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HMG-CoA reductase inhibitors: an updated review of biosynthesis and patent prospecting

Inibidores da HMG-CoA reductase: uma revisão atualizada da prospecção de biossíntese e patentes

Inhibidores de la HMG-CoA redutasa: una revision actualizada de la biosíntesis y la prospección de patentes

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Abstract
HMG-CoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A reductase) is the enzyme that plays a limiting role in cholesterol biosynthesis. Among the HMG-CoA reductase inhibitor molecules, statins stand out, a class of drug used in the treatment of atherosclerosis and in the reduction of high cholesterol levels, therefore they are biomolecules of medical and pharmaceutical importance. In this context, this work aimed to carry out a systematic mapping of patents and scientific articles related to the biosynthesis of HMG-CoA reductase inhibitors. The search was carried out in the databases of the National Institute of Intellectual Property (INPI), the European Patent Office (Espacenet), the Derwent Innovations Index, the World Intellectual Property Organization (WIPO) and also articles indexed in Scielo and Pubmed using as descriptors "statins", "production and statins and fungi", "statins and fungus". Of the 2561 cataloged patents, 09 were included because they met the inclusion criteria. The number of scientific articles found in the databases was higher (2820) when compared to the number of patents. As a country, China represents the largest holder on the subject, corresponding to 88.9% of patented products. Based on the mapping, advances in the search for strategies for the biotechnological production of statins can be highlighted. Some of the inventions used microorganisms such as filamentous fungi associated with agro-industrial substrates as an alternative and low-cost source for the production of statins to replace synthetic sources. However, future studies can be carried out using new fungi and new renewable substrates, considering the existing biodiversity worldwide.
Keywords: Statins; Fungi; Renewable substrates; Biopharmaceutical.

Resumo

A HMG-CoA redutase (3-hidroxi-3-metilglutaril-coenzima A redutase) é a enzima que tem papel limitante na biossíntese do colesterol. Entre as moléculas inibidoras da HMG-CoA redutase destacam-se as estatinas, classe de medicamento utilizado no tratamento da aterosclerose e na redução dos elevados níveis de colesterol, logo são biomoléculas de importância médica e farmacêutica. Nesse contexto, este trabalho teve como objetivo realizar um mapeamento sistemático de patentes e de artigos científicos relacionados com a biossíntese de inibidores da HMG-CoA redutase. A busca foi realizada nas bases do Instituto Nacional da Propriedade Intelectual (INPI), do European Patent Office (Espacenet), do Derwent Innovations Index, do World Intellectual Property Organization (WIPO) e também artigos indexados no Scielo e Pubmed utilizando como descritores "estatinas", "produção e estatinas e fungos", "estatinas e fungo". Das 2561 patentes catalogadas, 09 foram incluídas por atender aos critérios de inclusão. O número de artigos científicos encontrados nas bases de dados foi superior (2820) quando comparado ao número de patentes. Como país, a China representa o maior detentor sobre a temática, correspondendo a 88,9% dos produtos patenteados. A partir do mapeamento, pode-se destacar avanços na busca por estratégias para produção biotecnológica de estatinas. Algumas das invenções utilizaram micro-organismos como fungos filamentosos associados a substratos agroindustriais como fonte alternativa e de baixo custo para produção de estatinas em substituição a fontes sintéticas. No entanto, existe uma lacuna que pode ser preenchida pela atividade de novos fungos e de novos substratos renováveis, que ainda não foram pesquisados, considerando a biodiversidade existente mundialmente.

Palavras-chave: Estatinas; Fungos; Substratos renováveis; Biofármaco.

