Natural Statins Lovastatin, Pravastatin and Simvastatin.

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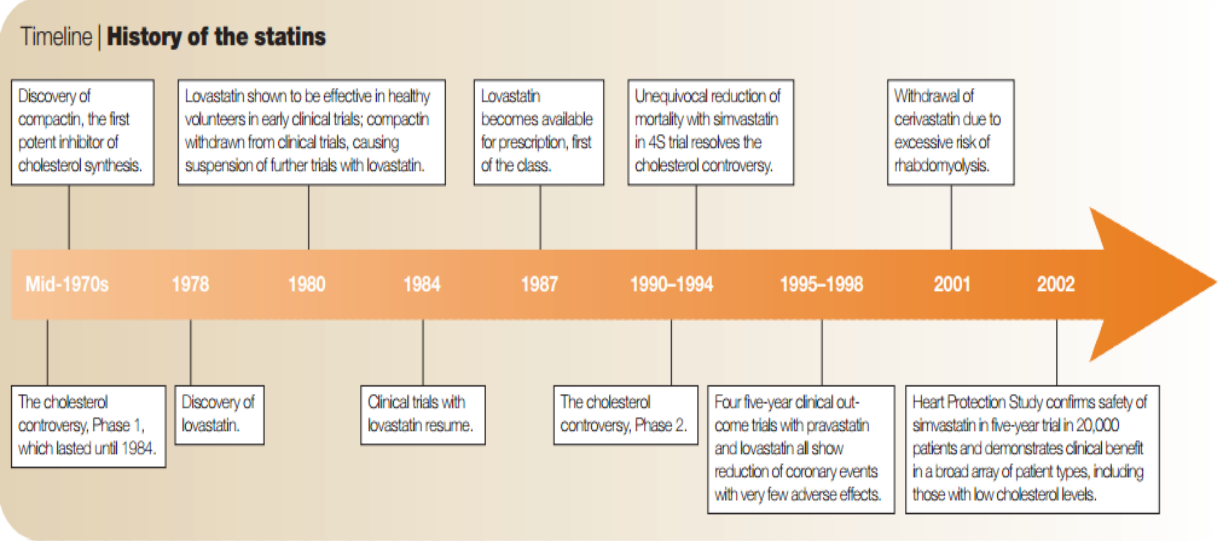

In the 1950s and 1960s, it became apparent that elevated concentrations of plasma cholesterol were a major risk factor for the development of coronary heart disease, which led to the search for drugs that could reduce plasma cholesterol. One possibility was to reduce cholesterol biosynthesis, and the rate-limiting enzyme in the cholesterol biosynthetic pathway,3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, was a natural target.

Triparanol, which inhibits a late step in the pathway, was introduced into clinical use in the mid-1960s, but was withdrawn from the market shortly after because of the development of cataracts and various cutaneous adverse effects. These side effects were attributable to tissue accumulation of desmosterol, the substrate for the inhibited enzyme.

In many countries one or both of the first two statins —Lovastatin and Simvastatin — are now available as generic products, which should increase access to statin therapy in health care systems with limited resources. Compactin and lovastatin are natural products. Pravastatin is derived from compactin by biotransformation and Simvastatin is a semi synthetic derivative of lovastatin. All other statins shown are totally synthetic.

Out of all statins Lovastatin isolated from fungal cultures of *Aspergillus' terreus* has proved to be potent inhibitor of HMG-CoA reductase and an effective hypocholesteromic agent in human [1]. Many microorganism *Monascus sp, Aspergillus flavus , Penicillium purpurogenum ,Pleurotus sp, Trichoderma viride* [2-3, 10-13] have been reported for producing Lovastatin. Simvastatin a more potent drug than Lovastatin is obtained by direct methylation of Lovastatin called as semi-synthetic Lovastatin derivative. The chemical transformations of side chain ether analogous of Lovastatin are reported to be weaker inhibitors of HMG-CoA reductase than corresponding ester analogues indicating carbonyl group role in determining intrinsic inhibitory potency and substitution of 4-fluro group on aromatic moiety had influenced the increase in potency[15].

