Article

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Bioreduction of the Chalcones by Fungus *Scedosporium apiospermum* EJCP13

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Abstract. Biotransformations are chemical reactions carried out by microorganisms on organic substrates. Biotransformations can be regio-, chemo-, stereo- and enantio-selective. Bioreductions are of great interest to the food and pharmaceutical industries as they help to reduce costs and impacts on the environment. In this work, the following biotransformations of chalcones were performed: (2E)-1-(4-hydroxy-phenyl)-3-(2-methoxy-phenyl)-prop-2-en-1-one (**1**), (2E)-1-(4-hydroxy-phenyl)-3-(4-methoxy-phenyl)-prop-2-en-1-one (**2**), and (2E)-1-(4-hydroxy-phenyl)-3-phenyl-prop-2-en-1-one (**3**) by the fungus *Scedosporium aspiospermum*, leading to formation through chemo-selective reduction of dihydrochalcones 1-(4-hydroxy-phenyl)-3-(2-methoxy-phenyl)-propan-1-one (**4**), 1-(4-hydroxy-phenyl)-3-(4-methoxy-phenyl)-propan-1-one (**5**), and 1-(4-hydroxy-phenyl)-3-phenyl-propan-1-one (**6**). Compounds **1-6** had their antimicrobial activities tested and were observed better activity to the biotransformation products compared with substrates. This is the first report of chemo-selective bioreduction by fungi of the genus *Scedosporium* in biotransformation reactions.
Keywords: Biotransformation; bioreduction; chalcones; *Scedosporium apiospermum*.

Resumen. Las biotransformaciones son reacciones químicas llevadas a cabo por microorganismos sobre sustratos orgánicos. Las biotransformaciones pueden ser regio-, quimio-, estereo- y enantio-selectivas. Las biorreducciones son de gran interés para la industria alimentaria y farmacéutica, ya que ayudan a reducir costes e impactos sobre el medio ambiente. En este trabajo se realizaron las siguientes biotransformaciones de las chalconas: (2E)-1-(4-hidroxi-fenil)-3-(2-metoxi-fenil)-prop-2-en-1-ona (**1**), (2E)-1-(4-hidroxi-fenil)-3-(4-metoxi-fenil)-prop-2-en-1-ona (**2**) y (2E)-1-(4-hidroxi-fenil)-3-fenil-prop-2-en-1-ona (***3***) por el hongo *Scedosporium aspiospermum*, que conduce a la formación mediante reducción quimio-selectiva de dihidrocalconas 1-(4-hidroxi-fenil)-3-(2-metoxi-fenil)-propan-1-ona (**4**), 1-(4-hidroxi-fenil)-3-(4-metoxi-fenil)-propan-1-ona (**5**) y 1-(4-hidroxi-fenil)-3-fenil-propan-1-ona (**6**). Se ensayaron las actividades antimicrobianas de los compuestos **1-6** y se observó una mejor actividad para los productos de biotransformación en comparación con los sustratos. Este es el primer informe de biorreducción quimio-selectiva por hongos del género *Scedosporium* en reacciones de biotransformación.
Palabras clave: Biotransformación; biorreducción; chalconas; *Scedosporium apiospermum*.

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Introduction

Biotransformations are chemical reactions carried out by microorganisms on organic substrates that can cause from simple to large changes in the structure of the substrate as there is a wide variety of types of biotransformation reactions that can be performed by microorganisms. Biotransformation reactions, when carried out on natural products, may lead to the formation of several products, as in the case of biotransformations into terpenes, alkaloids, and steroids [1].

Classic organic syntheses generally require special conditions, such as temperature and/or pressure controls, use of specific solvents and catalysts, and other processes that often make synthesis expensive and environmentally inadequate. On the other hand, biotransformations can be made in aqueous solutions. They operate in mild conditions. Products with greater enantioselectivity and regioselectivity can be obtained [2]. Thus, biotransformation can be considered a useful tool to produce new compounds in ecologically friendly conditions [3] and offers the possibility of obtaining products of rearrangements and unusual reactions in classical synthesis [4].

The hydrogenation of C-C double bond is an important synthetic tool for applications in academia and industry, including the large-scale production of drugs and fine chemicals products. However, applications are limited by hard reaction conditions, high costs, and safety concerns. As an alternative to direct hydrogenation, bioreactions using microrganisms have been employed. Microorganisms are well known for their abilities to catalyze different types of biotransformation reactions, including hydroxylation, reduction (double bonds and ketones), O-alkylation and dealkylations, glycosylation, and sulfatation [5].