Resumen

La HMG-CoA reductasa (3-hidroxi-3-metilglutaril-coenzima A reductasa) es la enzima que juega un papel limitante en la biosíntesis del colesterol. Entre las moléculas inhibidoras de la HMG-CoA reductasa destacan las estatinas, una clase de fármaco utilizada en el tratamiento de la aterosclerosis y en la reducción de los niveles elevados de colesterol, por lo que son biomoléculas de importancia médica y farmacéutica. En este contexto, este trabajo tuvo como objetivo realizar un mapeo sistemático de patentes y artículos científicos relacionados con la biosíntesis de inhibidores de la HMG-CoA reductasa. La búsqueda se realizó en las bases de datos del Instituto Nacional de Propiedad Intelectual (INPI), la Oficina Europea de Patentes (Espacenet), el Derwent Innovations Index, la Organización Mundial de la Propiedad Intelectual (OMPI) y también artículos indexados en Scielo y Pubmed utilizando como descriptores "estatinas", "producción y estatinas y hongos", "estatinas y hongos". De las 2561 patentes catalogadas, se incluyeron 09 porque cumplían con los criterios de inclusión. El número de artículos científicos encontrados en las bases de datos fue mayor (2820) en comparación con el número de patentes. Como país, China representa el mayor poseedor en la materia, correspondiendo al 88,9% de los productos patentados. A partir del mapeo se pueden destacar avances en la búsqueda de estrategias para la producción biotecnológica de estatinas. Algunas de las invenciones utilizaron microorganismos tales como hongos filamentosos asociados a sustratos agroindustriales como fuente alternativa y de bajo costo para la producción de estatinas en reemplazo de las fuentes sintéticas. Sin embargo, se pueden realizar estudios futuros utilizando nuevos hongos y nuevos sustratos renovables, considerando la biodiversidad existente a nivel mundial.

Palabras clave: Estatinas; Hongos; Sustratos renovados; Biofarmaceutico.

1. Introduction

HMG-CoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A reductase or HMGR) is an enzyme of the mevalonate pathway responsible for the synthesis of cholesterol. It isenzyme is a target for numerous drugs, as it participates in the rate-limiting step of endogenous production of cholesterol (Cedraz; Lavorato, 2020; Ram et al, 2021). Among the drugs most used in the treatment of dyslipidemia are statins, which because they have structural similarity to the substrate 3-hydroxy-3 methylglutaryl CoA (HMG-CoA), inhibit the enzyme HMG-CoA reductase (EC. 1.1.1.34), essential for the cholesterol biosynthesis (Morofuji et al., 2022; Mouafi; Ibrahim; Elsoud, 2016).

The world market for HMG-CoA reductase inhibitors (statins) is estimated at 39.8 billion by 2025 according to iHealthcareAnalyst. The role of this classtherapy in the reduction of lipids in the blood is already evidenced, however, studies clinical evidence evidence other beneficial effects of statins exhibiting action anti-inflammatory, antioxidant and immunomodulatory, providing them with an therapeutic in the treatment of various diseases (Kashour et al., 2021; Mihos; Pineda; Santa, 2014).

Biotechnological production is preferred for industrial production ofHMG-CoA reductase inhibitors that can be produced as metabolites secondary to several microorganisms, such as *Penicillium* sp., *Monascus ruber* and *Aspergillus terréus* (Gholami-Shabani et al., 2022; Moreira et al., 2018).

Filamentous fungi are the main producers of statins considering the presence of an enzyme system analogous to that of humans, Cytochrome P450 (CYP,P450), responsible for drug metabolism. These biomolecules are produced basically biosynthetically by submerged fermentation (Hasan et al.,2022; Huang; Liao; Li, 2018; Mclean et al., 2015).

HMG-CoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A reductase or HMGR) is an enzyme of the mevalonate pathway responsible for the synthesis of cholesterol. It isenzyme is a target for numerous drugs available on the market to reduce the levels of cholesterol, known as statins that participate in the limiting step of production endogenous cholesterol. The main drugs available on the market are: Simvastatin, Pravastatin, Atorvastatin, Rosuvastatin (Morofuji et al., 2022;Cedraz; Lavorato, 2020; Mouafi; Ibrahim; Elsoud, 2016).

