KAVAKA 61(4): 1-9 (2025) DOI: 10.36460/Kavaka/61/4/2025/1-9

Biotransformation of Lovastatin to Simvastatin by *Rhizopus stolonifer* (ITCC-6439) and *Aspergillus* spp.

Bhargavi SD, Sukrutha S K, Savitha J*

Department of Microbiology, Biotechnology and Food Technology, Jnana Bharathi Campus, Bangalore University, Bengaluru - 560 056, Karnataka, India.
**Corresponding author Email: drsvtj@yahoo.co.in*

(Submitted on July 23. 2025; Accepted on September 2, 2025)

ABSTRACT

Simvastatin is a semisynthetic derivative of natural lovastatin and exhibits anticholesterol property by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase enzyme activity. Our study establishes a simple, ecofriendly and economical method of solid substrate fermentation for the biotransformation of lovastatin to simvastatin using the fungus *Rhizopus stolonifer* (ITCC-6439). Our results indicated that, maximum biotransformation of lovastatin to simvastatin (46%) was achieved when wheat bran was used as a solid substrate, compared to submerged fermentation (12%). The above results were confirmed using TLC, HPLC and ESI-MS/MS method. This is the first report to achieve 46% bioconversion of lovastatin to simvastatin by *R stolonifer* (ITCC-6439) using wheat bran at 28°C for 7 days under static condition. Overall, our results suggest the potential application of solid substrate fermentation process as an ancillary platform to the currently used multistep semisynthetic approach for pharmaceutically valuable simvastatin production.

Keywords: Lovastatin, Simvastatin, Biotransformation, *Aspergillus* sp. (N-15), *Rhizopus stolonifer* (ITCC-6439)

INTRODUCTION

Hypercholesterolemia is caused due to the increased level of low-density lipoprotein in the bloodstream (Alvarez-Lueje *et al*., 2005). It is considered as the 'Bad cholesterol', leave behind fatty deposits in the blood vessel, thus resulting in atherosclerosis (Atli *et al*., 2013, Balling *et al*., 2023), Ischemic stroke (Balraj *et al*., 2023, Berg *et al*., 2009) and myocardial infarction (Bhattarai *et al*., 2020). Statins such as lovastatin, simvastatin, pravastatin, fluvastatin and atorvastatin are a class of drugs used commonly for alleviating cholesterol (Bocate *et al*., 2019, Booth 1971). Hypocholesterolemic property of statins is attributed to the competitive inhibition of 3-hydroxy-3- methylglutaryl coenzyme A (HMG-CoA) reductase (Boren *et al*., 2020, Brilhante *et al*., 2015).

Lovastatin, a polyketide compound, also known as Mevinolin, Monacolin K and Mevacor is a secondary metabolite synthesized from various fungi such as *Aspergillus terreus* (Dastghaib *et al*., 2020, De Carvalho, 2017, Dikshit *et al*., 2015), *Monascus* spp. (Dominguez *et al*., 2023, Endo *et al*., 2010), *Penicillium* spp. (Gu *et al*., 2015) and *Pleurotus* (Hajiahmadi *et al*., 2023). It is the first statin to be approved by the United States Food and Drug Administration (He *et al*., 2022, Huang *et al*., 2018). A more potent statin known as simvastatin is a semisynthetic derivative of natural lovastatin. The molecular difference between lovastatin and simvastatin exists in the side chain on the C-8 position. Lovastatin carries a 2-methylbutyrate moiety, while simvastatin has a 2,2-dimethylbutyrate (DMB) on C8 position (Kamath *et al*., 2015). Therefore, simvastatin differs from lovastatin with one extra methyl group. In addition to the cholesterol lowering property, simvastatin exerts potential anticancer activity (Kimura *et al*.,1990, Liao *et al*., 2005, Maron *et al*., 2000), antimicrobial activity against various pathogens such as *Mycobacterium ulcerans*, oral bacteria, *Salmonella* spp, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, Methicillin resistant *Staphylococcus aureus* (Mehrbod *et al*., 2014, Na *et al*., 2024, Oliveira *et al*., 2021), yeast such as *Candida* spp., *Cryptococcus* spp., *Aspergillus* sp., *Saccharomyces cerevisiae* (Paz *et al*., 2018, Qiao *et al*., 2012; 2022), Influenza virus (Radha and Divya, 2013).

Synthesis of simvastatin using natural lovastatin in industries involves a semi-synthetic route. It employs expensive chemicals, various steps and results in lower yield (Samiee *et al*., 2003). Thus, there is colossal attention among researchers round the globe to quest for the synthesis of lovastatin derivatives having potential activity and reduced

toxicity through a sustainable microbial biotransformation. Therefore, the present study was aimed to develop a novel method for the bioconversion of lovastatin to simvastatin by employing fungi such as *Aspergillus* sp. (N-15) and *Rhizopus stolonifer* (ITCC-6439) using submerged and solid-state fermentation. This led to some interesting findings and they are presented in this paper and the results showed that amongst the two fungi, rate of biotransformation using *R.stolonifer* (ITCC-6439) is better compared to *Aspergillus* sp. (N-15).

