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PRODUCTION OF LOVASTATIN FROM FUNGAL SOURCES AND ITS MEDICAL APPLICATIONS

Hannana Maryam, Sana Maqsood, Zuriat Jabbar and Sikandar Ali*

Institute of Industrial Biotechnology, GC University Lahore, Pakistan.

***Corresponding Author: Dr. Sikander Ali**

Institute of Industrial Biotechnology Govt. College University, Lahore.

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ABSTRACT

Lovastatin and other natural as well as synthetic statins are considered as wonder drugs for treatment of hypercholesterolemia. Statins are produced by many fungal sources mainly from *Aspergillus terreus* on industrial scale. Lovastatin lowers blood cholesterol levels dramatically by inhibition of hydroxymethyl glutaryl-coenzyme A (HMG-CoA) reductase which is enzyme required for catalyzing rate limiting step for de novo cholesterol synthesis. This competitive inhibition is due to structural similarity between HMG-CoA and acid form of lovastatin. Lovastatin possess a hydroxyl hexahydro naphthalene ring which is polyketide chain to which different side chains are attached. Lovastatin synthesis starts from linkage of acetate units in head to tail fashion establishing main polyketide chain. First intermediate formed during synthesis is monacolin L which is then turned into monacolin J by hydroxylation which in turn gets converted into lovastatin. Molecular studies revealed that genetic cluster involved in biosynthetic pathway includes genes LovB, LovC,LovA,LovD,LovF and Lov H. Industrially lovastatin is produced by liquid submerged fermentation but now a day's use of solid state fermentation is gaining importance. Lovastatin serves as drug of choice for cardiovascular diseases like peripheral vascular disease, atherosclerotic plaque, peripheral arterial disease, cerebro vascular disease, sepsis and ischemic heart disease. It also shows many other biological effects beyond just lowering cholesterol level that include its effects on bone maturation, renal disorders treatment, anticancer and metabolic syndrome.

KEYWORDS: Lovastatin, hydroxymethyl glutaryl-coenzyme A, *Aspergillus terreus*,submerged fermentation, solid state fermentation.

INTRODUCTION

Cholesterol is an organic substance produced by complex metabolism and is essential component of cell membranes.[1] It serves as precursor for production of bile, vitamins, steroids and VLDL (very low density lipoproteins) that helps in transfer of fats to peripheral tissues for storage or metabolism purpose.[2,3] There are various types of cholesterols in body, some are considered beneficial for health such as high density lipoproteins (HDL) while some are bad for health such as low density and very low density lipoproteins (LDL and VLDL). Abnormal levels of these cholesterols cause various cardio vascular problems including atherosclerosis, hypercholestrolermia, atheroma, myocardial infarction, coronary heart disease.

Hypercholesterolemia, which is cholesterol deposition in blood vessels, is leading cause of cardio vascular diseases around the globe. Blockage of vessels due to cholesterol plaques leads to myocardial infarction and death in many cases. World Health organization reported deaths of around 17 million people due to Cardio Vascular Disorder (CVD) in year 2008 and predicted that deaths of over 23.6 million people can occur by the end of year 2030 which is a constant threat for human population.

Generally, in a person with normal metabolism, cholesterol derived from diet is only one third while remaining is produced by intracellular precursors in other organs mainly liver.[2]Hencecontrolling cholersterogenesis is an important method for lowering plasma cholesterol levels.[4] Endogenous cholersterogenesis follows mevalonate pathway involving more than 25 enzymes. The main step in cholesterol biosynthetic pathway is formation of mevalonate by HMG-CoA conversion by HMG-CoA reductase (Fig.1).

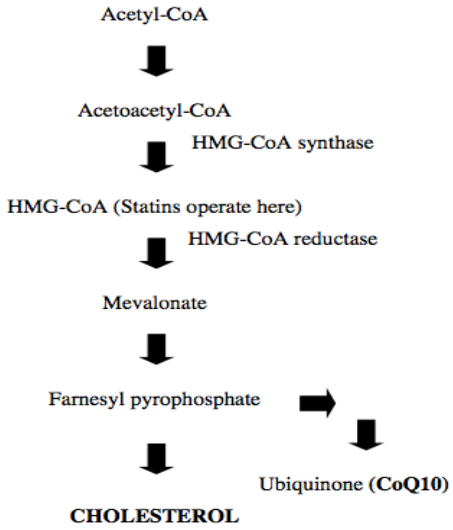

Figure 1: Cholesterol synthesis

Statins are cholesterol loweing drugs which control endogenous synthesis of cholesterol by inhibiting conversion of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) to mevalonate.[5] Statins are naturally synthesized compounds that are produced from several filamentous fungi as metabolite of their secondary metabolism.[6] These are group of drugs that lower plasma cholesterol levels by decreasing low density lipoproteins and slightly increasing high density lipoproteins.[7]

