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A review on lovastatin and its production

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Abstract

Natural statin like lovastatin which is mainly produced by *Aspergillus terreus* strains is an inhibitor of HMG-CoA reductase, an enzyme involved in the biosynthetic pathway of cholesterol. The mechanism involved in controlling plasma cholesterol levels is the reversible competitive inhibition of HMG-CoA which binds to the HMG-CoA reductase due to the structural homology between the β-hydroxyacid form of the statins and the HMG-CoA intermediate formed. Mainly Lovastatin are produced industrially by liquid submerged fermentation which decreases the production cost compared to costs of chemical synthesis. Lovastatin application part is in various field like management of hypercholesterolaemia, cholesterol lowering actions, reduce the prevalence of Alzheimer's and renal disease etc. This review deals with the structure, properties, biosynthetic pathway, submerged fermentation, applications and side effects of lovastatin.

Keywords: Lovastatin, Mode of Action, Biotechnological production, Application and side effects.

Introduction

Biotechnology can be defined as the controlled and deliberate manipulation of biological systems (whether living cells or cell components) for the efficient manufacture or processing of useful products. Biotechnology is the practice of using plants, animals and micro-organisms such as bacteria, Fungus etc as well as biological processes such as the ripening of fruit or the bacteria that break down compost to some benefit. For example, biotechnology is used in industry, medicine and agriculture to produce foods, medicines, test for diseases and remove waste (Shuler and Kargi 2008).

Statins are compounds of natural origin that are biosynthesized as secondary metabolites of several filamentous fungi and act as competitive inhibitors of HMG-CoA reductase (Bizukojc and Ledakowicz 2007). They are bulky and literally get "stuck" in the active site. This prevents the enzyme from binding with its substrate, HMG-CoA. Today, there are two classes of statins: Natural Statins: Lovastatin (mevacor), Compactin, Pravastatin (pravachol), Simvastatin (Zocor).Synthetic Statins: Atorvastatin (Lipitor),Fluvastatin (Lescol). The most common statins are atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor, Altocor), pravastatin (Pravachol), simvastatin (Zocor), and rosuvastatin (Crestor).

Lovastatin, a specific and potent competitive inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) is a powerful serum cholesterol-lowering drug in humans and other species. It is formerly called as mevinolin; monacolin K, and mevacor® and it is a fungal secondary metabolite which inhibits HMG-CoA reductase (E.C 1.1.1.34), the first committed enzyme of cholesterol biosynthesis (Seraman et al. 2010). The endogenous synthesis of cholesterol is carried out by the mevalonate pathway, in which the rate limiting reaction is the conversion of (S) HMG-CoA to (R) mevalonate, catalyzed by HMG-CoA reductase. The history of statin began in 1987 when the lovastatin received Food and Drug Administration (FDA) approval in the USA (Manzoni and Rollini 2002). Lovastatin have revolutionized the treatment of hypercholesterolemia and it is proven that lovastatin is also therapeutically and preventatively effective in the treatment of major kind of diseases like atherosclerosis, sepsis, peripheral arterial disease, peripheral vascular disease, cerebro vascular disease, ischemic disease, and bone fracture.(Seraman et al. 2010).

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Structure

Lovastatin is [(1S,3R,7R,8aS)-8-[2-[(2R,4R)-4-hydroxy-6-oxo-oxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl](2S)-2methylbutanoate (IUPAC name). The empirical formula of lovastatin is $C_{24}H_{36}O_5$ and its molecular weight is 404.55. Its 3D structural of Lovastatin is shown in Fig. 1.