MATERIAL AND METHODS

Isolation of Fungi from Soil Samples

For the isolation of different types of fungi, 110 soil sample were collected from different parts of Karnataka, India. A serial dilution technique was followed and a 10^{-6} dilution of each sample was seeded on potato dextrose agar (PDA) and incubated at 28°C for 96 hours. Individual fungal colony developed was sub-cultured in PDA and were stored at 4°C (Seenivasan *et al*., 2015). *Rhizopus stolonifer* (ITCC-6439) was obtained from Indian Type Culture Collection Centre (ITCC), New Delhi, India for a comparative study purpose and stored at 4°C, till further use.

Biotransformation of Lovastatin to Simvastatin

Submerged fermentation

A. Screening and extraction of Simvastatin by whole cell biocatalysis (WCB)

Standard lovastatin (100mg/L, M2147, Sigma-Aldrich, USA) was added to 250ml of Potato Dextrose Broth (PDB). Spore suspension (10^7spores/ml) of *Aspergillus* sp. (N-15) and *R stolonifer* (ITCC-6439) were inoculated individually to PDB and incubated at 28°C under shaken condition (120 rpm) for 7 days. After 7 days of growth, biomass was harvested, filtered using the muslin cloth and simvastatin was extracted with ethyl acetate. Extract obtained was concentrated using rotary vacuum evaporator and further analyzed by TLC and HPLC methods (Seydametova *et al*., 2012).

B. Screening and extraction of Simvastatin by cell free extract (CFE)

Potato dextrose broth (250ml) was inoculated with a spore suspension (10^7spores/ml) of *Aspergillus* sp. (N-15) and *R stolonifer* (ITCC-6439) individually, incubated at 28°C under shaken condition (120 rpm) for 7 days. After 7 days of growth, the culture broth was filtered using Whatman No. 1 filter paper. The filtrate was centrifuged with equal volume of 0.1 M phosphate buffer (pH 7.2) at 4^0C for 10 minutes. The resultant supernatant was considered as cell-free extract and used for further studies. A mixture containing equal volume of standard lovastatin (100mg/L, (M2147, Sigma-Aldrich, USA) and cell-free extract was incubated at 25^0C for 24 hours under shaken condition (120 rpm). Simvastatin was extracted using ethyl acetate. The extract obtained was concentrated using rotary vacuum evaporator and further analyzed by TLC and HPLC methods (Shojaei *et al*., 2020).

Solid State Fermentation

Wheat bran (2 grams) mixed with lovastatin (10mg/g, M2147, Sigma-Aldrich, USA) was inoculated with a spore suspension (10^7 spores/ml) of *Aspergillus* sp. (N-15) and *R stolonifer* (ITCC-6439), incubated at 28°C for 7 days under static condition. After seven days, wheat bran along with the mycelial mat was dried at 35ºC for 24 hours, crushed and extracted using ethyl acetate and filtered by Whatman No.1 filter paper. The extract obtained was concentrated using rotary vacuum evaporator and further analyzed by TLC and HPLC method (Shojaei *et al*., 2020).

Analysis of Simvastatin

A. Thin Layer Chromatography (TLC)

Silica gel TLC plates (20× 20 cm) were purchased from Merck and activated at 700C. Standard simvastatin (1 mg/ml, S6196, Sigma-Aldrich, USA) and 10 µl of fungal crude extract was dissolved in ethyl acetate and spotted on the silica gel plate. It was placed in the development chamber containing dichloromethane and ethylacetate (70:30, v/v) as mobile phase. The spots were observed under Ultra-violet lamp (254 nm) and exposed to Iodine vapour (Stevenson *et al.,* 2012).

B. High Performance Liquid Chromatography (HPLC) analysis

A reverse phase HPLC (Shimadzu, Japan) was equipped with a capillary C18 column (250 mm x 4.6 mm) and diode array detector. Crude extracts were filtered by membrane filter (0.45 µm) and solvents for mobile phase were degassed prior to

use. All the solvents used were HPLC grade. Analysis was carried out using a mixture of acetonitrile and water (acidified with 1.1% phosphoric acid, 70:30 v/v) as mobile phase under isocratic mode. Fungal crude extract (10µl) of *Aspergillus* sp. (N-15) and *R. stolonifer* (ITCC-6439) was injected in the injection port. The eluent flow rate was maintained at 1 mL/minute and detected at 238nm (Suraiya *et al.,* 2018). Simvastatin was detected using authentic simvastatin standard (S6196, Sigma-Aldrich, USA). The rate of biotransformation of lovastatin to simvastatin was expressed in percentage. All the values were means of triplicate determination.

