Review Article

J Babol Univ Med Sci
Vol 18, Issu 12; Dec 2016. P:40-48

A Review of the Effective Factors for Lovastatin Production by Aspergillus Terreus Atcc 20542 in Liquid Submerged Fermentation

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J Babol Univ Med Sci; 18(12); Dec 2016; PP: 40-8.
Received: Aug 16th 2016, Revised: Sep 27th 2016, Accepted: Nov 26th 2016.

ABSTRACT

BACKGROUND AND OBJECTIVE: Deposition of cholesterol in the arteries is the one of the main causes of cardiovascular disease. Lovastatin is a blood cholesterol-lowering drug that inhibits 3-Hydroxy 3-methyl glutaryl-CoA reductase (HMG-CoA reductase) enzyme. The aim of this study was to evaluate the effective factors for lovastatin production by Aspergillus terreus ATCC 20542.

METHODS: This study is a literature review, In order to gather information, articles containing one of the words in their text, including: Cardiovascular disease, Lovastatin, HMG-CoA reductase, Liquid submerged fermentation, Aspergillus terreus were searched between 1960 and 2016 in PUBMED, NATURE, SCIENCE DIRECT and WHO databases.

FINDINGS: A total of 180 papers found that of these, 70 were diagnosed article suitable for this study. According to the results, lactose as the best carbon source, soya been and yeast extract as the nitrogen source, C/N ratio of 41.3, the 107 spores/ml, the pH equal to 6.5, Fe, Zn, Mn as mineral elements and inducer such as linoleic acid at a optimum concentration causes the highest amount of lovastatin.

CONCLUSION: The study shows, the source of carbon and nitrogen, the C/N, the amount and type of inoculation, pH, minerals and inducer are the most important factors affecting the morphology and oxygen uptake by the, Aspergillus terreus and hence also affect the production of lovastatin.

KEY WORDS: *Biosynthesis, Cardiovascular disease, Lovastatin, HMG-CoA reductase, Aspergillus terreus.*

Please cite this article as follows:

Jaberi Ansari F, Jafari Mansoorian H, Jalili H, Azizi M. A Review of the Effective Factors for Lovastatin Production By Aspergillus Terreus Atcc 20542 in Liquid Submerged Fermentation. J Babol Univ Med Sci. 2016;18(12):40-8.

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[DOR: 20.1001.1.15614107.1395.18.12.6.2]
[DOI: 10.22088/jbums.18.12.40]

Introduction

Over the past six decades, many fermentation and synthetic compounds have been made that has been known to reduce blood cholesterol and thereby prevent and treat cardiovascular diseases. These drugs that block the production of cholesterol called statins, in 1971, a scientist named Akira Endo isolated Compactin or ML-236B from the culture of Penicillium citrinium.

It is considered as beginning of statin drugs. Because of the similarity of lovastatin to mevalonate (a precursor in the synthesis of cholesterol) significantly inhibits competitivly the HMG-CoA reductase enzyme. Lovastatin is a white substance and non-hygroscopic crystalline powder which is insoluble in water but soluble in ethanol, methanol, and acetonitrile, the molecular formula is C24H36O5 and its molecular weight is 404.55 grams per mole (1,2). Jaberi Ansari and colleagues in 2016 optimized the compound medium to increase production of lovastatin by Aspergillus terreus and showed the palm sap is a rich source of carbohydrates and minerals for growing fungy and production of lovastatin (3). Mansoori et al in 2015 performed a study on the optimization of production of monacolin (a precursor in the production of lovastatin) and their results showed that maltose in concentration of 10g/1 and MgSO4 in concentration of 0.78g/1 are effective on the production of Lovastatin and biomass (4).