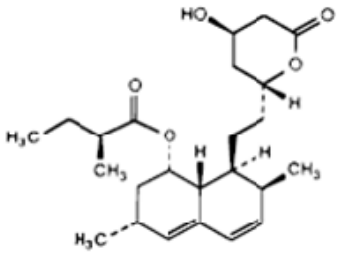

Figure 1**:** Structure of Lovastatin

Properties

Lovastatin is a white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol, and acetonitrile. Experimental evidences from literature revealed the presence of 18 proteins involved in lovastatin biosynthesis of *A. terreus,* ATCC 20542 (Subazini and Kumar 2011). Out of the 18 lovastatin biosynthetic cluster proteins it is found that 2 proteins are involved in regulatory mechanisms, 3 in transportation, 9 enzymes, 2 unknown proteins of thiolases acyl-enzyme intermediate signature and PQ loop repeat, and 2 megasynthases, Lovastatin Nonaketide Synthase (LNKS) and Lovastatin Diketide Synthase (LDKS) (Subazini and Kumar 2011).

Mode of Action

Mevalonate is a required building block for cholesterol biosynthesis and lovastatin interferes with its production by acting as a reversible competitive inhibitor for HMG-CoA which binds to the HMG-CoA reductase. The inhibition is due to the structural homology between the β-hydroxyacid form of the statins and the HMG-CoA intermediate formed (Fig. 2). Lovastatin and related compounds, with the exception of pravastatin, are produced as predrugs, being a mixture of the lactone and the β-hydroxyacid form. The lactone ring is converted into the corresponding β-hydroxyacid form in vivo (Samiee et al. 2003). Lovastatin, being inactive in the native form, the form in which it is administered, is hydrolysed to the β-hydroxy acid form in the body and it is this form which is active.

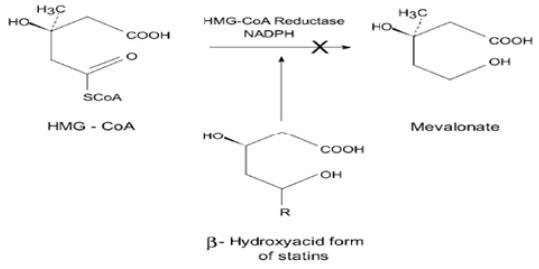

Figure 2: Structural analogy between HMG-CoA and the β-hydroxyacid form of statins and mechanism of inhibition.

History

Statin was firstly discovered by the Japanese microbiologist Akira Endo in a fermentation broth of *Penicillium citrinum* in the 1970s, during a search for antimicrobial agents (Tobert 2003). The first agent isolated was mevastatin (ML-236B), a molecule produced by the fungus *"Penicillium citrinum*". The reason was microorganisms may produce inhibitors of the enzyme to defend themselves against other organisms, as mevalonate is a precursor of many substances required by organisms for the maintenance of their cell wall (ergosterol) or cytoskeleton (isoprenoids).

The pharmaceutical company Merck & Co. showed an interest in the Japanese research in 1976, and isolated lovastatin (mevinolin, MK803), the first commercially marketed statin, from the fungus *"Aspergillus terreus*". In April 1980, after animal safety studies had been performed, Merck began clinical trials of lovastatin in healthy volunteers. Lovastatin was shown to be dramatically effective for lowering LDL cholesterol in healthy volunteers, with no obvious adverse effects. However, this promising start was soon to be interrupted. Clinical trials with compactin had been proceeding, but for reasons that have never been made public (but which were believed to include serious animal toxicity) the trials were stopped by Sankyo in September 1980. Because of the close structural similarity between compactin and lovastatin, Merck promptly suspended clinical studies with lovastatin, and initiated additional animal safety studies. The future of the drug seemed extremely doubtful. History of statin is shown in Fig.3.

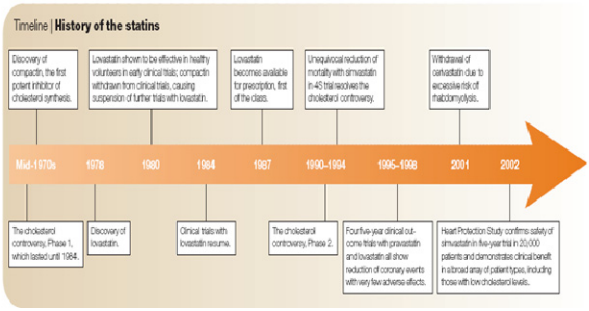

Figure 3: History of statin (Tobert 2003)