Alarcon et al [6] demonstrated that the fungus *Aspergillus niger* was able to cyclize chalcones into flavonoids, providing an imitation of the biosynthetic processes of plants. The chalcones were biotransformed into other modified chalcones and into flavanones [6]. The chemo-selective reduction of the carbon-carbon or carbon-oxygen double bond is also observed in some cases [7].

In study carried out by Sanchez-Gonzalez and Rosazza [8], a strain of *Aspergillus alliaceus* biotranformed 3-(2",3"-dimethoxyphenyl)-1-(2'-hydroxyphenyl)propenone(2'-hydroxy- 2,3-dimethoxychalcone) for three flavanones and for O-demethylated and hydroxylated chalcones. This work showed that microorganisms are able to cyclize chalcones to form flavonoids, thus imitating the biosynthetic processes of plants [8]. Cell cultures from the plant *Cassia didymobotrya* were able to cyclize chalcones into auronas and aronols [9]. In another study, a strain of *Saccharomyces cerevisiae* performed stereo-selective bioreduction of chalcones and β-diketones in a biphasic system, forming hydroxy-derived products [7].

Biotransformation reactions are modern and environmentally friendly strategies for modifying the structure of organic substrates in order to change their biological activities [10,11]. Chalcones are compounds with large variety of biological activities and due these activities are very interesting to academicals and industry researches [12]. There are few studies describing the chemical study of fungi of the genus *Scedosporium* and its potential in biotransformation reactions [13]. Thus, we aim to study the biotransformation potential of *Scedosporium apiospermum*, using chalcones as substrate, to the chemo-hydrogenation the carbon-carbon double bond of chalcones.

Experimental

General procedures

ESIMS data were acquired in positive and negative ion mode using a Waters Acquity TQD instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ascend 400, using solvent signal as reference. The chemical shifts are given in delta (δ) values and the coupling constants (*J*) in Hertz (Hz).

Microorganism

Scedosporium apiospermum was obtained from a collection of the *Laboratório de Bioensaios e Química de Micro-organismos (LaBQuiM), Programa de Pós-graduação em Química - Universidade Federal do Pará*. One strain is deposited in the LaBQuiM with the code EJCP13.

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Synthesis of chalcones 1-3 and dihydrochalcones 4-6

In a flat-bottomed flask (125 mL), placed in an ice bath, 15 mL of EtOH, 11 mmol of acetophenone or derivatives, 15 mL of 10% NaOH solution and 12 mmol of benzaldehyde or derivatives were added. The reaction mixture was kept on magnetic stirring at 40 ºC for 40 min [14]. After this period, the mixture was cooled and left in freezer for 48 h and then filtered under vacuum. The product was crystallized in methanol. (2E)-1-(4-hydroxy-phenyl)-3-(2-methoxy-phenyl)-prop-2-en-1-one (**1**) was obtained in 62.6% yield, (2E)-1-(4-hydroxy-phenyl)-3-(4-methoxy-phenyl)-prop-2-en-1-one (**2**) was obtained in 29.7% yield and (2E)-1-(4-hydroxy-phenyl)-3-phenyl-prop-2-en-1-one (**3**) was obtained in 82.5% yield. Chacones **1-3** were hydrogenated, resulting in dihydrochalcones. In a 250 mL flask, 1 g of each chalcone (**1**-**3**), 50 mL of methanol (PA) and 0.2 g of 5% Pd-C were added. Subsequently, it was subjected to pressure with hydrogen (2 atm) and agitation. The reaction was monitored by MS until the absence of the starting material (4 h). After completion, the reaction mixture was filtered over on silica gel column eluted with ethyl acetate, resulting in the dihydrochalcones 1-(4-hydroxy-phenyl)-3-(2-methoxy-phenyl)-propan-1-one (**4**), 1-(4-hydroxy-phenyl)-3-(4-methoxy-phenyl)-propan-1-one (**5**), and 1-(4-hydroxy-phenyl)-3-phenyl-propan-1-one (**6**).