Cardiovascular diseases are the leading cause of death worldwide according to World Health Organization (WHO), representing 32% of total global deaths. In Brazil, more than 39 thousand people died from January to February 5, 2022 due toheart diseases according to the Brazilian Society of Cardiology (SBC). In this in this sense, the public health problem worsens even more, when added to the pandemic caused by the new coronavirus, since patients with infection caused by SARS-CoV-2 poses risks of cardiovascular and thrombotic complications, increasing the number of patients (Ÿahin; Ÿlgün, 2022; Kashour et al., 2021; Lima Martínez et al., 2020).

It is also noteworthy that hypercholesterolemia is considered an important factorrisk of coronary heart disease in humans. In this sense, several studies epidemiological studies demonstrate a direct relationship between cardiovascular diseases (CVD)and atherosclerosis at high levels of total blood cholesterol (Alizadehsani et al., 2022; Neto et al., 2019; González-Rivas et al., 2018).

In this context, the current world trend is the search for a bioprocess efficient and sustainable for the production of biomolecules with high added value, however, a major challenge is to find microorganisms with high enzymatic potential that allows the production of these biomolecules. The biotechnological production of the HMG-CoA reductase inhibitor gains prominence due to the possibilities of using renewable and low-cost sources for their achievement, contributing to the essential requirements of sustainability (Morofuji et al., 2022; Mahmoud; Abdel_Hadi, 2022; Kashour et al., 2021; Suwannarat et al., 2019; Mouafi;Ibrahim; Elsoud, 2016; Jaivel; Marimuthu, 2010).

The production of new drugs and medicines requires the prospection of information obtained from scientific articles and patents. Therefore, this review aims to objective to carry out a technological prospection and provide an updated overview of theinnovations regarding the biotechnological production of HMG-CoA reductase inhibitorsthrough patents deposited in open access banks using fungi as statin producers as well as the methods used to obtain these biomolecules.

2. Methodology

The study in question is a technological prospection, which aims to present and discuss the systematic mapping of scientific development through patents and technological development of the biosynthesis of HMG-CoA reductase inhibitors. The research was carried out from carried from January from 2015 to July 2022. The searches were carried out in the Institute's database Industrial Property National Institute (INPI) (https://gru.inpi.gov.br/), aiming at the analysis of patents deposited in national territory. In addition, there were also research was carried out in the Derwent Innovations Index – DII (Web of Science/Clarivate Analytics), European Patent Office (Espacenet) (https://worldwide.espacenet.com), being known to have patent applications for approximately 100 countries and World Intellectual Property Organization (WIPO) (https://www.wipo.int), since it has a wider range of patents.

On the other hand, research in scientific articles was carried out on the basis of dados Scielo (Scientific Eletronic Library Online), Pubmed (U.S National Library of Medicine National Institutes of Health). Descriptors and natural language

were used in combination with Boolean operators from the terms and their correlates “statins”, “production and statins and fungi”, “statins and fungus”. The criteria for inclusion applied to the results were: (1) the text available in full; (2) articles and patents published between 2015-2022; (3) written in Portuguese, English or Spanish and, finally, (4) be directly related to the object of study here introduced.

The journals resulting from the search were analyzed based on inhibitors of HMG-CoA reductase produced by fungi, and the use of agro-industrial substrates for their production. At the same time, the patents found were distributed in patents containing HMG-CoA reductase inhibitors and redistributed by patents related to the types of HMG-CoA reductase inhibitors and their production biotechnology. Finally, the data obtained were stored and processed in the Microsoft Excel (Microsoft Office®2016) for interpretation and discussion of results.

3. Results and Discussion

3.1 Mapping of Biotechnological Production of HMG-CoA Reductase Inhibiotors

According to Tigre and Kupfer (2004), technological monitoring through patents aims at the development scientific and technological linked to the expansion of knowledge that are capable of contribute to decision making and the search for new technologies and innovations.

The results obtained through the content analysis were identified 2561 patents through a search in the databases on the four platforms according to the descriptors conform (Table 1). It can be seen that, according to Table 1, the Derwent Innovations Index base is the one that holds the largest number of patents on the subject, with 1303 patents found, followed by World Intellectual property (WIPO) with 1028 and a European Patent Office (Espacenet) with 228 patents.