Razeghi yadak et al in 2009 reported that Medium composition, pH and temperature has been effective on the growth rate of mycelium and low pH of 5.4 and a temperature of 25 ° C lead to the highest growing of fungi (5). Tvana and colleagues in 2012 optimized the composition of the liquid culture medium of ganoderma lucidum to enhance the production of biomass and extracellular polysaccharides and according to the obtained results, maltose resulted in the biggest production of biomass and extracellular polysaccharides of ganoderma lucidum and the best combination for production of biomass was maltose in concentration of 50g/1 and a pH of 4.5 and the best combination for production of extracellular polysaccharides was maltose in concentration of 40g/1 and the pH of 3.5 (6).

Azizi et al in 2012 performed a study on various waste products (bran) as a substrate ganoderma lucidum and showed that the highest spore-forming efficiency is achieved by using the hornbeam (7). Kamath and colleagues conducted a study regarding to the optimization of environmental conditions for production of lovastatin by aspergillus terreus and concluded that most of the production of lovastatin was achieved at pH 6, the temperature of 30-28 ° C and insemination of 108 spores per ml (8). Karthika and colleagues have investigated the effects of whey on the production of lovastatin and the results showed that in the predicted optimum conditions, the maximum production of lovastatin was 358.2 mg/1 (9). Sripalakit and colleagues examined the effects of vegetable oils on the production of lovastatin and the results showed that lovastatin production with palm oil and soybean oil was significantly 4.5 to 1.5 times greater than the control sample (10).

Pecyna et al. also examined the effect of lactose, and glycerol on production of lovastatin and concluded that when glycerol as feed and lactose as early bed were used, the production of lovastatin reached to 122.4mg/1, but when glycerol was uesd as early bed, the amount of lovastatin was reduced (11).

Porcel and colleagues studied the effect of sporulation conditions on the lovastatin production and concluded that at the age of spores inoculated 16 days, the amount of lovastatin production was 186.5mg/1 (12). The economic justification for the pharmaceutical industry and the production of secondary metabolites depends on the product and its profit. Studying the parameters and methods that enhance the efficiency of products is a competitive advantage for manufactured products economically and reduce costs in the existing market. This study was conducted to determine the parameters affecting the morphology of aspergilus terreus including carbon source, nitrogen source, carbon to nitrogen ratio (C/N), the amount of spores and type of inoculation, aeration, viscosities, pH, enzymes involved in the production, elements minerals and inducers which are effective in production and efficiency of lovastatin.

Methods

This review was limited to the results of studies published by researchers in the field of effective factors on production on lovastatin by the aspergillus terreus ATCC 20542 between 1960 and 2016. To access articles several databases, Nature, Science Direct and WHO were used. To collect the required data, the key words cardiovascular disease, Lovastatin, HMG-CoA reductase, Liquid submerged fermentation, Aspergillus terreus was used to search.

[DOR: 20.1001.1.15614107.1395.18.12.6.2]
[DOI: 10.22088/jbums.18.12.40]

Results

A total of 180 papers were found, articles investigated factors in the production of lovastatin by the aspergillus terreus ATCC 20542 such as source of carbon and nitrogen, the C/N ratio, the amount and type of insemination, pH, minerals elements and inducers. 70 cases were appropriate for this study.

Microorganisms producing lovastatin: lovastatin is a secondary metabolites secreted further during the second phase of growth (idiophase)(13), these metabolites are produced by cultured species including Penicillium, Monaokus, Aspergillus, pleurotus, hypomyces, Doratomyces, Fuma, Gimnoascus and Trichoderma(14-16). Among them, aspergillus terreus, Monascus and Penicillium are the most important (1,17-20).

Aspergillus Terreus and its products: According to the taxonomic classification aspergillus terreus is classified at the command of the fungi, Ascomycetes category, category of Eurotiomycetes, the order of Eurotiales, Tricomycetes family, aspergillus genus and aspergillus terreus species.

Aspergillus terreus is the most important strain of lovastatin production in liquid medium. This microscopic fungi found in the soil around the globe. Aspergillus terreus is reproduced through both asexual and sexual (21).