Merck decided, in 1983, to re-initiate the clinical development programme, initially in patients at very high risk of myocardial infarction. The pharmaceutical company Merck continued research and isolated the first statin, lovastatin in 1978. In November 1986, Merck applied for regulatory approval of lovastatin. In February 1987, a US FDA advisory panel fully considered the various safety issues arising out of the animal toxicology studies and the clinical results. The panel voted unanimously for the approval of the drug, and FDA approval was obtained on 31 August 1987. Lovastatin had patent protection only in certain other countries, all of which later granted approval. Dr. Endo was awarded the 2006 Japan Prize for his work on the development of statins, and the Clinical Medical Research Award from the Lasker Foundation.

Biosynthetic Pathway

Early research on *Monascus ruber* indicated that monacolin L and J were intermediates in the lovastatin biosynthetic pathway (Endo et al. 1985). It was shown that monacolin L is the first to be synthesized from nine molecules of acetate and is, in turn, converted to monacolin J by hydroxylation. Subsequent experiments demonstrated the transformation of monacolin J tolovastatin

(Kimura et al. 1990). Research with *Aspergillus terreus* (Chan et al. 1983; Greenspan and Yudrovitz 1985; Moore et al. 1985; Shiao and Don 1987), using labeled precursors indicated that the lovastatin biosynthetic pathway also starts from acetate units linked to each other in head-to-tail fashion to form two polyketide chains. The methyl group is present in some statins in the side chain or at C6 derives from methionine, and is inserted in the structure before closure of the rings (Shiao and Don 1987).The main chain is then cylized and in some statins esterified by a side chain at C8. The oxygen atoms present in the main chain are inserted later by aerobic oxidation. Studies carried out in *P. citrinum* and *M. ruber* indicated a similar pathway. Hence, it had been shown that lovastatin was derived from acetate via a polyketide pathway (Chakravarti and Sahai 2004; Endo et al. 1985). Pioneering genetic research by Reeves, McAda, and workers at MDS Panlabs Inc., identified a type I polyketide synthase (PKS) gene essential for lovastatin biosynthesis by A. terreus (Hendrickson et al. 1999). Its product, now called lovastatin nonaketide synthase (LNKS) has been shown (Ma and Tang 2007) to contain seven active sites (in order: KS = ketosynthase; MAT = malonyl-CoA:ACP acyltransferase; DH = dehydratase; MT = methyltransferase; KR = ketoreductase; ACP = acyl carrier protein; CON = condensation domain).

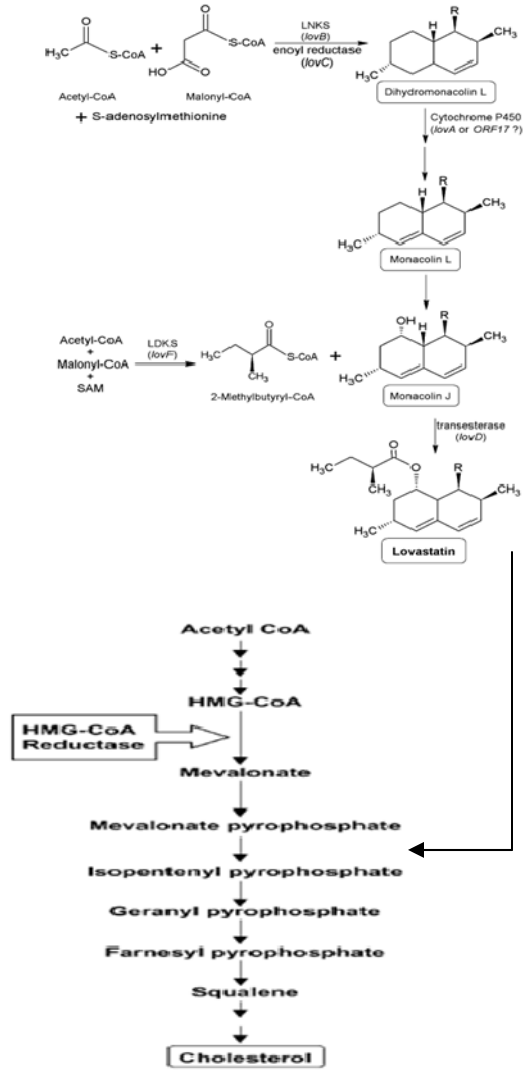

Figure 4: Biosynthetic Pathway. (González et al. 2010 and Manzoni et al. 2002)