Table 1 - Number of patents by keywords in title and abstract found in the databases used for research in the period from 2015 to 2022

Descriptors	INPI	Espacenet	Derwent	WIPO
Statins	02	226	1265	1020
Production and statins e fungi	0	01	11	06
Statins and fungi	0	01	27	02
Total:	02	228	1303	1028

Source: Authors.

At the National Institute of Industrial Property (INPI), 02 patent registration. However, as Brazil is part of the Cooperation Treaty of Patents (PCT), it is possible that the patents found at the INPI are the same as those are in WIPO, as they have the same scope due to the agreement.

Neto et al (2021) using technological prospecting as an innovative perspective described that the number of patents deposited in Brazil is considered low, corroborating the results obtained in the present work.

In according to Kandil (2004), this fact can be explained due to the high cost for the drug development, these costs serve international interests both to justify the high princes of their drugs and to discourage pharmaceutical companies from developing countries, such as Brazil, to invest in discovery of new drugs due to the high cost.

The Derwent Innovations Index database covers over 30,5 million detailed in over 65 million patent documents worldwide world, therefore, one can explain the fact of obtaining the greatest number of results (1303) on this platform.

Also according to Table 1, the keyword "Statins", in a general, is the one that stands out the most, obtaining the greatest amount on the Derwent platform with 1265 patents, 1020 on WIPO and 226 on Espacenet. However, in Brazil, the production of patents on this subject is not expressive when compared to other bases, obtaining only 02 patents found.

Two new analyzes were carried out: In the first one, 546 patents, corresponding to 21,31%, followed by the second screening with the objective of carry out a technological prospection of the HMG-CoA reductase inhibitors produced by different genera of fungi. After reading and checking the detailed descriptions of inventions, another 541 patents were excluded for not meeting the needs of the authors, corresponding to 93,08% of the patents analyzes with duplicity or not related to the production of HMG-CoA reductase inhibitors, inability to extract data or not contain full text available. Thus, 10 patents (1,85%) were selected for analysis according to the objective of the study as shown in Table 2.

Table 2 - Patents for the production of HMG-CoA reductase inhibitors by microrganisms from 2015 to 2022.

Patent Nº	Publication date	Title	Inventor
CN113881572(A)	04-01-2022	High-yield lovastatin rede yeast rice as well as cultivation method and application thereof	Feng; Zhang ; Liu; Chen; Li; Zhu (2022)
CN112779301(A)	02-07-2021	Fermentation of lovastatin from red fermented rice by obtaining a fermentation product such as lovastatin from red fermented rice by inoculating fungal liquido f *Monascus purpureus* into a culture médium containing mainly rice for fermentation	Gao; Jlixzhong; Myao (2021)
WO2020038197(A1)	16-03-2020	The *Aspergillus* constructo for the production of monacolin J by direct fermentation comprises the complete blockade of polyketide synthase Lovf expression in *Aspergillus*	Xhuang; Xyang; Lteng (2020)
CN111718970-A	17-11-2020	High yield lovastatin fungal fermentation method by preparing seed bottle culture médium, inoculating colony suspension, shake cukture, preparing fermentation bottle culture médium, colony transplantation and shake culture	Wu; Hzhang; Wzheng (2020)
CN108977469-A	26-02-2019	Use of rice bran juice for the production of pravastatin by microbial fermentation, where the pravastatin production method involves inoculating activated *Actinomadura madurae* into the culture medium, adding mevastatin to the medium to fermente the pravastatin	Chen (2019)
CN109182142 (A)	10/09/2018	New *Penicillium crustosum* Pc-46 used for lovastatin fermentation production	Xu; Dzheng; Mwang, (2018)
CN108315265-A	10/09/2018	New strain of *Aspergillus versicolor* Av-2 useful for the fermentative production of lovastatin	Jiang; Cshou; Zzhang, (2018)
CN106479900-A	06/01/2017	New strain of *Penicillium oxalicum* is preserved at Canadian Clinical Trials Coordinating Centre, used to produce lovastatin	Jiang; Jqian; Yhan, (2017)
CN105219653(A)	08-01-2016	New strain Ac-32 of *Aspergillus clavatus* for high-yield production of lovastatin	Jiang; Hzhang; Mzheng, (2016)
CN105602856-A	08-01-2016	New strain of *Aspergillus niger* An-19 used to make lovastatin is preserved at the China Center for Type Culture Collection	Jiang; Hzhang; Xzheng, (2016)