The synthetic statins atorvastatin, fluvastatin, and cerivastatin [Fig.3a,bc,d] has in common only HMG CoA-like moiety (responsible for HMGCoA reductase inhibition) with natural statins and are quite different from them. Statins with appropriate hydroxyl or other gropu could improve their potency. Synthetic statins are obtained in hydroxy acid form. Fluvastatin, derived from mevalolactone, was the first entirely synthetic statin available, while atorvastatin and rosvastatin [7], pyridine derivatives, are a new generation of highly purified statins. The most recent statin is pitavastatin Fig.3e, marketed as Livalo from Kowa Pharmaceuticals and FDA approved for use in the USA in 2009. This is claimed to be the most effective statin yet for blocking cholesterol production, with fewer side effects and drug metabolism interactions. The relative potency of pitavastatin, the newest, has not yet been fully established. With the recent elucidation of the structures of the catalytic portion of human HMGCR enzyme, complexed with six different statins by a series of x-ray crystallography studies, new possibilities have opened up for further rational design and optimization of even better HMGCR inhibitors.

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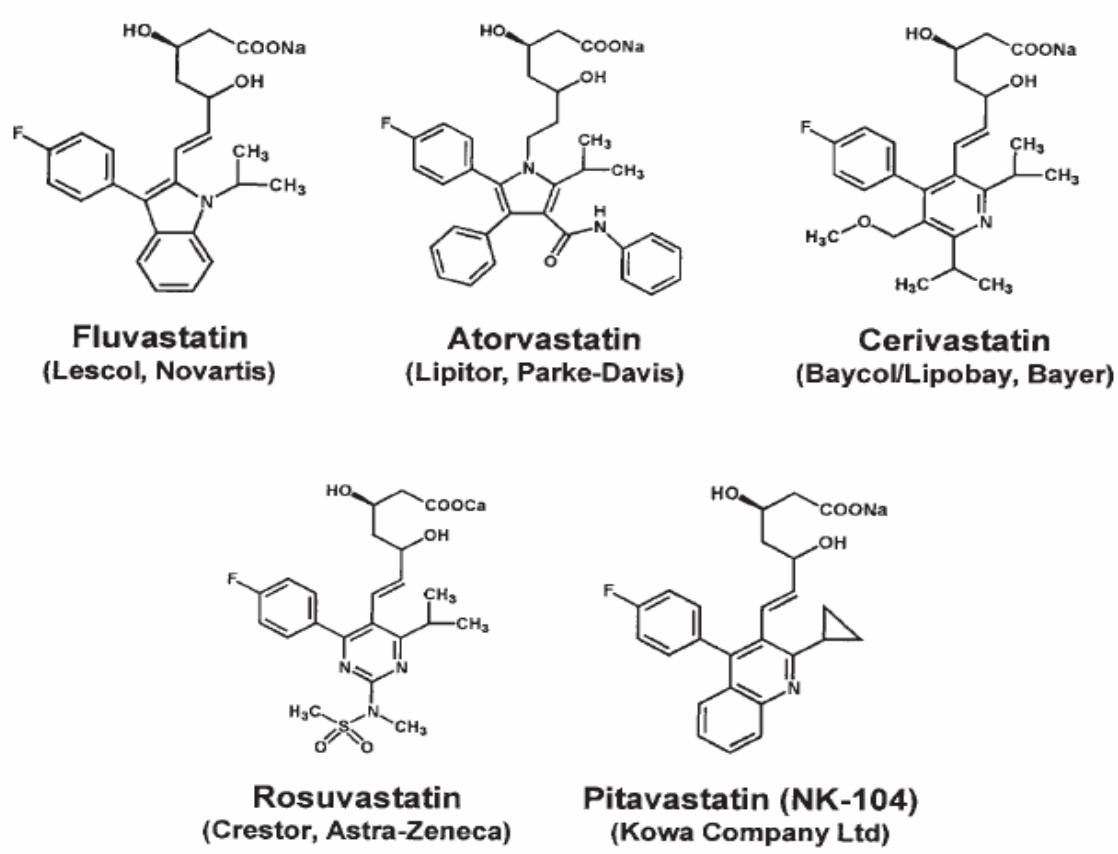
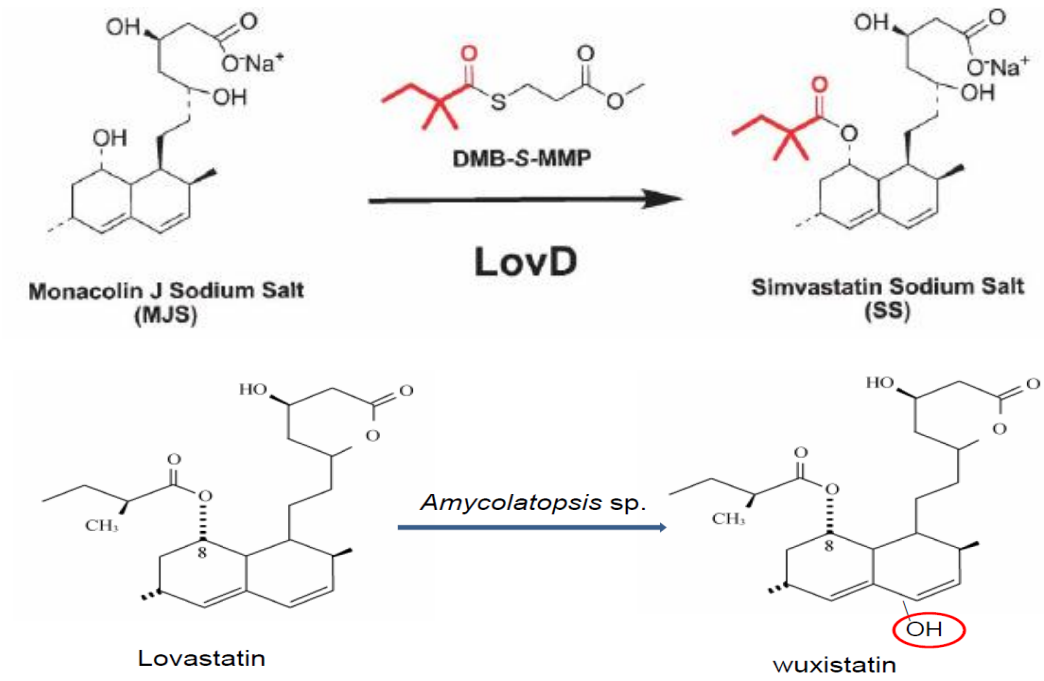