Biotransformation procedures

Initially, the fungus *S. apiospermum* was reactivated in a Petri dish containing PDA culture medium at room temperature for seven days. Then, for each substrate, nine 500 mL Erlenmeyer flasks containing 250 mL of Czapeck culture medium each were sterilized in a 75 L vertical autoclave (Prismatec) for 20 minutes at 121 ºC. After reaching room temperature, in a laminar flow hood (Panchane PA 320), two small cubes of 2 mm^3 of the fungus were added in eight flasks. Three flasks were used as controls (one flask containing fungus plus culture medium, another flask containing culture medium plus substrate, and another flask containing only culture medium). The system was mechanically agitated on an orbital shaker (Quimis Q315IA) at 120 rpm at a controlled temperature of 32 ºC for the growth of fungal colonies for three days. Then, 40 mg (per flask) of each substrate were solubilized into 100 µL of DMSO and added to the Erlenmeyer flasks. The system was kept under agitation, and the formation of the products was monitored by removing a flask every two days and extracellular medium was extracted with ethyl acetate (3x 75 mL). The ethyl acetate solution obtained were concentrated in a rotary evaporator to obtain the extracts of the bioreaction. The formation of biotransformation products was verified through the analysis of extracts of the bioreaction by HPLC-DAD. For that, a Waters chromatograph Alliance e2695 line (Waters) equipped with automatic sampler and detector of photodiode arrangement was used. The analyses were performed on a Sunfire C18 reverse phase column (150 mm x 4.6 mm inner diameter, particle size 5 µm; Waters, Ireland) with a C18 guard column (20 mm x 4.6 mm inner diameter, particle size 5 µm, Waters). The volume of injected sample was 20 µL and the column temperature was kept at 40 ºC. The chromatographic system was operated by the software Empower3 Personal Single System. The mobile phase was used in a linear elution exploratory gradient H_2O/MeOH 50:50 to 0:100 for 10 min. Chromatograms were obtained at a wavelength range of 210 nm to 600 nm. The formation of products was further confirmed by mass spectrometry using a Waters Acquity TQD spectrometer in positive and negative ESI ionization mode by direct infusion.

Biotransformation kinetics

The kinetics of biotransformations were evaluated. For this, the formation of biotransformation products was monitored by HPLC. First, for each product (**4**, **5** and **6**), previously prepared via synthesis, a stock solution of 1 mg/mL was prepared and diluted at concentrations of 12.5, 25.0, 50.0, 100.0 and 200.0 µg/mL. To obtain the calibration curves, the same chromatographic method as in the previous item was used. Thus, at every two days for each biotransformation reaction, an aliquot was removed and analyzed by HPLC-DAD and the formation of the bioreduction product was verified. The reactions were monitored until the 14^{th} day.

Antimicrobial test

Test microorganisms were *Escherichia coli* (ATCC 25922), *Salmonella typhimurium* (ATCC 14028) and *Bacillus subtilis* (ATCC 6633), which were obtained from *Instituto Evandro Chagas*, Belém, PA, Brazil.

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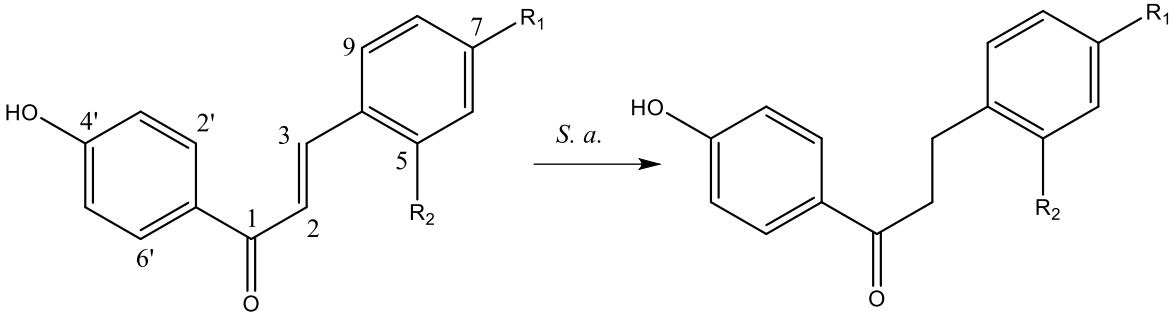
Susceptibility of the microorganisms to the test's compounds were determined by the microbroth dilution assay according Pinheiro *et al* [15].

Results and discussion

Bioreduction products

Through mass spectrometry analysis of the biotransformation products **4**, **5** and **6**, was observed that all products had two mass units in relation to their respective chalcones substrates **1**, **2** and **3**, suggesting hydrogenation of the C2-C3 double bond. To confirm bioreduction products, samples of the dihydrochalcones 1-(4-hydroxy-phenyl)-3-(2-methoxy-phenyl)-propan-1-one (**4**), 1-(4-hydroxy-phenyl)-3-(4-methoxy-phenyl)-propan-1-one (**5**) and 1-(4-hydroxy-phenyl)-3-phenyl-propan-1-one (**6**) were obtained by chemical hydrogenation of (2E)-1-(4-hydroxy-phenyl)-3-(2-methoxy-phenyl)-prop-2-en-1-one (**1**), (2E)-1-(4-hydroxy-phenyl)-3-(4-methoxy-phenyl)-prop-2-en-1-one (**2**) and (2E)-1-(4-hydroxy-phenyl)-3-phenyl-prop-2-en-1-one (**3**) and characterized by NMR and MS (Supplementary Information) [16-20]. Thus, both the chemical hydrogenation samples and the biotransformation products **4**, **5** and **6** were analyzed by HPLC-DAD. Their retention times showed total similarity, confirming that the products obtained by biotransformation are formed by chemo-selective reduction of the C2-C3 double bond of the chalcones **1**, **2** and **3** (fig. 1). The biotransformation products **4**, **5** and **6** were also analyzed by MS/MS and the fragments are in agreement with the obtained products (Supplementary Information).