C. Determination of molecular mass of lovastatin analogue by Liquid Chromatography Mass Spectroscopy (LCMS) analysis

LCMS analysis was carried out using LC-20AD pump and a SIL-20AC VP autosampler (Shimadzu, Columbia, MD, USA). The LC system was interfaced to an API 2000 ESI-MS/MS (Applied Biosystems, Foster City, CA, USA). C18 Analytical column (2.0 mm X 100 mm i.d.; 2.5 mm particle size, Shimadzu) was connected to a C18 guard column (Shimadzu, 2 mm X 4 mm; 5 mm particle size). An isocratic mobile phase of 75:25 (% v/v) acetonitrile: ammonium acetate (0.1 M, pH 5.0 adjusted with acetic acid) was used with a flow rate of 0.15 ml/minute. The injection volume was 10µl and the run time was 10 minutes. All the analytes and internal standard were detected on a triple quadrupole mass spectrometer (API 2000), equipped with a turbo ion spray source (MDS SCIEX, Toronto, Canada) and operated in the positive ion mode. Simvastatin (S6196, Sigma-Aldrich, USA) was used as an internal standard. Quantification was performed using Multiple Reaction Monitoring (MRM) of precursor/product ion transitions at m/z 419.3/199.3 for simvastatin (Thangamani *et al.,* 2015).

Statistical analysis

All the experiment were performed in triplicates and statistical analysis was carried out using SPSS version 22. Mean standard deviation was calculated from the test replicate values. $p \leq 0.05$ was considered significant.

RESULTS AND DISCUSSION

Screening of fungi for simvastatin synthesis by TLC

A total number of 110 fungi belonging to the genera *Rhizopus, Mucor*, *Penicillium*., *Aspergillus*., *Curvularia*, *Cladosporium*, *Helminthosporium*, *Trichoderma*, *Cunninghamella* and *Fusarium* were isolated from soil and screened for their efficiency to biotransform lovastatin to simvastatin under SSF and submerged fermentation.The isolate N-15, identified as *Aspergillus* sp. and *R stolonifer* (ITCC 6439) produced simvastatin, as evidenced by the R_f value of standard and fungal crude extracts (**Figure 1**). Therefore, these two fungi were selected for further study.

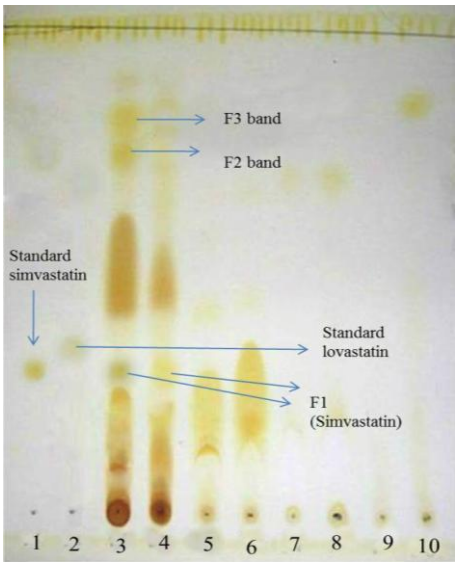

Figure 1: Screening of fungi for simvastatin production by Thin Layer Chromatography. Lane 1, Standard simvastatin; Lane 2, Standard lovastatin; Lane 3, Crude extract of *Rhizopus stolonifer* (ITCC-6439); Lane 4, Crude extract of *Aspergillus* sp. (N-15); Lane 5-10, other fungal isolates

Identification of simvastatin by HPLC and LCMS analysis

Biotransformation of lovastatin to simvastatin by *Aspergillus* sp. (N-15) and *R stolonifer* (ITCC 6439) was confirmed by standard simvastatin, having a distinct peak at the retention time of 13.61 minute (**Figure 2**).