Figure 3: a,b,c,d,e :Synthetic statins Fluvastatin, atrovastatin, erivastatn,Rosvastatin and Pitavastatin

Biotransformation are efficient and play a key role in structural modifications of naturally occurring complicated organic compounds imparting high stereo and region-selectivity and also ecofriendly. Generally biotransformation can successfully introduce functional group like OH more easily compared to chemical approach. Conversion of Monacolin salt to Simvastatin by LovaD enzyme [15], Lovastatin to Wuxistatin [16] and Mevastatin to pravastain [17] by Mucor is good examples of bioconversion with enhanced potency.



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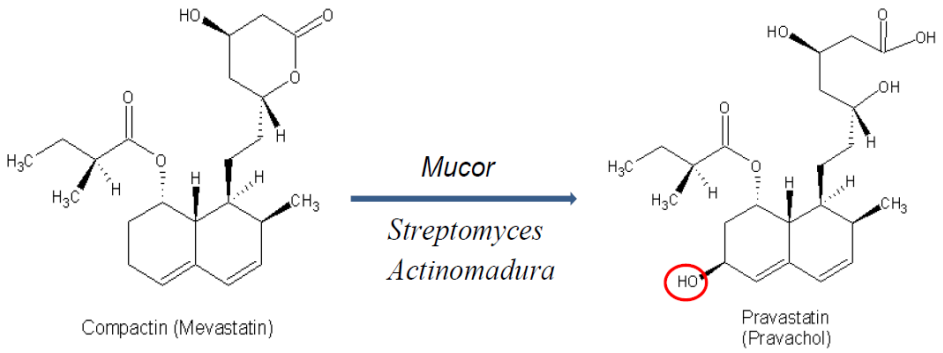

APPLICATIONS

Too much cholesterol in the blood can cause a buildup of plaque on the walls of the arteries and can eventually cause the arteries to narrow or harden. Sudden blood clots in these narrowed arteries can result in a heart attack or stroke. According to the Centers for Disease Control and Prevention (CDC), heart disease is the leading cause of death for both women and men in the United States. Statins have been shown in numerous studies to lower the risk of heart disease and stroke (FDA, 2010). The marked lipid-lowering effects of statins have led to a substantial reduction in coronary events, as revealed by clinical, epidemiological, and pathological studies. In addition to reducing the risk of cardiovascular morbidity and mortality, statins can prevent stroke and reduce the development of peripheral vascular disease. Statins have biological effects beyond the level of LDL-cholesterol reduction, including antithrombotic and anti-inflammatory effects [7], which may offer protection against atherosclerotic plaque growth. Other potential uses of statins may include hypertension, osteoporotic fractures, ventricular arrhythmia, and immune response [9, 13]. Further thorough investigations are nevertheless required before any clinical applications of statins .Currently there are five FDA-approved statins of proved effectiveness and safety (lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), and research into the pharmacological regulation of many diseases is ongoing. Statins clearly represent the first-line drug therapy for cholesterol lowering in the prevention of coronary artery disease. Women's Health Initiative (WHI) and other studies reported that certain statins protect against breast cancer and also statin use might help prevent gallstones from forming, mostly in diabetic women.

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