Solid culture: Generally methods of cultivation for the production of solid and liquid cultures for production of lovastatin divided into two categories. Solid culture is an inexpensive method to produce lovastatin (22). In this culure of agricultural waste such as Bzan honey, jaggery, jaggery palm, black gram, green gram, barley, sago, ground nut cake, waste sesame, millet, ragy, wheat bran, rice bran, fruit and rice are used as a power supply (23). This type of cultivation has simple extraction process, water and energy consumption is less compared with the liquid cultivation and production efficiency is also higher (24,25) .

Most microorganisms producing lovastatin on solid-state culture are included strains of monascus purpureus MTCC 369, monascus rober MTCC 1880, monascus pilosus 69-12 M and then aspergillus with strains of aspergillus flavus BICC 5174 and Aspergillus terreus ATCC 20549 (26-34).

Mansoori et al in 2015 optimized the production of lovastatin in liquid fermented by the monascus purpureus and reported that the optimal amount of lovastatin was achieved in 26g/1 maltose, MgSO4.7H2O 1 g/1, peptone 5 g/1, MnSO4 5 g/1, KH2PO4 4g/1, Vitamin B1 1g/L, pH of 7, rpm 130 and temperature of 30°C that was 63 g/1 (35). The study of Baneshi and colleagues in 2014 which examined pH of carbon sources and the impact of temperature on the production of colored pigments by this fungus, showed that the highest amount of colored pigments by the fungi was achieved at pH= 3, maltose concentration of 250 g/l and at 25 ^{0}C(36).

Liquid culture: Nowadays lovastatin is produced by the fungus aspergillus terreus in liquid culture and in a large scale. After optimization in flask, the bioreactor is used to control various parameters in order to produce more product and access of microorganisms to food increases because there are more volume in the bioreactor and because of the environment due to the mixer, Today, several types of liquid culture method are used to produce lovastatin including closed culture, dietary culture, semi-continuous culture, and two-stage culture (36).

In closed cultur due to lack of carbon source in the culture as well as the inhibitory effect of lovastatin on their own production, the less lovastatin is produced and because of this nutritional culture is used. Nutritional culture dilutes the liquid and reduces inhibitory effect of lovastatin and consequently increases the production of lovastatin (36-38). A new method for the production of lovastatin compared to nutritional culture is two-stage nutritional strategy that improves production of lovastatin by aspergillus terreus (39,40). Nutritional two-stage strategy increases production lovastatin by 315% compared with closed culture (41).

Spore concentration and age: spore inoculum concentrations and available light intensity are two effective factors on sporulation. Any increase in the intensity and concentration of spores is to reduce the time sporulation (11). Spore concentration is due to the rapid consumption of nutrients in high concentrations of spores causes faster sporulation (11). The light-induced morphogenic factor in the growth and development of many well-known fungi (43). As shown in table 1, the effect of age spore production and spore concentration of light intensity is much higher than lovastatin (11).

Source of carbon: carbon sources reportedly used as a precursor and cofactor for production of lovastatin. In addition, carbon source as a complex to regulate gene expression and enzyme activator used in the synthesis of lovastatin (27). Choose a suitable carbon source can affect the performance of lovastatin production rather

[DOR: 20.1001.1.15614107.1395.18.12.6.2]
[DOI: 10.22088/jbums.18.12.40]

than affect the efficiency of biomass (19). Media are usually designed to have the highest efficiency (44).

Table 1. Evaluation of the effect of light, age and spore concentration in the production of lovastatin (11)

Source	Sum of squares	Degrees of freedom	Average of squares	F-ratio
Age	47822	1	47822	43.57
Light	1.56	1	1.56	0.00
Concentration	132.85	1	132.85	0.12
Block	3462.68	1	3462.68	3.15
Error	27441.3	25	1097.65	
Total	78860.4	29		

Culture media to produce lovastatin are divided into two categories synthetic culture media and compound or complex culture media. The carbon material used in the first category usually contains glucose and fructose and sucrose (a drop rapidly metabolized carbon sources), lactose, and glycerol, and maltodextrin and starch polysaccharides (as late consumted carbon sources) (45).