Depending upon their synthesis, statins can be classified into three basic classes.[4] 1. Natural statins which can be synthesized by natural fermentation exploiting fungal sources, examples are paravastatin and lovastatin . 2. Semi synthetic statins: produced by alkylation of lovastatin and it includes simvastatin. The dimethylbutyrate moiety is formed by conversion of methylbutyrate chain.[8] Synthetic statins: There structure is different from natural statins except HMG-CoA like moiety which is responsible for inhibition of HMG-CoA reductase.[4] Examples of chemically synthesized statins include atorvastatin , fluvastatin and cerivastatin and rosuvastatin.

The first reported statin was discovered in 1976 by Akira endo, a Japanese microbiologist, and was produced from *Penicillum citrinum*.[9]. However when subjected to clinical trials,it showed side effects and thus did not gain approval.Scientists from Merck and co showed interest in this newly discovered compound and started their own fungal screenings. They produced another similar compound, named lovastatin, isolated from *Aspergillus terreus*.[2]

Lovastatin is potent inhibitor of HMG-CoA reductase which catalyzes rate limiting step in cholesterol synthesis.[10] Lovastatin previuosly known as mevinolin is first statin that acquired approval from Food and drug administration(FDA) authority.[4] It is produced on industrial scale by submerged fermentation but can be produced by advanced techniques like solid state fermentation.Lovastatin is an excellent cholesterol lowering drug which is effective in many diseases like atherosclerosis,cerebro vascular disease,sepsis, peripheral artery disease and other cardio vascular disaese.[10] It has also shown novel applications other than cholesterol lowering effect that is alzhemer's disease, bone fracture, metabolic syndrome and multiple sclerosis.[11]

HISTORY OF LOVASTATIN

The first ever statin was obtained from fungus, *Penicillium citrinum*, by Japanese microbiologist Akira endo in 1970.He was screening fungus for finding antimicrobial agents and that led to discovery of first statin named mevastatin.In 1976, pharmaceutical company Merck and co showed keen interest in endo discovery and they produced another important statin.It was produced from another fungus ,*Aspergillus terreus*,and known as lovastatin.[2]

Endo and co researchers also worked further on statins and they independantly produced same product from another fungus called *Monascus ruber* but this strain could not be used for production of lovastatin on industrial scale as it produces product in low amount.Lovastatin was tested in animals and then in healthy volunteers,it extraordinarily reduced blood cholesterol levels in healthy volunteers and showed no obvious side effects.Hence, lovastatin became first statin to be approved by FDA USA in 1987 after successful clinical trials with market name Mevacor.[7] Dr Endo was awarded Japan prize in 2006 and the Lasker foundation awarded him with Clinical and Medical Research Award for his tremendous contribution towards the discovery of statins.

Merck proceeding further in their work produced semisynthetic derivative of lovastatin,simvastatin, which is second leading statin in market after lovastatin.Merck and endo's dicoveries led to draw other pharmaceutical companies towards the production of synthetic statins as well.That resulted in development of first synthetic statin,fluvastatin(Sandoz AG lescol) followed by atrovastatin with trade name Lipitor that later became the best selling drug.

STRUCTURE OF LOVASTATIN

Lovastatin posesses hydroxy-hexahydro naphthalane ring system which forms polyketide portion of lovastatin. Different side cahins are linked to this ring system at C6 (6 alpha methyl group) site and C8 (methylbutyric group) site. (Fig. 2) Several metabolites of lovastatin and its derivatives have been isolated and characterized. Composition at C8 is different in Monacolin X and M while in monacolin L and monacolin J ,there is no methylbutyric side chain. It is substituted by hydroxyl group in monacolin J and by hydrogen in monacolin L.[12,13,14]