The lovastatin biosynthesis cluster contains two type I polyketide synthase genes (lovB and lovF). In addition, lovE encodes a transcription factor regulatory protein with the typical binuclear Zn^{++} finger motif. Its disruption mutants did not produce lovastatin or intermediates, while the over expression resulted in increased metabolite production. It is assumed that lovE regulates lovastatin production at the transcriptional level. However, there is a second gene (lovH) with a similar structure (Hutchinson et al. 2000). It is not obvious how lovastatin biosynthesis uses two regulatory genes, since most other secondary metabolites clusters contain one dedicated regulatory gene (Keller and Hohn 1997). The biosynthetic pathway was shown in Fig.4.

Fermentative Production

Source

The organisms reported to produce lovastatin as a secondary metabolite include *Aspergillus terreus*, *Monascus sp, Aspergillus niger ,Aspergillus flavus Penicillium purpurogenum, Pleurotus sp, Trichoderma viride*, *Penicillium* sp but for commercial purpose *Penicillium* sp. , *Monascus ruber*, and *Aspergillus terreus* appears to be the most commonly used . *Aspergillus terreus* is a filamentous ascomycota, which is prominent for its production of lovastatin, an antihypercholesterolemic drug. *Aspergillus terreus*, an important fungus is a major source for lovastatin, which treats cardiovascular disease by effectively inhibiting HMG CoA reductase activity, the rate limiting step in cholesterol biosynthesis (Lai et al. 2007; Pecyna and Bizukojc 2011; Subazini and Kumar 2011).

Production of Lovastatin by Submerged Fermentation

Medium Design

Secondary metabolism of microorganisms is parts of their normal maturation processes . The design of fermentation media is critical, especially when the products are secondary metabolites. Although major improvements are generally ascribed to the development of superior strains, nutrient supplies also affect cellular productivity. This gives rise not only to scientific inquiry but also to commercial interests to secondary metabolite production. To produce secondary metabolites, the uncertainties came from lack of knowledge dealing with the sophisticated interactions of environments with microorganisms (Bizukojc and Ledakowicz 2007; Lai et al. 2007; Lai et al. 2001).

Designing a fermentation medium is a critical and important process as the medium composition can significantly affect the product yield (Kennedy et al. 1999). An optimally balanced culture medium was mandatory for maximal production of the secondary metabolites. Of the major culture nutrients, carbon and nitrogen sources generally play a dominant role in fermentation productivity because these nutrients are directly linked with the formation of the biomass and the metabolite. Also, the nature and concentration of the carbon source can regulate secondary metabolism through phenomena such as catabolic repression. Biosynthesis of lovastatin has been found to depend on the carbon and nitrogen sources, but the results have been inconsistent as the observed effects depend on strain used and culture conditions, that is, the composition and concentration of other culture medium components (Casas López et al. 2003).

Submerged batch fermentation of lovastatin production was reported in various literatures and its commercial production of lovastatin is based on *A.terreus* batch fermentation. *Aspergillus terreus* fermentations were typically carried out at 28°C and pH 5.8-6.3 and Production of lovastatin by fermentation decreases the production

cost compared to costs of chemical synthesis (Bizukojc and Ledakowicz 2007; Lai et al. 2007; Lai et al. 2001).

Sitaram Kumar *et.al* (2000) has performed a experiment of Submerged cultivation on a high yielding strain of *Aspergillus terreus* DRCC 122 for the production of lovastatin in the batch process and also performed a cost effective repeated fed-batch process with maltodextrin and corn steep liquor feed as carbon and nitrogen sources, respectively which showed a significant increase in lovastatin yield (Sitaram Kumar et al. 2000). Among several organic and inorganic defined nitrogen sources metabolized by *A. terreus*, glutamate and histidine gave the highest lovastatin biosynthesis level (Casas López et al. 2003) in the chemically defined fermentation medium.