Most of lovastatin and biomass production were at a glucose concentration of 6% (w/v) concentrations greater than this amount does not lead to increased production of lovastatin (table 2) (46-48). The higher concentration of glucose leads to catabolic repression of secondary metabolites and in conclusion reduces production of lovastatin (49, 21).

Table 2. Effect of glucose in the development and production of lovastatin (51)

The concentration of lovastatin(ml/l)	Biomass production(g/l)	Glucose concentration(w/v)
65	5.2	1.5
90	9.1	3
96	10	4.5
105	11	6
100	10	7.5
100	10	9
95	9.5	12

The use of fructose leads to producing the greatest amount of biomass among other carbon sources, in contrast to fructose, lactose has the least amount of biomass (19). Use of rapidly metabolized carbon source leads to the uncontrolled growth of filamentous fungi and increases viscosities and decreased dissolved oxygen and the reduction of lovastatin (36,49,50). The late consumpted carbon sources are used when the use of rapidly metabolized carbon source such as glucose is binded or not in the environment. Use of late consumpted metabolites not only prevent from inhibitingthe catabolic state, but also provides the enough materials needed for growth and metabolite production. Use of the late consumpted carbon sources in morphology is as the form of pellets, this morphology is useful for the production of secondary metabolites and is due to higher production capacities of lovastatin with late consumpted carbon sources (45). Glycerol is another carbon source that produce high lovastatin (45).

In an experiment to produce lovastatin, use of glycerol improved lovastatin production to 30% compared to glucose in aspergillus terreus (14). 1, 3 and 5% glycerol are appropriate to produce lovastatin that the rate of 3 percent led to highest production. It should be noted that the increase in glycerol concentration higher than 5 to 10 percent due to increased permeability of fungal cells reduced the production of lovastatin (33).

Compound media are usually cheaper than synthetic media, and sometimes has several carbon sources. Also they include substance with minerals and other essential ingredients for microbial growth and therefore usually grow and production of lovastatin in these media is higher than basic media. So far, the paste and vegetable oil were used as a carbon source for the production of lovastatin in submerged culture of aspergillus terreus including sesame oil, sunflower, olive, soybean, palm and corn. Lovastatin and biomass production in combining several of these oils has been more than control environment. The excessive amounts of plant oil also reduces production of lovastatin (9,52). The use of whey powder as a carbon source resulted in high amounts of lovastatin(53).

Sources of nitrogen: Regulation of nitrogen in industrial microbiology is important and affects regulating the synthesis of enzymes involved in primary and secondary metabolismes. Many secondary metabolic pathways whch are favorable for the growth, accepting negative impact from nitrogen. Therefore, in fermentation with complex media, sources of protein with late consumpted amino acids such as proline should be used to produce high amounts of secondary metabolites (54). Nitrogen prevents the formation of Lovastatin, but small amount of nitrogen is necessary for the production of lovastatin (19,43). Nitrogen sources can be organic such as yeast extract, soy, corn, peptone, and casein and inorganic such as sodium

[DOR: 20.1001.1.15614107.1395.18.12.6.2]
[DOI: 10.22088/jbums.18.12.40]

nitrate, ammonium sulfate and urea. Yeast extract, soy and corn nitrogen sources are the biggest boost for synthesis of lovastatin and are the most widely used sources of nitrogen for production of lovastatin (19,33,47,48,55).