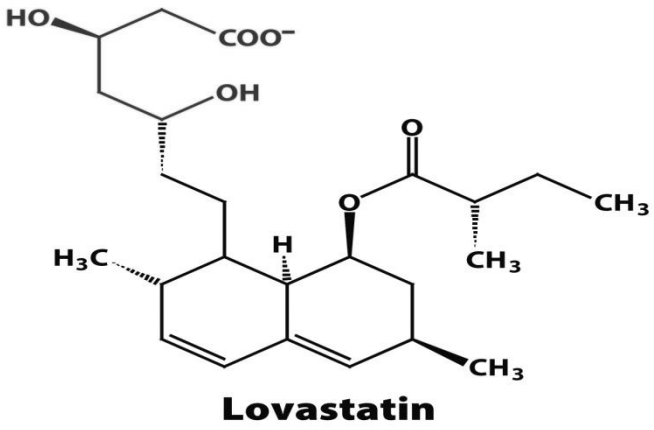

Figure 2: Structure of lovastatin

Properties

Lovastatin is nonhygroscopic crystalline powder which is white in color with no solubility in water but slight solubility in organic solvents like methanol, ethanol and acetonitrile.The methyl group present at C6 side chain derives from methionine,a process which frequently occurs in fugal metabolism just before the closing of ring.[15] The oxygen atoms are inserted later using deoxygenated precursor by aerobic oxidation in main chain.[16] Experimental evidences showed that biosynthesis of lovastatin using *A.terreus* strain as source involves 18 proteins.[17] Out of these 18 proteins it is found that 9 are enzymes, 3 are involved in transportation , 2 proteins perform regulatory role , 2 unknown proteins, and 2 major synthases that are Lovastatin Diketide Synthase (LDKS) and Lovastatin Nonaketide Synthase (LNKS).[17]

BIOSYNTHESIS

Studies carried out with *M.ruber* showed that there are two main intermediate metabolites in lovastatin biosynthetic pathway which are monacolin L and monacolin J.[5] Monacolin L is first intermediate which is synthesized from 9 acetate molecules and then by hydroxylation it transforms into monacolin J.18 oxygen atoms incorporate during hydroxylation reaction through monoygenase system involving P-450 cytochrome present in cell free extract of *M.ruber*.[18] Further experiments revealed conversion of monacolin J to lovastatin.[14] (Fig.3)

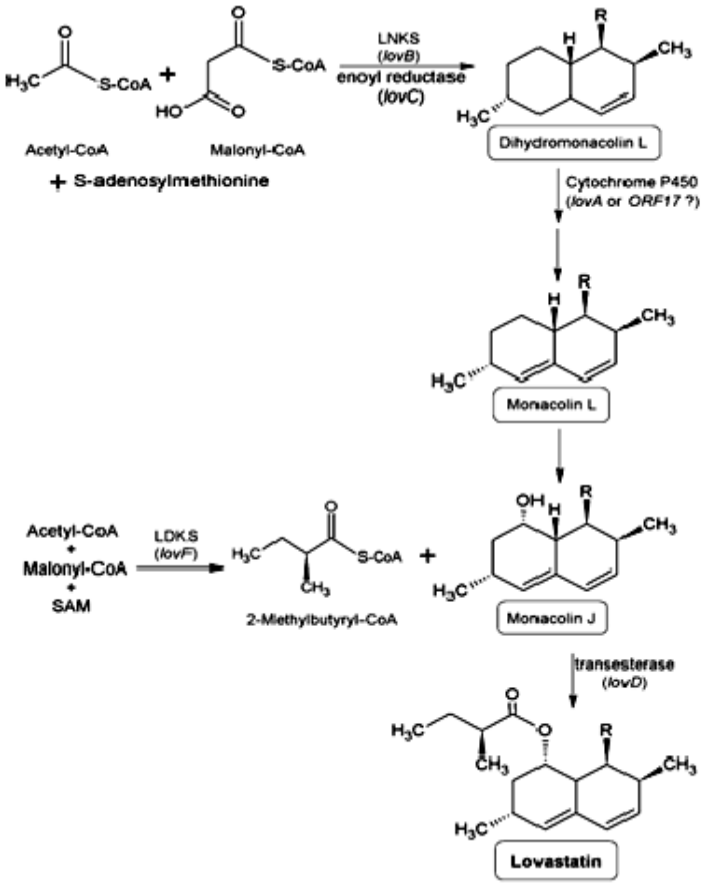

Figure 3: Lovastatin biosynthesis

Early investigations done on *A.terreus* revealedthat biosynthesis of lovastatin involves specific precursors.[19,15] It indicated that biosythetic pathway of lovastatin starts with formation of polyketide chain by head to tail linkage of acetate units.The methyl group is inserted in ring before closure and this methyl group is derived from methionine as occurs during secondary metabolism of many fungi.[15]