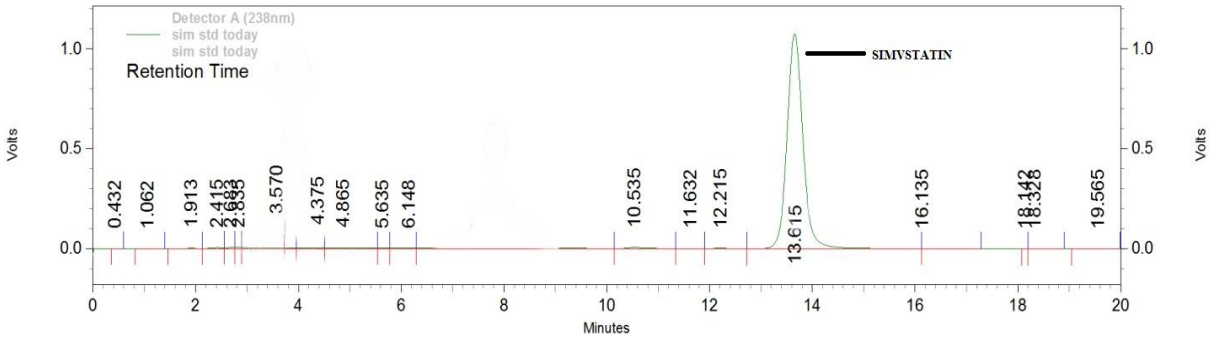

Figure 2: HPLC chromatogram of standard simvastatin

Differences in the percentage of biotransformation of lovastatin was seen under submerged (WCB, CFE) and SSF method. Our results indicated that, under WCB method, maximum simvastatin production of 18% was observed in *R stolonifer* (ITCC 6439), compared to 9% in *Aspergillus* sp. (N-15, **Figure 3** and **4**). Similarly, under CFE method, maximum simvastatin production of 8% was observed in *R stolonifer* (ITCC 6439), compared to 6% in *Aspergillus* sp. (N-15, **Figure 5** and **6**). These results suggest that, among submerged fermentation, compared to CFE method, WCB favored biotransformation of lovastatin to simvastatin in *R. stolonifer* (ITCC 6439) than *Aspergillus* sp. (N-15). Growing body of lines suggest that, compared to CFE, WCB are relatively effective and economical (Kamath *et al*., 2015, Morofuji *et al*., 2022).

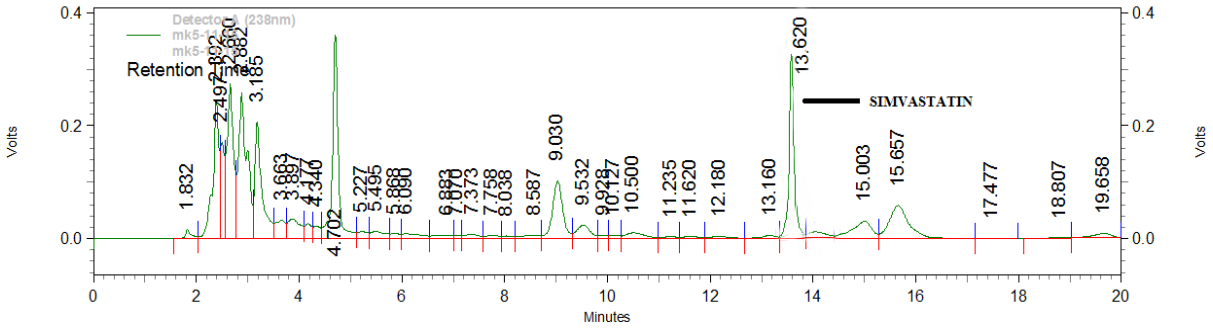

Figure 3: HPLC chromatogram of *Rhizopus stolonifer* (ITCC-6439) extract, incubated with lovastatin by whole cell biocatalysis method

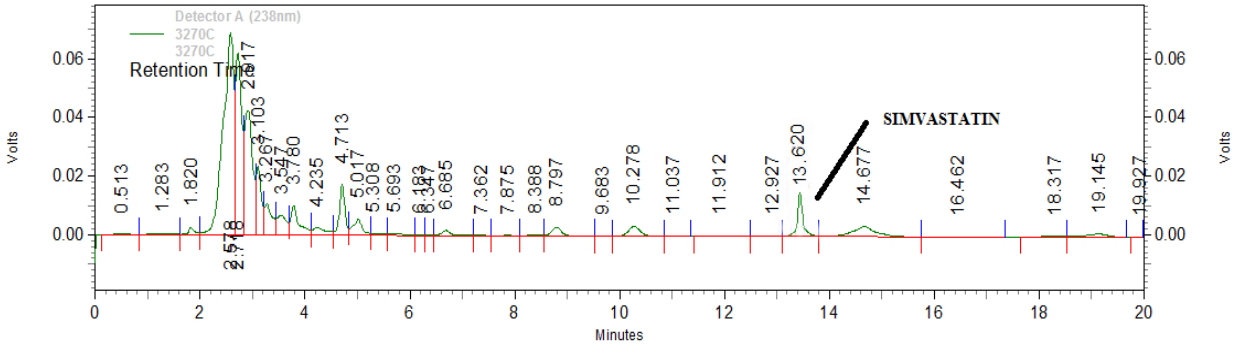

Figure 4: HPLC chromatogram of *Aspergillus sp.* (N-15) extract, incubated with lovastatin by whole cell biocatalysis method

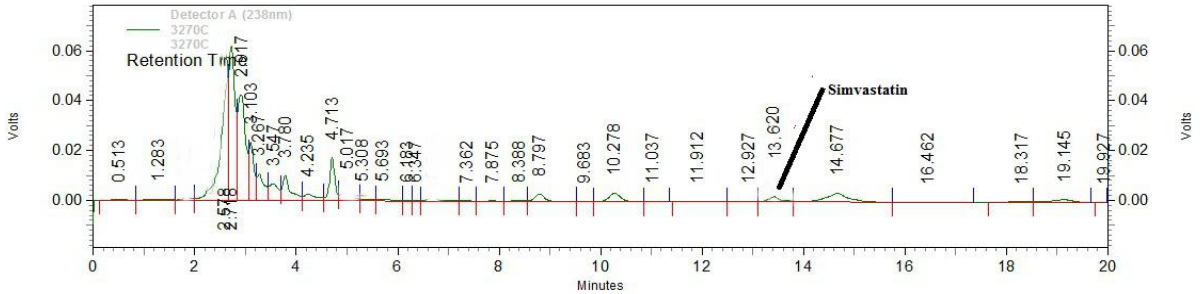

Figure 5: HPLC chromatogram of *Rhizopus stolonifer* (ITCC-6439) extract, incubated with lovastatin by cell free extract method