C/N ratio: lovastatin and biomass production in addition to the carbon source and nitrogen source are affected by the C/N ratio that the optimal beginning amount of C/N for most production is about 41.3. With the increase in C/N ratio of 14.4 to 23.4 and 41.3 the ability of aspergillus terreus increases for production of lovastatin. The lowest C/N ratio is used in aspergillus terreus for production of biomass (19). In the lowest concentration of nitrogen, addition of carbon has no effect on biomass production. In this case, nitrogen is a limitor and production of lovastatin is maximum, but in high concentrations of nitrogen concentration of biomass significantly increases with increasing carbon concentration, because carbon limits the growth and production of lovastatin is low (56) (Fig 1).

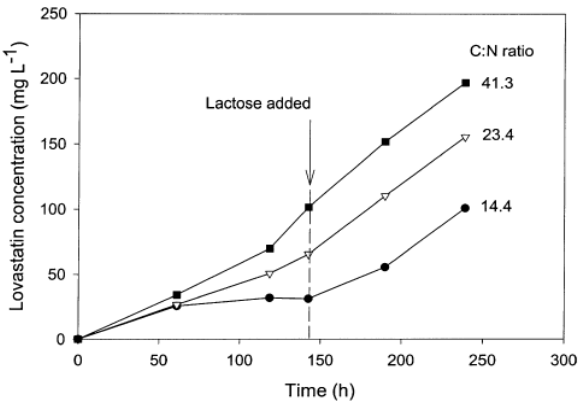

Figure 1. The effect of C/N ratio on production of lovastatin (19)

pH: pH directly control metabolism and the biosynthesis of lovastatin (57). High levels of lovastatin are achieved on the initial pH of 5.6 (58). As the optimal pH (5.7-5.6) increase progressively production of lovastatin is reduced due to damage and disable microbial strains. Because strong pH affects transit of different substants across cell membranes that are effective in the development and production of lovastatin (2).

The use of different carbon sources affects the pH during the growth. In a medium containing lactose, on the first day pH increases from 6.5 to 9.6 and then decreases and again increases with a very gentle slope. But in the medium containing glucose, pH dropped from 6.5to 3.5 and then increases with a gentle slope (Fig 2) (57). Initial pH of environment has a strong effect on carbon capture and use of resources. The curved shape in cultures with initial pH of 5.9-5.7 is sunken or concave and means that the volume of absorption of carbohydrates is high and in cultures with an initial pH of 5.5-5.3 pH curve is convex and indicates that carbohydrate absorption is low. At pH equal to 5.6 the curve is intermediate (convex and concave).

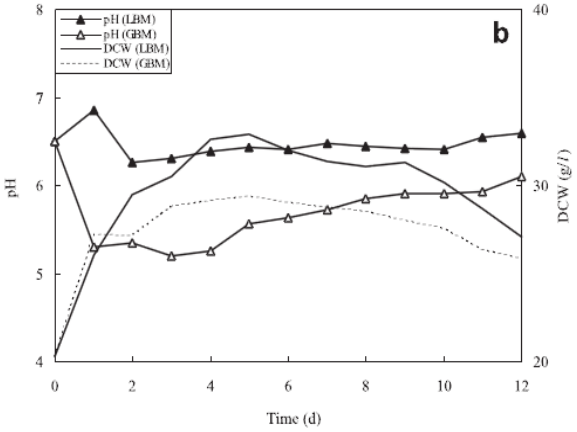

Figure 2. pH changes in the culture with carbon sources containing glucose and lactose (57)

Mineral elements: addition or deletion of mineral elements has a negative effect on the production of metabolites or cell growth. For investigation of mineral elemens, the effects of six of the most important minerals divalent metal cations containing Fe, Zn, Ca, Cu, Mg, Mn as sulphate has been investigated on the growth and production of lovastatin. Reports suggest that divalent metal cations have significant effect on cell proliferation and biosynthesis of lovastatin. These reports show that it is true that minerals are essential for microbial growth but they also have opposite effect in high levels on growth and prevents from the growth and production of lovastatin (59).