More recent studies carried out in *A.terreus* has shown enzyme kinetics along with genetic expression and regulation during lovastatin biosynthesis.Lovastatin biosynthetic pathway is related to approximately 18 genes which are arranged into clusters of 64 kb.[20] Pioneering genetic research indicated the mechanisms involved in lovastatin biosynthesis,particularly with respect to two polyketide chains.It is revealed that multifunctional polyketide synthase comprised of lovastatin nonketide synthase(LNKS) and lovastatin diketide synthase(LDKS).LNKS is involved in cyclization of main polyketide chain to form hexa hydro naphthalene ring system.Initially lovastatin was predicted to consist of six active sites; ketoreductase ,malonyl-CoA:ACP acyltransferase, methyltransferase enoylreductase ,acyl carrier protein, and condensation domain .Later on another site, ketosynthase was also demonstrated so now there are seven active domains.[21]

Lovastatin diketide synthase (LDKS) which is encoded by LovF also contains seven catalytic sites which are similar to active domains of lovastatin nonketide synthase.Methylbutyryl side chain transfer to monacolin J occurs with the involvement of lovastatin diketide synthase.[22] The LNKS is product of LovB gene,it catalyzes the reactions of first part in biosynthetic pathway of lovastatin by interacting with LovC resulting in formation of dihydromonacolin L.[20] Further two steps are carried out by LovA leading to formation of monacolin J by carrying out conversion of one intermediate to another .Last step is formation of lovastatin by monacolin J catalyzed by LovD encoded enzyme transferase.[20] (Fig.4)

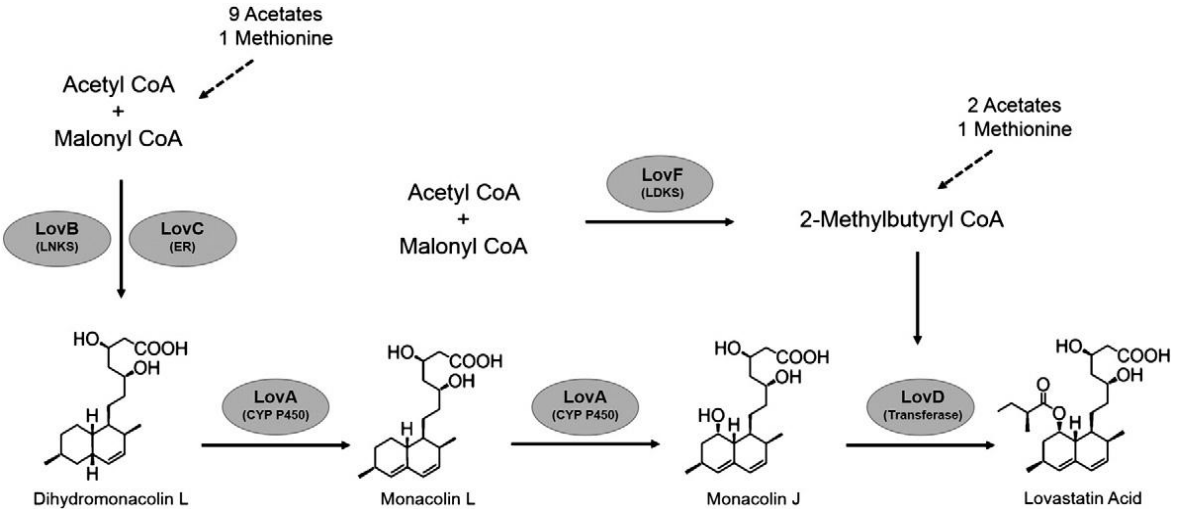

Figure 4: genetic cluster of lovastatin

Thus all these researches and experiments revealed that genes LovC, LovD, LovF , Lov H and LovE have central role in biosynthetic pathway of lovastatin.The lovastatin biosynthesis cluster also contains LovE and LovH that encode transcription factors for regulatory proteins with binuclear ZN++ finger motifs known to bind DNA.It is supposed that lovastatin biosynthesis is regulated at transcriptional level by Lov E.The overexpression and deletion of these transcription factprs cause reduction and increase in production of lovastatin. It is concluded that advances in gene cloning have allowed identification of genes and enzymes involved in synthesis of lovastatin and their effects on production as hypothesized in investigations carried out earlier.[23]

MECHANISM OF ACTION

Lovastatin and related compounds are synthesized as predrugs that are combination of β-hydroxyacid acid form and lactone ring. This lactone ring is then transformed into β-hydroxyacid form in vivo.[2] The hypocholesterolemic effect of statins is carried out by a mechanism which is inhibition of HMG-CoA reductase by competitive mechanism.This inhibition occurs due to same structures of HMG-CoA and β-hydroxyacid form of statins. The affinity of statins for reductase is several times greater than affinity of HMG-CoA intermediate. The statin occupy active site of enzyme thus blocking site for access by substrate of enzyme.The binding of statin with enzyme is due to van der walls interactions between enzyme and its inhibitor.[24] Due to this competitive inhibition of reductase,conversion of HMG-CoA to mevalonate does not occur which is essential building block for cholesterol biosynthesis.This results in lowering of cholesterol level by inhibiting its synthesis.