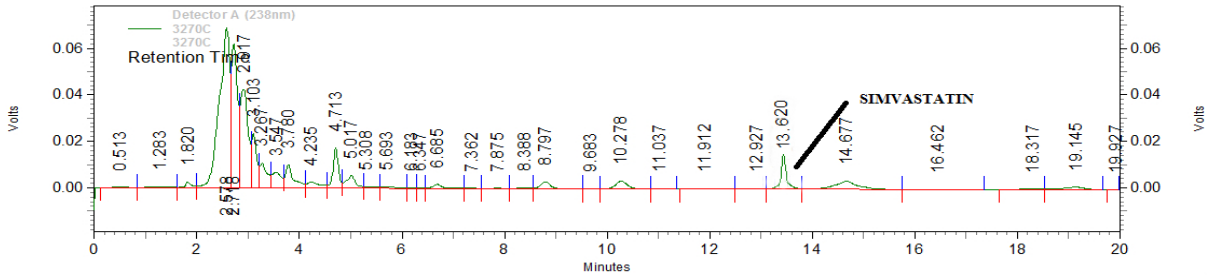

Figure 6: HPLC chromatogram of *Aspergillus sp.* (N-15) extract, incubated with lovastatin by cell free extract method

Interestingly, under SSF, when wheat bran was used as a solid substrate, *R stolonifer* (ITCC 6439) displayed a significant increase in simvastatin production (46%), compared to *Aspergillus* sp. (N-15, 10%, **Figure 7** and **8**). Wheat bran is attractive candidate for SSF and confers several advantages such as owing to easy growth and desired metabolite synthesis in various microorganisms. It comprises of polysaccharides such as cellulose, arabinoxylans, lignin, protein and fats which could contribute as acyl donors for the microbial biomachineries for biotransformation process (Xie *et al*., 2007). This is the first report to show that, an ecofriendly, agro-industrial waste and economical wheat bran could serve as a suitable substrate for efficient fungal biotransformation of lovastatin to pharmaceutically valuable simvastatin. The possible reactions in fermentation media, which could favor lovastatin biotransformation are hydrolysis, hydroxylation, lactone hydrolysis and methylation. In general, the enzyme LovD (acyltransferase) plays a pivotal role in the lovastatin biosynthesis and has a broad substrate specificity towards the acyl carrier group. Further, in 2007, Xie X *et al*. reported that, direct acylation of monacolin J (an intermediate compound between lovastatin and simvastatin) to simvastatin is also mediated by LovD (acyltransferase) enzyme. Thus, we can envisage that, wheat bran could be a potential candidate to stimulate the LovD (acyltransferase) and aid in fungal biotransformation of lovastatin to simvastatin. Molecular mass of the simvastatin was determined by LCMS and was found to be 419 m/z (**Figure 9** and **10**). Similar such findings were reported in *Streptomyces carpaticus* by *Zhang et al.* (2020).

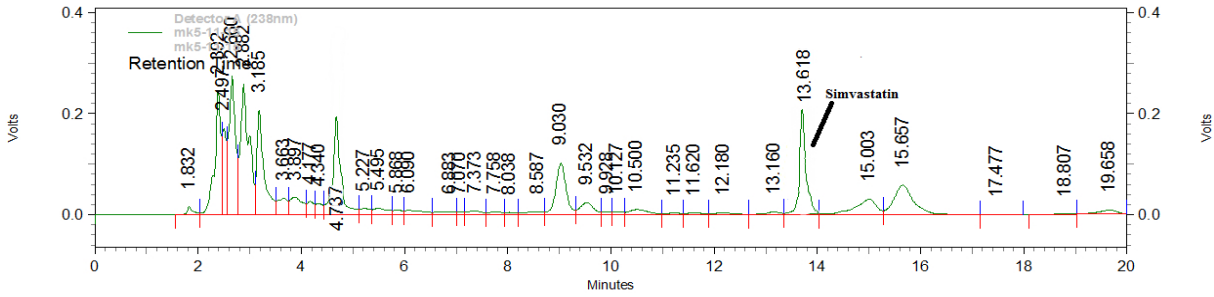

Figure 7: HPLC chromatogram of *Rhizopus stolonifer* (ITCC-6439), incubated with lovastatin under solid substrate fermentation using wheat bran