Inducers: inducers are effective in each of the stages of development by affecting enzymes and addition of them is effective in the production of secondary metabolites. Researchers examined variety of inductors such as hydrated magnesium silicate, itaconic acid, amino acid methionine, antibiotics and linoleic acid, chromium Snsyng and linoleic acid for the production lovastatin are (60-62) Gonciarz et al in 2014 reported that addition of Hydrated magnesium silicate to medium of aspergillus terreus leads to creation of smaller, more compact pletes and more production of

[DOR: 20.1001.1.15614107.1395.18.12.6.2]
[DOI: 10.22088/jbums.18.12.40]

lovastatin (60). Sorrentino and colleagues conducted a study on the effect of linoleic acid on the production of lovastatin and concluded that addion of 160 and 320 micro-molar of linoleic acid in zero-day leads to 6.1 and 8.1 more times production of lovastatin, but additionof 32 micro-molar does not have any effect on the production of lovastatin (52).

Temperature: for maximum production of lovastatin using temperature factor culture begins with optimum temperature for growth and for continuing the producton of lovastatin lower temperature is preferred that stopping the growth of microscopic organisms. Separating the growth phase from the production phase is performed by changing temperature from 30 to 23°C, which produced a 20-fold lovastatin compared with the constant temperature of the medium (63). Conversely, increasing temperature to 35 ° C inhibits the production of lovastatin by fungus aspergillus terreus (64).

Discussion

For industrial production of lovastatin is commonly used two main methods including cultivation of solid and liquid. Results have shown that the production of lovastatin on solid lovastatin cultivation from Monascus purpureus and Monascus rober is more than liquid culture (65). But in the liquid medium production of lovastatin by aspergillus terreus was reported more than Monascus fungi (66).

The optimum conditions for the production of lovastatin on solid culture in most articles is almost the same, although in some experiments used very different proportions, these factors include temperature (between 20-30 °C), pH (between 5.5-6) and humidity (between 40-70%) is. The disadvantage of this type of culture can be a lack of control of process parameters (such as oxygen, temperature, humidity) in industrial production and the problem of scale change from laboratory to industrial level, therefore usually this type of cultivation in industrial production is not used (67, 68). In liquid culture, the spores should be kept constant for repeat of tests and an average of 107 spores per ml should be inoculated into culture medium (42). In addition to the spores, the spore's age also plays a role in the production of lovastatin, according to the report when spores inoculation age increases from 9 days to 16 days, the amount of lovastatin will also increase to 52% (11).

Glucose as a carbon source is associated with the higher production of lovastatin (47,48). Most production of lovastatin at a concentration of 6% (w/v) of glucose was obtained. The highest biomass production also achieved by using fructose (21,49). Lactose has also the lowest amount of biomass production and maximum production yields of lovastatin on its biomass (45). In trrm of Nitrogen sources, the largest productivity of lovastatin is associated with the use of soy or yeast extract (19). Most of the C/N ratio is used for the production of lovastatin and the lowest for the production of biomass in aspergillus terreus (19). The rimary pH has an important role in the growth of fungi and lovastatin production so that high levels of lovastatin on top of pH 5.6 is obtained (58). Mineral elements like pH are used to regulate genes, most notably in the production of lovastatin elements are Fe and Zn (59).

Inducers are other factors in the production of lovastatin that the addition of certain concentration and time, thereby increasing the production of lovastatin, addition of these substances in higher or lower concentrations has adverse effect and reduces the production of lovastatin (52,69,70). Out of the parameters temperature is another important, by changing the temperature (from 30 to 23°C) the growth phase could be seperated from the production phase that enhance the production of lovastatin compared with a constant temperature of the medium (63), on the contrary, an increase in temperature caused inhibition of lovastatin production by aspergillus terreus (64).

Acknowledgments

Hereby, we would like to thank the National Elites Foundation and President of the National Elites Foundation Dr. Surena Satari.

[DOR: 20.1001.1.15614107.1395.18.12.6.2]
[DOI: 10.22088/jbums.18.12.40]

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