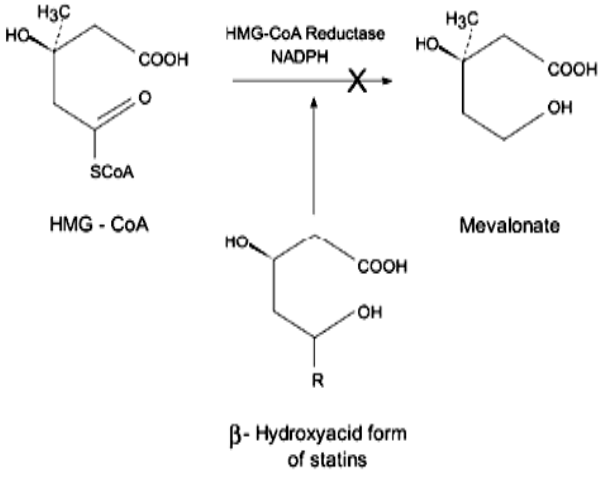

Fig 5: Mechanism of action

The cholesterol lowering effects of statins begin to appear only few days after start of therapy.It was observed that 40 mg lovastatin causes mean reduction of 30% reduction in total plasma cholesterol level, 40% for LDL cholesterol ,35% for VLDL cholesterol and 25% reduction in levels of triglycerides while increasing HDL cholesterol levels which is good for health by a factor of 10%.[3]

COMMERCIAL PRODUCTION OF LOVASTATIN

The production of lovastatin on industrial scale was started in 1980 exploiting an *A.terreus* starin.Different fermentation parameters were analyzed during process development.These parameters included the analysis of culture homogenity,pH effects ,various carbon and nitrogen sources for maximum yield, agitation and aeration designs.

Reisolation of producer strain along with pH control and slow use of carbon source especially glycerol resulted in five fold increased yield than initial lovastatin production.It was revealed from scaling up of process from 800-I to 19,000-I scale that one crucial limiting factor in productivity of lovastatin is oxygen transfer.The solution to this limitation was achieved by setting up more efficient impeller with reduced power requirements,66% of that of the Rushton standard turbine, and enhanced hydrodynamic thrust.[25]

Sources

The organisms which produce lovastatin as a metabolite of their secondary metabolism are *Aspergillus terreus, , Aspergillus niger ,Aspergillus flavus, Monascus spp, Penicillium purpurogenum, Trichoderma viride*. .Among all these producer starins which are used mostly on industrial scales are *Aspergillus terreus ,Penicillium spp* and *Monascus ruber*. *Aspergillus terreus* which is major source for production of lovastatin is a filamentous ascomycota. It produces lovastatin which is antihypercholesterolemic drug having tremendous contribution towards treatment of cardiovascular diseases by effectively lowering levels of cholesterol.[26]

Media composition and culture conditions

Medium composition can significantly effect yield of lovastatin,so designing of fermentation medium is very crucial.[20] A balanced and maintained culture media with optimized conditions is necessary for obtaining maximum yield.Many nutrients play their role in producing maximum yield and among all nutrients most important one are carbon and nitrogen sources.Carbon and nitrogen possess central role in fermentation media as they are directly linked to biomass and metabolites formation.Catabolic repression is phenomenon through which secondary metabolism is regulated by concentration as well as nature of carbon source.[8] Lovastatin biosynthesis is not only dependant on carbon and nitrogen sources but strain used and culture conditions are also important considerations.[27]

Other environmental factors which are important include agitation,aeration,pH and temperature.Interaction of agitation with environment of culture effects product formation in a certain way.[28,29] Morever an optimum size of inoculum also contribute towards maintaining optimum conditions for yield.[27] Moisture content also has its imapct on production as higher moisture content tend to decrease production due to reduced oxygen availability as well as low moisture content reduces metabolic heat during fermentation.[30] pH optimization is yet another important factor that effects production in a positive way.pH range suitable for maximum production is reported to be 7-8.5 but further increase in pH slows down fermentation.[31] Temperature is considered as most important parameter in a fermentation process as it influences the productivity by activating and inducing enzymes required for lovastatin biosynthesis.A range of 25 to 30 degree C was observed to enhance cultivation with optimum temperature of 30 degreeC that resulted in high yield.