Plackett-Burman screening, factorial designs, and second-order response surface methodology (RSM) (Lai et al. 2003) were used for lovastatin production by a high-producing mutant of *Aspergillus terreus* in submerged cultures. The method used was effective in screening for nutritional requirements in a limited number of experiments. Production of lovastatin and microbial biomass by *Aspergillus terreus* ATCC 20542 were influenced by the type of the carbon source (lactose, glycerol, and fructose) and the nitrogen source (yeast extract, corn steep liquor, and soybean meal) used and the C:N mass ratio in the medium (Casas López et al. 2003). López *et al.* (2003) showed the effect of carbon source (lactose) in combination with either soybean meal or yeast extract under *N*-limited conditions (Casas López et al. 2003). Lopez *et al.* (2004) firstly used statistical analysis in to study the interactions between oxygen supply and nutrient concentrations in lovastatin production. The Box–Behnken design identified the oxygen content in the gas phase as the principal factor influencing the production of lovastatin (Casas Lopez et al. 2004).

The influence of culturing environments on lovastatin production by *Aspergillus terreus* in submerged cultures was performed a experiment on *Aspergillus terreus* ATCC 20542 and demonstrated that the cell productivity of *A. terreus* could be enhanced significantly by controlling the culturing environments in the submerged culture (Lai et al. 2005). Porcel *et al* (2006) worked on Gas-Agitated Slurry Reactor and investigate the effects of nonmechanical low-intensity agitation on development of broth rheology and fungal pellet morphology during production of lovastatin by the filamentous fungus *Aspergillus terreus* and they also studied the biomass and lovastatin production by spore-initiated submerged fermentations of *Aspergillus terreus* ATCC 20542 and showed that it depends on the age of the spores used for inoculation. Cultures started from older spores produced significantly higher titers of lovastatin (Porcel et al. 2006). Porcel *et al* (2007) enhanced production of lovastatin in a bubble column by *Aspergillus terreus* using a two-stage feeding strategy compared with conventional batch fermentation (Porcel et al. 2007). Sayyad *et al.* (2007) worked on optimization of nutrient parameter for production of lovastatin by Monascus purpureus MTCC 369 under submerged fermentation using the medium compostion 100 g dextrose, 10 g peptone, 2 g KNO_3, 2 g NH_4 H_2PO_4, 0.5 g $MgSO_4 \cdot 7H_2O$, and 0.1 g $CaCl_2$ in 1,000 ml distilled water, adjusted to pH 6.0 (Sayyad et al. 2007) .

Two-staged feeding operation for the production of Lovastatin by *Aspergillus terreus* (Porcel et al. 2008) showed that Semi-continuous operation enhanced productivity of lovastatin by 315% compared with a conventional batch operation. The composition of a fermentation medium influences the supply of nutrients and metabolism of cells in a bioreactor and therefore the productivity of a fermentation process depend on the culture medium used of the major culture nutrients, carbon and nitrogen sources generally play a dominant role in fermentation productivity because these nutrients are directly linked with the formation of biomass and metabolites. Also, the nature and concentration of the carbon source can regulate secondary metabolism through phenomena such as catabolic repression (Seenivasan et al. 2008).

Lovastatin Production was enhanced by Supplementing Polyketide Antibiotics to the Submerged Culture of *Aspergillus terreus* ATCC 20542 (Jia et al. 2010). The production of lovastatin was enhanced by supplementation of linoleic acid (Sorrentino et al. 2010) and B-group vitamins (Bizukojc and Ledakowicz 2007) in *Aspergillus terreus* two stage submerged fermentation. The highest level for lovastatin production has been found in cultures grown on oat meal (Osman et al. 2011) with Oat meal conc. 20g/l for production of lovastatin by *Aspergillus terreus* in a two-steps submerged fermentation. Utilisation of palm oil and soya bean oil significantly improved lovastatin production (Sripalakit et al. 2011) by *Aspergillus terreus* ATCC 20542 in submerged cultivation.