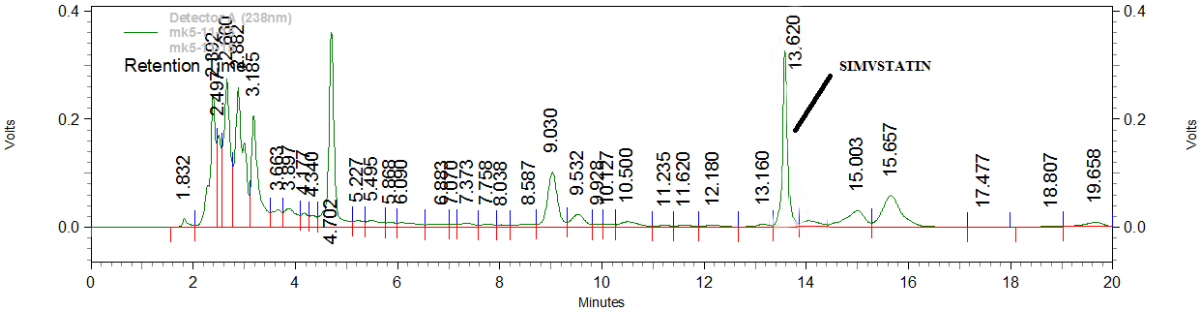

Figure 8: HPLC chromatogram of *Aspergillus sp.* (N-15) incubated with lovastatin under Solid substrate fermentation using wheat bran

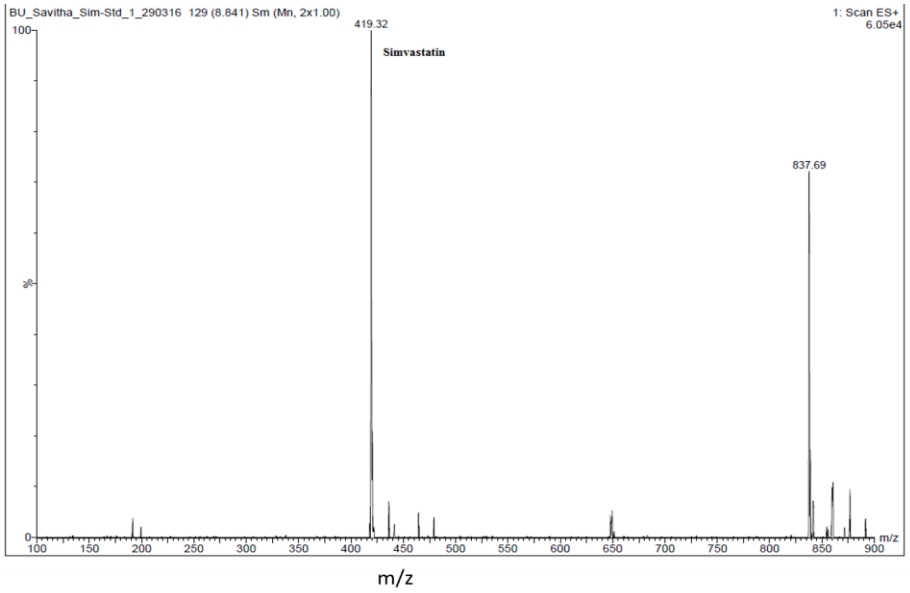

Figure 9: ESI-mass spectrum of standard simvsatatin

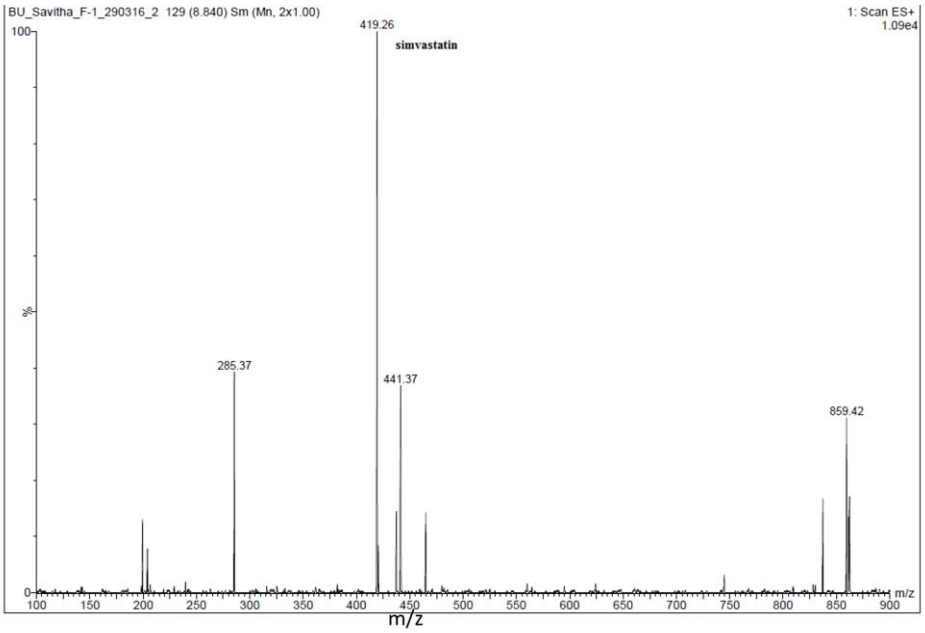

Figure 10: ESI mass spectrum of *Rhizopus stolonifer* (ITCC-6439) extract incubated with lovastatin under solid substrate fermentation