FERMENTATION TECHNIQUES

Production of lovastatin by submerged fermentation

Literature review showed that submerged batch fermenatation is most commonly used fermentation technique for production of lovastatin using *A.terreus* strain of fungus.*A terreus* is soil fungus that has been mostly utilized for commercial production of lovastatin.[26] Submerged batch fermentation with A.terreus is typically carried out in optimal conditions with pH 5.8-6.3 and temperature at 28 $^{\circ}$C.

Experiments were performed on *A.terreus* DRCC 122 which is producer strain for lovastatin with high yielding capacity to explore culture conditions and nutritional requirements for maximum production of lovastatin in submerged fermentation.Maltodextrin as carbon source and corn steep liquor as nitrogen source showed a significant increase in lovastatin production.[28] Production was greatly influenced by type of carbon sources, nitrogen sources and C:N mass ratio of medium.[27] Statistical analysis was done to study interaction between concentration of nutrients and oxygen supply during biosynthesis of lovastatin.Box-Benhken design demonstrated that oxygen content in gas phase influences production.[27]

Continuous efforts to maximize the yield has been made and for that high yielding strains has been produced and exploited.Enhanced production can be achieved by nourishing submerged culture of *A.terreus* strain ATCC 20542 with polyketide antibiotics.Increased production was obtained by supplementation of linoleic acid and vitamins of B group[6] in submerged fermentation of two stages using *A.terreus.*Palm oil and soya oil utilization enhanced lovastatin production by *A.terreus* ATCC 20542 in submerged fermentation.

Solid state fermentation

Production by Solid state fermentation (SSF) is a process that utilizes agricultural waste for growth of fungi on wide scale.SSF is a method of choice for growth of fungi and bacteria due to ease of optimization ,maximum consumption of substrate and simple down streaming processes.[32] The use of solid substrate is a cost effective method for production of drugs,enzymes and other useful products.

The fungal strains that are producers of lovastatin can grow on various solid substrates.When *A.terreus* was grew on wheat bran (982.34 ug/g),it showed maximum production of lovastatin.Many other fungal species like *Monascus spp*, *Pleurotus spp* and , *Penicillium funiculosum* also utilize wheat bran for production of lovastatin as substrate. Rice bran was also utilized by fungal strains as substrate for production of lovastatin. *A.terreus* and its starins showed ability to grow on various substrates like rice bran, rice straw ,paddy straw etc[33] (Table 1).

Table 1: Solid state fermentation (SSF) of *A. terreus* species using raw substrates.

Sr.No.	A. terreus Strain	Solid Substrate	Yield	References
1.	MTCC 279	Green peas, Millet	389.34 mg/gds	[34]
2.	ATCC 74135	Rice straw	0.261 mg/g	[35]
3.	4	Wheat bran	9.7 mg/g	[36]
4.	20	Oat bran	9.5 mg/g	[37]
5.	UV 1718	Wheat bran	3.723 mg/g	[37]
6.	ATCC 20542	Rice powder, Glucose	2.9 mg/g	[38]

An expression analysis of two genes (Lov E and Lov F) was performed to analyse molecular events that are responsible for difference in production levels of lovastatin by SSF and submerged fermentation(SmF).It was revealed by molecular analysis that higher production by SSF was due to high transcript levels of both genes (Lov E and Lov F) in SSF as compared to SmF.These results showed that higher production of lovastatin in SSF is because of higher transcription of its biosynthetis genes and probably this is cause for higher production of other secondary metabolites in SSF.[7]

OPTIMIZATION OF FERMENTATION PARAMETERS

Optimization of fermentation parameters is crucial for obtaining maximum yield by fermentation.pH optimization, temperature optimization, appropraite agitation mechanism and proper aeration are important parameters in any fermentation technique.Carbon and nitrogen sources play central role in fermentation media because they serve as substrate for micobes,source of precursors and cofactors for biomass synthesis. Manipulation of carbon and nitrogen sources results in different yields. Experiments were performed with various carbon and nitrogen sources and yield was measured(Table 2).

Table 2:Carbon and nitrogen sources in submerged fermentation (smf) of A. Terreus species.