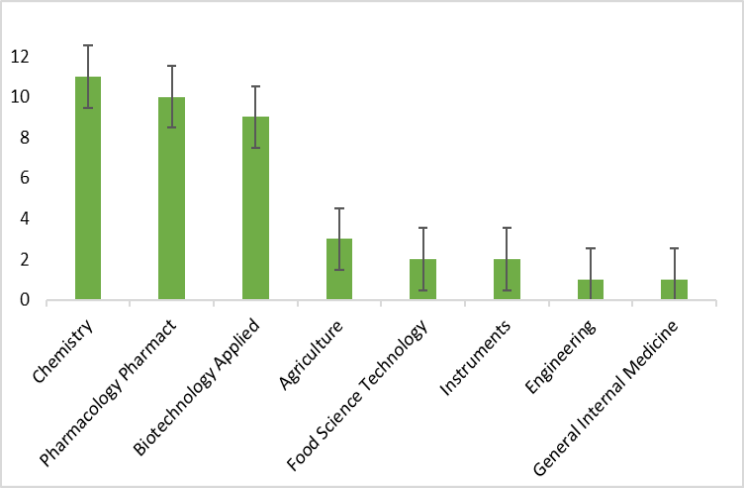
Source: Authors.

Also according to Table 2, it is observed that the patents deposited and selected came from China (09), followed by the World Property Organization Intellectual (WIPO) (01). As a country, China is the main patent holder, signaling its potential for HMG-CoA inhibitor production technologies reductase corresponding to 90% of the patented products. Simão, Wanderley, Nunes and Fritzen-Freire (2022) described the largest deposit of patents by private sector companies in China.

3.1.1 Classification of patent records related to the biotechnological production of statins

On the Derwent platform, 11 patents using the keyword "Production and statins and fungi" were classified in 08 areas of knowledge according to picture in Figure 1. It is observed that 11 documents, 100%, are in the area of "*Chemistry*", "*Pharmacology Pharmacy*" (10 records) with 90, 91%, and the "*Biotechnology Applied Microbiology*" presented 09 record generating a percentage of 81,82%.

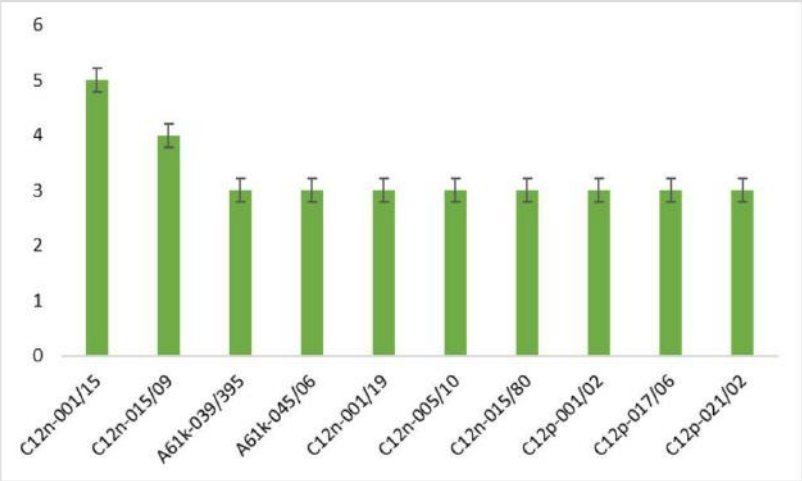
Figure 1 - Patent registration on the DERWENT platform with the keywords "Production and statins and fungi" for the period 2015 to 2022 evaluated by areas of knowledge.