Optimization of physicochemical parameters

In defined medium, the carbon and nitrogen sources play a critical role as a source of precursors and cofactors for synthesis of biomass building blocks and lovastatin production. In addition, the carbon source may exert complex regulation on gene expression and enzyme activities for polyketide synthesis. Different carbon sources (Table 1) are used like Lactose, glycerol, fructose and ethanol as the sole C source or combined with glucose (Hajjaj et al. 2001).

Table 1: Influence of carbon source on lovastatin production (Hajjaj et *al.* 2001).

C source	Initial C source concn (g liter^{-1})	Residual C Source concn (g liter^{-1})	Residual glutamic concn(g liter^{-1})	Lovastatin production (mg liter^{-1})
Glucose	20	0	0	37
Glucose	45	0	0.4	35
Glucose	70	0	2.5	<2.5
Lactose	45	6.3	0	25
Glycerol	20	0.3	0.2	6
Ethanol	20	8.1	4.4	4
Lactose plus glucose	20 and 20	11.3 and 0.4	0.4	54
Glycerol plus glucose	20 and 20	0.3 and 0	1.4	33
Ethanol plus glucose	20 and 20	12.2 and 0	0.3	14

Combination of lactose and glucose rapidly and slowly metabolized sugar may be beneficial to lovastatin production. López *et al.* (2003) showed that irrespective of the N-source, using fructose as the carbon source gave the highest biomass concentration after 72 h of culture (Casas López et al. 2003).The type of the nitrogen source used affects the productivity of lovastatin. Yeast extract and soybean meal are the preferred nitrogen sources when compared to CSL. Apparently, the metabolic pathways for the synthesis of lovastatin from carbon are much slower than the pathways that convert carbon to biomass. Therefore, nitrogen limitation (i.e. growth suppression) helps with synthesis of lovastatin by diverting more carbon to its synthesis. The final attainable biomass concentration for a given N-source depended on the C-source used. In comparison with the other N-sources, the relatively high final biomass concentration attained with soybean meal was because of a high initial concentration of nitrogen. A high productivity and final yield of lovastatin are generally obtained using a slowly metabolized carbon source under conditions of nitrogen limitation. Ammonia,

which also plays a central role in nitrogen metabolism in filamentous fungi , was tested beside urea and nitrate, which can be consumed by some fungi . *A. terreus* grew on all nitrogen sources listed in Table 2, indicating their consumption. Glucose was exhausted after 140 h in all experiments except for that with ammonium acetate. Although inorganic nitrogen sources like ammonium tartrate, ammonium nitrate, ammonium acetate, sodium nitrate, or urea were consumed for biomass formation, lovastatin production was very poor after 140 h of cultivation.

Amino acids can act both as a nitrogen source and a carbon source in filamentous fungi. Since no free ammonium could be detected in the supernatants during growth on amino acids, we assume that they were primarily used as a nitrogen source. Best lovastatin production was obtained with cultures grown on sodium glutamate (12.5 g liter-1) or histidine (12.5 g liter-^{1}) (Table 2). A glutamate concentration of 12.5 g liter-1 was more favorable than 7 or 18 g liter^{-1} (Table 2). Glycine, arginine, and isoleucine (Table 2) were assimilated but gave poor lovastatin production. Because glutamate was consumed twice as fast as histidine during batch experiments, glutamate was chosen as the nitrogen source for the chemically defined medium in order to allow rapid biomass formation.

Table 2: Influence of nitrogen source on lovastatin production (Hajjaj et *al.* 2001).