Sr.No.	A.terreus strain	Carbon source	Nitrogen source	Yield	References
1.	ATCC 20542	Lactose,glycerol	Yeast extract	161.8	[39]
2.	Z15-7	Glycerol	Corn meal	916.7	[40]
3.	LA414	Soluble starch	Sodium glutamate	523.9	[41]
4.	LA414	Soluble starch	Yeast extract	952.7	[42]
5.	ATCC 20542	Lactose	Soybean meal	140	[43]
6.	NRRL255	Glucose,maltextract	Milk powder	920	[29]
7.	ATCC 20542	Lactose	Soybean meal	80	[44]
8.	ATCC 20542	Lactose	Soybean meal	186.5	[45]
9.	GD13	Lactose	Soybean meal	1242	[46]

APPLICATIONS OF LOVASTATIN

Lovastatin reduces cholesterol levels in plasma by inhibiting its synthesis.It binds to active site of reducatse enzyme and inhibits binding of HMG-CoA to its enzyme.This competitive inhibition results in failure of rate limiting step in cholesterol biosynthesis.Lovastatin decreases low density lipoproteins (LDL) levels thus preventing atherosclerosis and slightly increase high density lipoproteins (HDL) that avoids leison formation in arteries but mechansim is not known.[47]

These striking lipid loweing effects of lovastatin has reduced coronary events and resulting deaths as demonstrated by clinical and epidemiological studies.[48,8] Lovastatin therapy has multiple effects including prevention of thrombus formation ,modification of atherosclerosis progression,improved endothelial functions and plaque stability.[11,8]

Lovastatin shows vast variety of biological effects beyond just hypocholesterolemic effect (Fig.5). These pleiotropic effects are because inhibition of HMG-CoA

reductase not only reduces cholesterol levels but also reduces isoprenoid intermediates.These intermediates are involved in cell growth, differentiation, proliferation/apoptosis balance, regulation of inflammatory cytokines and messages mediated by G protein.[8] Involvement of these intermediates in diverse cellular functions and single transduction pathways makes lovastatin applicable to not only cardiovascular diseases but also non cardiovascular events.[49]

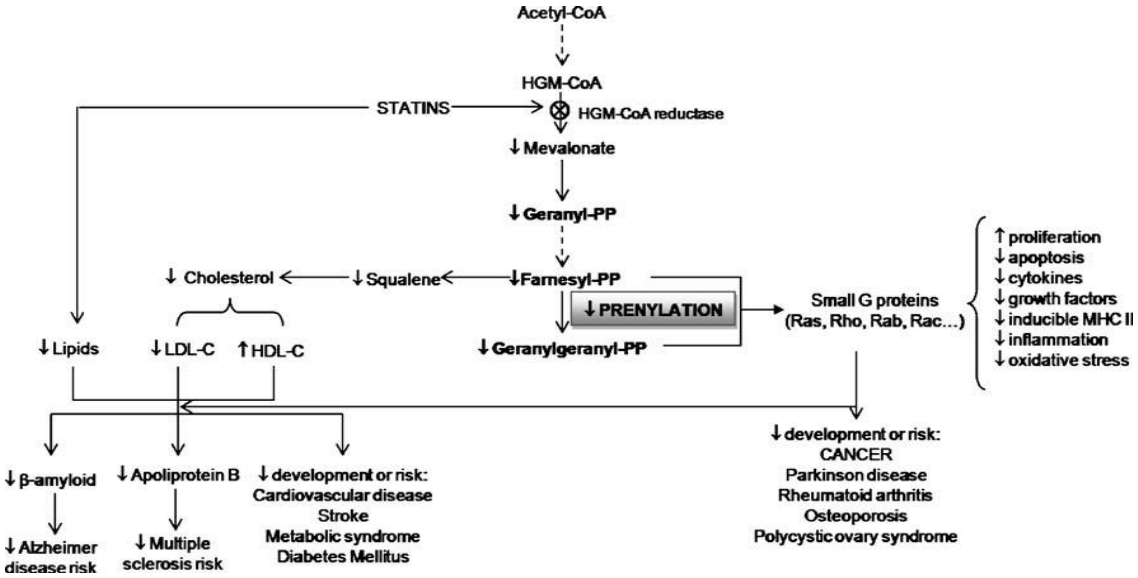

Figure 5: Multiple effects of Lovastatin

Metabolic syndrome

Metabolic syndrome is collection of symptoms and risk factors like dyslipidemia,elevated blood glucose levels ,high LDL levels and high blood pressure.These risk factors makes it strongly associated with type 2 diabetes mellitus and also leads to cardiovascular disaeses.Metabolic syndrome and diabetes are linked to underlying inflammation.[48] Lovastatin may have slight antihypertensive effect and effects on glucose metabolism as well as on insulin sensitivity.[50] Several studies have shown that lovastatin and its related compounds can reduce the risk of cardiovascular events in diabetes mellitus.[49]