Source: Derwent Innovations Index (2022).

Patents filed are classified according to Category International Patent Office (CIP) which is composed of letters and numbers, divided into sections, classes, subclasses and groups; It is a system recognized worldwide, which has with the objective to standardize the varied themes in the technological scope for an accessible language. Specifically, the classification in which most of the analyzes patents is the C12N area (18) (microorganisms or enzymes; their compositions; propagations, preservation, or maintenance of microorganisms or tissue; genetic or mutation engineering. Culture media), followed by the A61K patents (16) (preparations for medicinal, dental or hygienic purposes) and the third most cited class C12P (12) (fermentation process or processes using enzymes to synthesize a desired chemical composition or compound or to separate optical isomers of a racemic mixture) (Figure 2).

Figure 2 - Number of patents filed classification (CIP) related to biotechnological production of statins.



Source: Derwent Innovations Index (2022).

3.2 Scientific mapping to identify the number of published articles with the biotechnological production of statins

The results obtained in research carried out in scientific databases are described in Table 3, where the total number of articles found in the two databases used in the search with all keywords was 2820, higher than number of patents which was 2561 in the same period, representing 91% of the number of published articles.

Table 3 - Number of articles by keywords in title and abstract retrieved in the Scielo and Pubmed databases from 2015 to 2022.

Descritors	Scielo			Pubmed		
	Portuguese	English	Spanish	Portuguese	English	Spanish
Statins	112	134	112	10	2266	10
Production and statins and fungi	0	0	0	0	45	0
Statins and fungi	0	0	0	01	130	0
Total:	112	134	112	11	2441	10

Source: Authors.

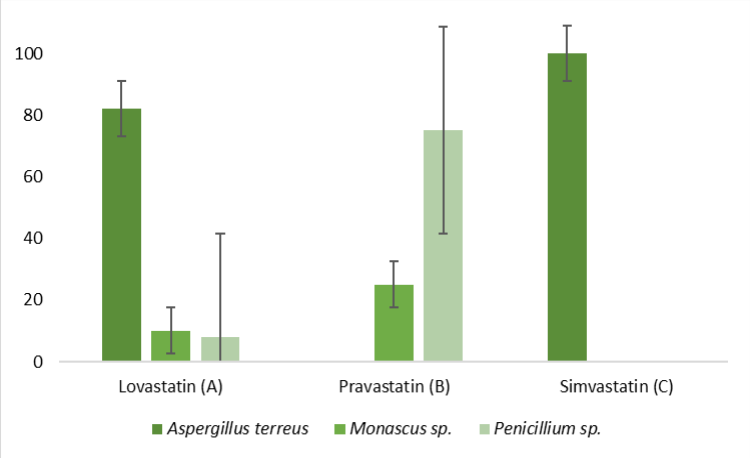
The keyword "*statins*", as in the Search for patentes, obtained the highest number of documents in the Scielo and Pubmed databases, obtaining 358 and 2286 articles, respectively.

According to Table 3, as with patentes, the search for articles with the descriptor "*Production and statins and fungi*" obtained the least publications. However, on the Scielo platform, there was no publication using the descriptors "*Production and statins and fungi*" and "*Statins and fungi*" and 130 results for and "*Statins and fungi*", which portrays studies scientific studies by other countries on the subject.

The analysis of scientific articles revealed that the main synthesized statin is lovastatin, obtained mainly by *Aspergillus terreus* (82%) and by diferente species of *Monascus* sp. (10%) but also by Other genera of fungi filamentous, such as *Penicillium* sp. (8%), as shown in Figure 3A. At the however, through Figure 3B it can be seen that the main fungal genera

pravastatin producers are *Penicillium* sp. (75%) and *Monascus* sp. (25%) respectively. Namestova et al. (2015), reports the production of the HMG-CoA inhibitor reductase (simvastatin) by *Aspergillus terreus* (Figure 3C).

Figure 3 - Potential of fungi in the production of statins: (A) Lovastatin; (B) Pravastatin and (C) Simvastatin.