N source	Initial csonc. (g liter^{-1})	Residual conc. (g liter^{-1})	Residual glucose conc. (g liter^{-1})	Lovastatin production (mg liter^{-1})
Di-ammonium tartrate	13.7	—	0	<1
Ammonium nitrate	4	—	0	<1
Ammonium acetate	11	—	2.5	<1
Sodium nitrate	4	—	0	<1
Urea	4.5	—	0	<1
Sodium glutamate	7	0.1	0	25
Sodium glutamate	12.5	0.4	0	47
Sodium glutamate	18	6.5	0	39
Histidine	7	6.0	0	46
Glycine	7	0.0	0	17
Arginine	7	7.0	0	1.5
Isoleucine	7	2.0	0	<1

Lai *et al.* (2004) shows the effect of agitation on *A. terreus* fermentation between the range 225 rpm – 425 rpm. In the 5-l fermenter, at 225 rpm the fungus grew to long and reported sparsely branched mycelia (Lai et al. 2004). On the other hand, *A. terreus* apparently suffered from extensive shear damage using 425 rpm because a number of shaved-off or called frayed pellets were observed under microscopic examinations. If the agitation was further increased to be higher than 425 rpm, the broken hyphae seemed not regrow and thus provided no benefit to product formation. Using a 325 rpm of agitation, lovastatin production achieved 305 mg/l at day 8, which was 29% or 33% higher than that using 225 rpm or 425 rpm, respectively. When the impeller speed was reduced lower than 225 rpm, it was found that O_2 limitations which inevitably required for product formation. The fungal morphology was seriously influenced by increasing agitation intensity where the cells probably were directed to the pathway other than lovastatin synthesis.

There is a need of sufficient DO supply but without affecting pellet formation was essential. Agitation might also interact with the culturing environments, which in turn affected product formation. Normally, lower DO corresponded to lower agitation. With the DO controlled at 20%, highly entangled mycelia occurring at earlier stages further clumped to form spherical, compact pellets. Effects of the C:N ratio and the principal nutrients on growth and metabolite production. By submerged fermentation at 150 rpm was shown by López *et al*. (2003).

Chen and Johns reported that cell growth of the fungus *M. purpureus* favored at a low pH. In the production of red pigment and citrinin by *M. ruber* (Chen and Johns 1993) Hajjaj *et al.* reported that its pigmentation was inhibited by the accumulation of organic acids in the fermentation broth (Hajjaj et al. 2001). The authors suggested that the action of dicarboxylic acids must be localized in reactions specific to the polyketide pathway of the fungus. Besides, probably because of enzyme activation or degeneration, Buckland et. al reported the broth pH could play a crucial role in the behaviors of secondary metabolite production as well as cell growth of fungi. Through manipulating the fermentation broth at a different pH at a certain time interval, in the work we hypothesized that cell metabolism might be altered whereas lovastatin production could be somehow enhanced.

The pH also effect the biomass production.. Any increase in optimum pH resulted in gradual decrease of lovastatin production due to the denaturation or inactivation of the microbial strain because pH strongly influences the transport of various components across the cell membrane which in turn supports the cell growth and product formation and most of the fungi are active in the pH range of 3.5-7 and also lower pH avoids the contamination by other microbes.

Application and Side Effects

Statins are the treatment of choice for the management of hypercholesterolaemia because of their proven efficacy and safety profile and they can exert antiatherosclerotic effects independently of their hypolipidemic action. Lovastatin basically improves the endothelial function, modulates inflammatory responses, maintain plaque stability and prevent thrombus formation, with which all sorts artery related diseases could be cured and it has been suggested that the consequence of the shrinkage of the lipid core of the atherosclerotic plaque, avoiding plaque rupture that would otherwise trigger intramural hemorrhage and intraluminal thrombosis (Palmer et al. 1990).

Lovastatin shows Cholesterol Lowering Actions. Lovastatin is the hydrophobic ring structure that was covalently linked to the substrate analogue which involved in binding to the reductase enzyme and inhibiting the cholesterol synthesis. This rate-limiting step in cholesterol biosynthesis is blocked by statins. This also reduce the LDL level which cause arthrosclerosis and increase the level of HDL which it avoids the lesion formation in the artery that leads to narrow down the blood circulation through the arteries but the mechanism was unknown (Goldberg et al. 1990). Lovastatin treatment was observed to reduce the prevalence of Alzheimer's Disease AD in patients suffering from hypercholesterolaemia. (Ohm and Meske 2006).