Alzheimer's disease

Alzheimer's disease is brain cells degenearting disease which causes by production and accumulation of neurotoxic β amyloid proteins.Lovastatin treatment showed reduction in prevelance of Alzheimer's disease in patients suffering from hypercholesterolaemia. Lovastatin was observed to reduce levels of Aβ in blood of patients upto 40%.[51] Studies also showed that there is an association between cholesterol metabolism and Alzheimer's disease.Although mechanism is not clearly understood but lovastatin reduces risk of Alzheimer's disease.[51]

Multiple sclerosis

Clinical studies showed that lovastatin has ability to reduce morbidity and mortality rate in patients suffering with multiple sclerosis.It was observed that lovastatin suppressed the tumor necrosis factor (TNF α) and also decreased level of inflammatory response.These events occurred due to regulation of antigen presenting cells and major histocompatibility complex proteins (MHCII).

Kidney disorders

Lovastatin reduces inflammatory response and cytokine activity of GTPases RAS superfamily thus helping in treatment of kidney disorders.Exact mechanism of action is still not known but it helps in preventing kidney damage particularly glomerulonephritis associated kidney damage.[52]

Osteoporosis

The effect of lovastatin on bone formation was first demonstrated by Mundy et al,1999. Statis have beneficial effects on bone formation and bone mineral density, reducing risk for fractures.[53] Researchers performed experiments by injecting nano dosage of lovastatin to study effects of lovastatin on bone formation.It revealed that high dosages resulted in stimulation of bone formation both in vivo and in vitro also when injected on particular sites it caused healing of femoral fractures and decreased the cortical fracture gap.However mechanism of action of lovastatin on bone formation is still to be elucidated.[54]

Anticancer

Lovastatin and related compounds showed wonder effects on cancer cells but site of action and mechanism of action is poorly understood.Study done by Tandon et al revealed antiproliferative effects of lovastatin on cancerous cells. A study was performed on the proliferation of cancer in human glioblastoma cells and

reduction in the cancer was observed by lovastatin through inhibition of RAS farsonylation.[55]

SIDE EFFECTS OF LOVASTATIN

Lovastatin as like other drugs also shows some possible side effects but these side effects are minor one.Not every person who takes lovastatin develpos these side effects and most of the people are usually tolerant to lovastatin.When side effects develop they are not major and can be treated easily by person himself or any health care professional.

Previous studies showed that about 4.6 percent people stopped their mediaction because of occurrence of side effects.Hence,people should be aware of side effects before starting regular consumption of lovastatin.There are several side effects related to lovastatin that include signs of liver damage such as yellow mucous membranes, skin, pale eyes, pain in upper right abdomin, dark urine ,elevated levels of liver enzymes (ALT,AST), muscular pain, weakness, tenderness, particularly with fever or illnes,as these are signs of serious muscular breakdown known as rhabdomyolysis.Kidney problems may also occur causing significant unexplained changes in amount of urine production. Severe allergic reactions can also occur due to lovastatin that include rashes,hives, itching, difficulty in breathing,tightness and heaviness in chest, dizziness, swelling of mouth,face,lips or tongue.Red swollen lips, blisters, peeling of skin, tomach pain, yellowing of skin and eyes are some other possible effects.

CONCLUSION

Lovastatin serves as potent inhibitor of rate limiting enzyme in cholesterol biosynthesis which is 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase.In this way it lowers cholesterol levels in plasma effectively with nearly no side effects.Mechansim of action for lovastatin is structural similarity between acid form and HMG-CoA intermediates.

Lovastatin is first statin to be approved by Food and Drug administration (FDA) USA in 1987 and since then it is used for treatment of hypercholesterolemia world wide.It is first line of drug for preventing cardiovascular events, athersoclerotic plaques and coronary heart disease.Lovastatin as also an effective drug against several other disorders other than lowering of cholesterol levels.It has shown good effects on treatment of metabolic syndrome, Alzheimer's disease ,bone fractures, osteoporosis and cancer.On industrial scale,lovastatin is mainly produced by liquid subeusmerged fermentation using *Aspergillus terreus* as source.There is an ongoing research and technological developments for increasing production of lovastatin while decreasing cost of production making it more economical.It can be predicted that cost of lovastatin will be reduced and more affordable in coming years.

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