Source: Authors.

3.2.1 Use of renewable sources as a strategy for the production of Inhibitors of HMG-CoA reductase

Sinha & Häder (2021), Neto et al., (2019) e Subhan; Farval; Macreadie (2016), we affirm that carbon and nitrogen sorces are essential components of the synthesis of metabolites in microorganisms and that the definition whixh source to use in the process production is critical to define which HMG-CoA reductase inhibitor will be produced, in addition to being related to yield. In this context, the substrates agro-industrial products can be reused as alternative and low-cost sources, in replacement of synthetic sources because they present nutrients such as sugars, fibers, minerals and proteins.

Table 4 depicts the ability of microorganisms to use substrates agroindustries as an alternative source for the production of HMG-CoA inhibitors reductase, converting them into products of high commercial value and contributing to reduction of these materials in the environment. Furthermore, it can be observed that the substrates most used in the production of HMG-CoA reductase inhibitors are: bran wheat (60%), rice husk (25%, corn husk (15%).

Table 4 - Substrates of agro-industrial origin as na alternative source for the production of HMG-CoA reductase inhibitors by filamentous fungi.

Substrate	Microorganisms	References
Wasterwater from sago processing	*Aspergillus terreus* KPR12	Srinivasan, Thangavelu, Uthandi (2022)
Wheat bran	*Aspergillus flavipes* BICC 5174	Seenivasan *et al.*, (2018)
Palm Seed Cake	*Aspergillus wentii* NCIM 661	Pallem; Parasa; Manipati, (2018)
Wheat bran	*Aspergillus niger* GCBL-45 *Aspergillus flavipes* GCBL-72 *Aspergillus flavus* GCBL-60	Javed *et al.* (2017)
Olive Pie (Olive Cake); pea pod; potato peel; sugarcane bagasse; wheat bran; rice husks; beet husk; peanut shell	*Aspergillus fumigatus* *Aspergillus niger* NRRL595 *Rhizopus oligosporus* NRRL2710 *Penicillium citrinum*	Mouafi; Ibrahim; Elsoud, (2016)
Wheat bran	*Monascus Sanguineos*	Dikshit; Tallapragada, (2016)
Rice bran	*Aspergillus Fischer* NCIM509	Prasanna Latha; Hemalatha, (2015)

Source: Authors.

4. Final Considerations

From the data found in the specialized literature, it can be observed that biotechnological methods are preferred for the production of HMG-CoA reductase inhibitors that can be biosynthetically obtained as secondary metabolites by several microorganisms, mainly *Aspergillus terreus* (75%), *Penicillium* sp. (20%) and *Monascus* sp. (5%).

The innovations analyzed show the use of secondary metabolites of microorganisms of the same genus, but they differ through their characteristics by to be local strains, in addition to the use of different methods to obtain of HMG-CoA reductase inhibitors.

It is possible to say that innovation in medicines based on biodiversity through the biotechnological production of HMG-CoA reductase inhibitors is a effective alternative for the production of biopharmaceuticals, as it is sustainable process of production of clean technology, a fact that enables competition at a commercial level.

The use of sustainable technology in the pharmaceutical area meets the demands socioeconomic conditions, through the reduction of production costs of the biomolecule and environment, generating an advantageous bioprocess from renewable sources and the minimization of the environmental impact caused by the accumulation of these residues agro-industrial activities in the environment, thus broadening the horizons for innovation in the pharmaceutical sector.

Therefore, the study highlights strategies such as the use of renewable and low-cost sources for the production of HMG-CoA reductase inhibitors, highlighting the substrates wheat bran (60%), rice husk (25%), husk of corn (15%).

Finally, it is worth noting that a perspective to expand the biotechnological production of HMG-CoA reductase inhibiotors is related to the challenge of finding new fungi with high enzymatic potential that are able to convert renewable

substrates as alternative sources of carbon and nitrogen, and that allow the generation of a sustainable process in the production of these biomolecules. In addition, it is necessary to encourage the protection of technology by individual inventors.

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