The important advances have been used in the treatment of patients with progressive renal disease. The inhibitors of HMG-CoA reductase can provide protection against kidney diseases characterized by inflammation and/or enhanced proliferation of epithelial cells occurring in rapidly progressive glomerulonephritis, or by increased proliferation of mesangial cells occurring in IgA nephropathy (Buemi et al. 2002). In primary cultures of human glioblastoma cells, inhibition of Ras farnesylation by lovastatin is associated with reduction of proliferation and migration. So the proliferations of the cancer cells were inhibited by lovastatin.

However, the inhibition of cell growth by lovastatin may be independent of Ras function (Xia et al. 2001).

One of the recent trends is that the treatment of bone fracture is by lovastatin . Lovastatin stimulate bone formation *in vitro* and *in vivo* and, when given in large doses or by prolonged infusions, stimulate biomechanical strength of murine long bones with healing fractures. Garrett *et al (2007)* found that these nanobeads, stimulated bone formation in vitro at 5 µg/mL, increased rates of healing in femoral fractures when administered as a single injection into the fracture site, and decreased cortical fracture gap at 4 weeks as assessed by microcomputed tomography. These preclinical studies were suggested that lovastatin administered in a nanobead preparation may be therapeutically useful in hastening repair of human fractures (Garrett et al. 2007).

Lovastatin is also used for the inhibition of the induction of inducible nitric oxide synthase and proinflammatory cytokines in rat astrocytes, microglia and macrophages and to repress MHC-II mediated T-cell activation. Moreover, lovastatin treatment decreased neuroinflammatory activity and clinical signs in experimental allergic encephalomyelitis, an animal model for multiple sclerosis (MS) . In the last few years many studies have demonstrated that statins, in addition to their lipid lowering effects, have antiinflammatory and immunomodulatory properties. These properties of statins have suggested that they could have beneficial effects in immune mediated neurological disorders. Lovastatin therapy can significantly reduce morbidity and mortality in diabetics.

There are possible side effects with lovastatin. However, not everyone who takes lovastatin will develop problems. In fact, most people tolerate lovastatin well. When side effects do occur, they are usually minor and either require no treatment or can easily be treated by you or a healthcare professional. In previous research studies, up to 4.6 percent of people taking lovastatin stopped their medicine because of side effects.

There are a number of side effects with lovastatin and these include: Signs of liver damage, such as yellow eyes or skin, upper right abdominal pain, dark urine, and elevated liver enzymes, Muscle pain, tenderness, or weakness, especially if you also have a fever or feel ill, since these may be signs of serious breakdown of muscle, known as rhabdomyolysis. Significant, unexplained changes in the amount of urine you produce (which may be a sign of kidney problems).

Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); chest pain; dark urine; muscle pain, tenderness, or weakness (with or without fever or fatigue); pale stools; red, swollen, blistered, or peeling skin; severe stomach pain; yellowing of the skin or eyes.

Conclusions

3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway, was an attractive target in the search for drugs to reduce plasma cholesterol concentrations. Lovastatin, natural products with a powerful inhibitory effect on HMG-CoA reductase, were discovered in the 1970s, and taken into clinical development as potential drugs for lowering LDL cholesterol. Large-scale trials confirmed the effectiveness of lovastatin. Observed tolerability continued to be excellent, and lovastatin was approved by the US FDA in 1987.Lovastatin at its maximal recommended dose of 80 mg daily produced a mean reduction in LDL cholesterol of 40%, a far greater reduction than could be obtained with any of the treatments available at the time. Equally important, the drug produced very few adverse effects, was easy for patients to take, and so was rapidly accepted by prescribers and patients. The only important adverse effect is myopathy/rhabdomyolysis. This is rare and occurs with all HMG-CoA reductase inhibitors.For commercial purpose lovastatin is prodeuced by *Penicillium* sp. , *Monascus ruber*, and *Aspergillus terreus* by submerged fermentation. Various media deign and parameter optimization was studied to enhance the production of lovastatin. In spite of various application lovastatin shows side effects which limits its use for long time

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