CONCLUSION

Uncertain supplies and multistep chemical synthesis of simvastatin is posing serious economic issues in the global market. Though harnessing fungi for biotransformation studies is well documented, the present study for the first time has uncovered the ability of *Rhizopus stolonifer* (ITCC-6439) to efficiently biotransform lovastatin to simvastatin using wheat bran under solid substrate fermentation. Though we could identify an isolate *Aspergillus* sp. (N-15) which shows biotransformation of lovastatin to simvastatin, the rate of biotransformation was very less compared to *Rhizopus stolonifer* (ITCC-6439). Our findings could be further exploited for the bioprocess development of pharmaceutically important simvastatin.

ACKNOWLEDGEMENT

The authors thank the financial support provided by Science and Engineering Research Board, Department of Science and Technology, Govt. of India vide grant number DST/SO F.No.SERB.SR/SO/PS/046/2011.

CONFLICT OF INTEREST

The authors declare that they have no competing financial interests.

REFERENCES

Álvarez-Lueje, A., Valenzuela, C., Squella, J.A., *et al.,* 2005. Stability study of simvastatin under hydrolytic conditions assessed by liquid chromatography. *Journal of AOAC International*, ***88*(6)**:1631-1636.

Atli, B., Yamac, M., Yildiz, Z., 2013. Optimization of submerged fermentation conditions for lovastatin production by the culinary-medicinal oyster mushroom, Pleurotus ostreatus (Higher Basidiomycetes). *International Journal of Medicinal Mushrooms,* **15(5)**.

Balling, M., Nordestgaard, B.G., Varbo, A., *et al.,* 2023. Small Dense Low-Density Lipoprotein Cholesterol and Ischemic Stroke. *Annals of Neurology*, **93(5)**:952-964.

Balraj, J., Murugesan, T., Dhanapal, A.R., *et al.,* 2023. Bioconversion of lovastatin to simvastatin by Streptomyces carpaticus toward the inhibition of HMG-CoA activity. *Biotechnology and Applied Biochemistry*, **70(3)**:1162-1175.

Berg, V.D.M.A., Hans, M., Streekstra, H. 2009. U.S Patent 12/304, 283.

Bhattarai, A.K., Acharya, A., Karki, P.K., 2020. Use of statins as lipid lowering agent in hypercholesterolemia in a tertiary care hospital: a descriptive cross-sectional study. *JNMA: Journal of the Nepal Medical Association*, **58(232)**:1031.

Bocate, K.P., Reis, G.F., de Souza, P.C., *et al.,* 2019. Antifungal activity of silver nanoparticles and simvastatin against toxigenic species of Aspergillus. *International journal of food microbiology*, **291**:79-86.

Booth, C. 1971. Fungal culture media. 4th ed. Methods in Microbiology, London and New York, Academic Press, pp.50-93.

Boren, J., Chapman, M.J., Krauss, R.M., *et al.,* 2020. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. *European heart journal*, **41(24)**:2313-2330.

Brilhante, R.S.N., Caetano, E.P., Oliveira, J.S.D., *et al.,* 2015. Simvastatin inhibits planktonic cells and biofilms of Candida and Cryptococcus species. *Brazilian Journal of Infectious Diseases*, **19(5)**:459-465.

Dastghaib, S., Shojaei, S., Mostafavi-Pour, Z., *et al.,* 2020. Simvastatin induces unfolded protein response and enhances temozolomide-induced cell death in glioblastoma cells. *Cells*, **9(11)**:2339.

De Carvalho, C.C., 2017. Whole cell biocatalysts: essential workers from nature to the industry. *Microbial Biotechnology*, **10(2)**:25 0-263.

Dikshit, R. and Tallapragada, P., 2015. Bio-synthesis and screening of nutrients for lovastatin by Monascus sp. under solid-state fermentation. *Journal of food science and technology*, **52(10)**:6679-6686.

Dominguez, J., Mendes, A.I., Pacheco, A.R., *et al.,* 2023. Repurposing of statins for Buruli Ulcer treatment: antimicrobial activity against Mycobacterium ulcerans. *Frontiers in Microbiology*, **14**:1266261.

Endo, A., 2010. A historical perspective on the discovery of statins. *Proceedings of the Japan Academy, Series B*, **86(5)**:484-493.

Gu, H.M. and Zhang, D.W., 2015. Hypercholesterolemia, low density lipoprotein receptor and proprotein convertase subtilisin/kexin-type 9. *Journal of biomedical research*, **29(5)**:356.

Hajiahmadi, S., Lorzadeh, S., Iranpour, R., *et al.,* 2023. Temozolomide, simvastatin and acetylshikonin combination induces mitochondrial-dependent apoptosis in GBM cells, which is regulated by autophagy. *Biology*, **12(2)**:302.