1 - R_1 = H, R_2 = OMe
2 - R_1 = OMe, R_2 = H
3 - R_1 = H, R_2 = H

4 - R_1 = H, R_2 = OMe
5 - R_1 = OMe, R_2 = H
6 - R_1 = H, R_2 = H

Fig. 1. Bioreduction of chalcones (2E)-1-(4-hydroxy-phenyl)-3-(2-methoxy-phenyl)-prop-2-en-1-one (**1**), (2E)-1-(4-hydroxy-phenyl)-3-(4-methoxy-phenyl)-prop-2-en-1-one (**2**) and (2E)-1-(4-hydroxy-phenyl)-3-phenyl-prop-2-en-1-one (**3**) by *Scedosporium apiospermum* given chemo-selective bioreduction products of the C2-C3 double bond 1-(4-hydroxy-phenyl)-3-(2-methoxy-phenyl)-propan-1-one (**4**), 1-(4-hydroxy-phenyl)-3-(4-methoxy-phenyl)-propan-1-one (**5**) and 1-(4-hydroxy-phenyl)-3-phenyl-propan-1-one (**6**).

Microorganisms are chemo-specific biocatalysts. Generally, they promote only one type of reaction, which can be regio-specific when the microorganism attacks only one position in the molecule, or stereo-specific when it usually converts only one of the enantiomers when exposed to a racemic mixture or produces an optically active product instead of a mixture of enantiomers [21]. In our study, hydroxy-derived or cyclization products were not observed, but in a similar way to our study, a strain of *Aspergillus flavus* performed regio-selective bioreduction of chalcones by hydrogenating the C2-C3 double bond without formation of a carbonyl group reduction product [14]. The biotransformation of chalcones **1**-**3** by *S.*

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apiospermum EJCP13 showed chemo-selectivity and only the hydrogenation product of the C2-C3 double bond was observed. No reduction product was observed for carbonyl.

The C2-C3 double bond bioreduction products demonstrated the ability in chemo-selective reduction reactions of the fungus *S. aspiospermum*. In study carried out by us, we found that the fungus *S. aspidospermum* had as major secondary metabolite brefeldin A [13], whose biosynthesis is involved with the highly reducing polyketide synthase enzyme (HRPKSs), which is an enigmatic group of enzymes from multiple domains that catalyze the biosynthesis of structurally diverse compounds [22], suggesting that in this strain the genes encoding the dehydrogenase enzymes are the most up-regulated, which corroborates the observation of only reduction products.

The catalytic hydrogenation of organic compounds has wide applicability due to its apparent experimental simplicity, which allows its use both at the laboratory level and at the industrial level [23]. However, there is still the need to use inorganic catalysts, hydrogen gas, organic solvents, and heating, which end up making the process relatively expensive and not environmentally friendly. Ferreira et al [24] carried out bioreduction of the chalcones using the fungi *Penicillium* sp and obtain yield greater than 90 % of bioreduction. In another study, cyanobacterial strains examined were capable of transforming chalcone, and a few strains converted this substrate with a >99% yield upon fourteen (14) days of incubation [25]. These data corroborate with our results showing that fungi can be a good strategy to bioreduction application.

The use of microorganisms in hydrogenation reactions can be a good alternative to perform hydrogenation reactions with the advantage of being an environmentally friendly method. Moreover, the chemo-selective hydrogenation of chalcones **1**, **2** and **3** by *S. apiospermum* was very interesting due it has showed yield greater than 90% in the bioreactions studied, witch torn this fungi useful in future application of its biochemical potential.