He, Y., Gu, X., Hu, Y., *et al.,* 2022. Low-density lipoprotein receptor and apolipoprotein A 5, myocardial infarction biomarkers in plasma-derived exosomes. *Journal of Cardiology*, **79(5)**:605-610.

Huang, F.C. and Huang, S.C., 2018. Differential effects of statins on inflammatory interleukin-8 and antimicrobial peptide human β-defensin 2 responses in salmonella-infected intestinal epithelial cells. *International Journal of Molecular Sciences*, **19(6)**:1650.

Kamath, P.V., Dwarakanath, B.S., Chaudhary, A., *et al.,* 2015. Optimization of culture conditions for maximal lovastatin production by Aspergillus terreus (KM017963) under solid state fermentation. *HAYATI Journal of Biosciences*, **22(4)**:174-180.

Kimura, K., Komagata, D., Murakawa, S. *et al.,* 1990. Biosynthesis of monacolins: conversion of monacolin J to monacolin K (mevinolin). *The Journal of Antibiotics*, **43(12)**:621-1622.

Liao, J.K. and Laufs, U., 2005. Pleiotropic effects of statins. *Annual Reviews in Pharmacology and Toxicology*, **45(1):**89-118.

Maron, D.J., Fazio, S., Linton, M.F., 2000. Current perspectives on statins. *Circulation*, **101(2)** :207-213.

Mehrbod, P., Hair-Bejo, M., Tengku Ibrahim, T.A., *et al.,* 2014. Simvastatin modulates cellular components in influenza A virus-infected cells. *International Journal of Molecular Medicine*, **34(1)**:61-73.

Na, H., Zheng, Y.Y., Jia, Y., *et al.,* 2024. Screening and genetic engineering of marine-derived Aspergillus terreus for high-efficient production of lovastatin. *Microbial Cell Factories*, **23(1)**:134.

Oliveira, M.C.L.D., Paulo, A.J., Lima, C.D.A., *et al.,* 2021. Lovastatin producing by wild strain of Aspergillus terreus isolated from Brazil. *Preparative Biochemistry & Biotechnology*, **51(2)**:164-172.

Paz, J., Gorostiaga, J., Campra, P., *et al.,* 2018. Ensayo in vitro de la asociación de simvastatina y fluconazol en cultivos de criptococos de pacientes con meningoencefalitis criptocócica que concurrieron al hospital Ángel Padilla de San Miguel de Tucumán. *Neurología Argentina*, **10(1)**:2-7.

Qiao, L., Xie, D., Liu, Q., *et al.,* 2012. Microbial transformation of lovastatin by Beauveria bassiana. *Acta Pharmaceutica Sinica B*, **2(3)**:300-305.

Qiao, Y.N., Zou, Y.L., Guo, S.D., 2022. Low-density lipoprotein particles in atherosclerosis. *Frontiers in Physiology*, **13**: 931931.

Radha, K.V. and Lakshmanan, D., 2013. A review: Lovastatin production and applications. *Asian Journal of Pharmaceutical and Clinical Research*, **6(3)**:21-26.

Samiee, S.M., Moazami, N., Haghighi, S., *et al.,* 2003. Screening of lovastatin production by filamentous fungi. *Iranian Biomedical Journal*, **7(1)**:29-33.

Seenivasan, A., Gummadi, S.N., Panda, T., *et al.,* 2015. Quantification of lovastatin produced by Monascus purpureus.

Seydametova, E., Salihon, J., Zainol, N., *et al.,* 2012. Production of Lovastatin by Penicillium spp. soil microfungi. *International Journal of Chemical Engineering and Applications*, **3(5)**:337.

Shojaei, S., Koleini, N., Samiei, E., *et al.,* 2020. Simvastatin increases temozolomide-induced cell death by targeting the fusion of autophagosomes and lysosomes. *The FEBS journal*, **287(5)**:1005-1034.

Stevenson, L.E.O., Phillips, F., O'sullivan, K. *et al.,* 2012. Wheat bran: its composition and benefits to health, a European perspective. *International journal of food sciences and nutrition*, **63(8)**:1001-1013.

Suraiya, S., Kim, J.H., Tak, J.Y., *et al.,* 2018. Influences of fermentation parameters on lovastatin production by Monascus purpureus using Saccharina japonica as solid fermented substrate. *Lebensmittel-Wissenschaft & Technologie*, **92**:1-9.

Thangamani, S., Mohammad, H., Abushahba, M.F., *et al.,* 2015. Exploring simvastatin, an antihyperlipidemic drug, as a potential topical antibacterial agent. *Scientific reports*, **5(1)**:16407.

Xie, X. and Tang, Y., 2007. Efficient synthesis of simvastatin by use of whole-cell biocatalysis. *Applied and environmental microbiology*, **73(7)**:2054-2060.

Zhang, X.X., Wei, M., Shang, L.X., *et al.,* 2020. LDL-C/HDL-C is associated with ischaemic stroke in patients with non-valvular atrial fibrillation: a case-control study. *Lipids in Health and Disease*, **19(1)**:217.