Antibacterial assay

Microbial resistance to antibiotics is a serious public health problem worldwide, which creates the need for new antibiotics and synthesis methods less aggressive to the environment and the biotransformation reactions are in line with this aims. Then compounds **1-6** were tested against pathogenic bacteria. The substrates chalcones **1**, **2** and **3** showed weak antimicrobial activity, so the substrates had the C2-C3 double bond hydrogenated via biotransformation by *S. apiospermum* leading to the dihydrochalcones **4**, **5** and **6** which led to an improvement in antimicrobial activity (Table 1). The hydrogenation of substrate **1** in product **4** guided to an improvement in activity against *S. typhimurium* only. However, the product **5** showed a significant improvement in antimicrobial activity when compared to its precursor substrate **2**, the product **6** also showed better activity when compared to its precursor substrate **3**.

Table 1. Antibacterial activity of chalcones **1-3** and dihydrochalcones **4-6.**

Compound	MIC (µg/mL)		
	E. coli	***B. subtilis***	***S. typhimurium***
1	> 500	500	500
2	500	500	500
3	500	500	500
4	500	500	250
5	125	125	62.5
6	125	250	125

Biotransformation kinetics

With the structures of products identified, the biotransformation kinetics were evaluated by HPLC-DAD analysis (Fig. 2). We observed that until the second day of feed, no product was formed, but from the fourth day there was an increase in the formation of all products with a higher formation rate from the eighth to the tenth day, with the maximum formation of 134.03 µg/mL of **4,** 145.45 µg/mL of **5** and 150.00 µg/mL of **6** was observed. As of the twelfth day, there was a decrease in product formation. The decrease in the volume of

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products formed after the twelfth day is much probably due to the catabolism of the products formed. Thus, we found that the maximum yield of all products occurred on the tenth day of reaction. Generally, one of the aspects that make the use of biocatalysts on an industrial scale unfeasible is the low yield in biotransformation reactions, which even hinders the isolation and characterization of products obtained in the laboratory [26]. However, yields of 83.7% were obtained for **4**, 90.9% for **5** and 93.7% for **6**, which shows the potential use of the fungus *S. apiospermum* in bioreduction reactions of bonds double α,β-unsaturated carbonyl, which are important processes for the pharmaceutical and food industries, such as in the well-known production of (*S*)-DOPA, an effective amino acid in the treatment of Parkinson's disease and (*S*)-phenylalanine, a raw material for production of the artificial sweetener aspartame® [27].

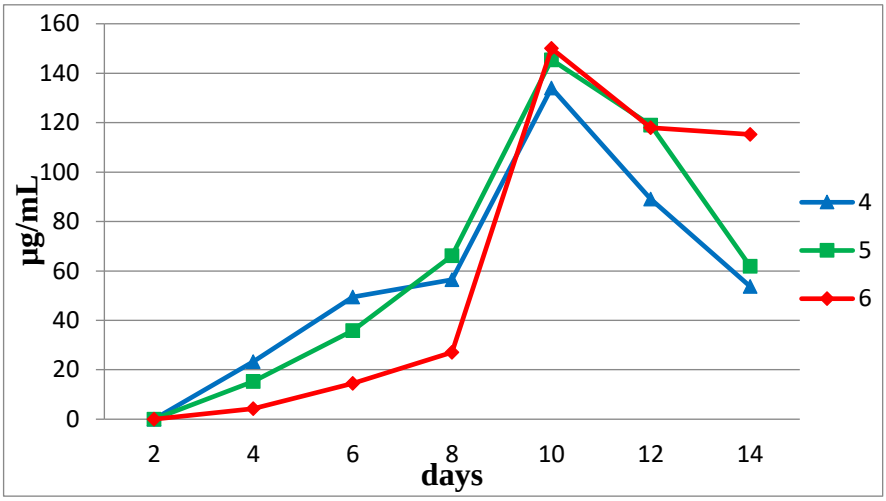

Fig. 2. Formation of dihydrochalcones **4**, **5** and **6** by *S. apiospermum* per day.

Conclusion

The biotransformation reactions of the chalcones 1, 2 and 3 by *S. apiospermum* EJCP13 led to the formation, through chemo-selective bioreduction, of the dihydrochalcones 1-(4-hydroxy-phenyl)-3-(2-methoxy-phenyl)-propan-1-one (4), 1-(4-hydroxy-phenyl)-3-(4-methoxy-phenyl)-propan-1-one (5) and 1-(4-hydroxy-phenyl)-3-phenyl-propan-1-one (6). The study of the kinetics of the reactions showed that the maximum yield is obtained on the tenth day of reaction. The fungus *S. apiospermum* showed to be a good selective bioreducer, which can be useful in synthetic applications to reduce costs and impacts on the environment. Compounds 1-6 were tested against bacteria *E. coli*, *B. subtilis* and *S. typhimurium* and the biotransformations products showed improvement in activities compared with their respective substrates. This is the first report of chemo-selective bioreduction by genus *Scedosporium* in biotransformation reactions.

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