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Review article

Candida parapsilosis: A versatile biocatalyst for organic oxidation-reduction reactions

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ABSTRACT

This review highlights the importance of the biocatalyst, *Candida parapsilosis* for oxidation and reduction reactions of organic compounds and establishes its versatility to generate a variety of chiral synthons. Appropriately designed reactions using *C. parapsilosis* effect efficient catalysis of organic transformations such as deracemization, enantioselective reduction of prochiral ketones, imines, and kinetic resolution of racemic alcohols *via* selective oxidation. This review includes the details of these biotransformations, catalyzed by whole cells (wild type and recombinant strains), purified enzymes (oxidoreductases) and immobilized whole cells of *C. parapsilosis.* The review presents a bioorganic perspective as it discusses the chemo, regio and stereoselectivity of the biocatalyst along with the structure of the substrates and optical purity of the products. Fermentation scale biocatalysis using whole cells of *C. parapsilosis* for several biotransformations to synthesize important chiral synthons/industrial chemicals is included. A comparison of *C. parapsilosis* with other whole cell biocatalysts for biocatalytic deracemization and asymmetric reduction of carbonyl and imine groups in the synthesis of a variety of enantiopure products is presented which will provide a basis for the choice of a biocatalyst for a desired organic transformation. Thus, a wholesome perspective on the present status of *C. parapsilosis* mediated organic transformations and design of new reactions which can be considered for large scale operations is provided. Taken together, *C. parapsilosis* can now be considered a 'reagent' for the organic transformations discussed here.

Contents

Abbreviations: Candida sp., *Candida* species; *C. parapsilosis*, *Candida parapsilosis*; FDH, formate dehydrogenase; PDH, phenylalanine dehydrogenase; ACE, angiotensin-converting enzyme; NEP, neutral endopeptidase; KR, kinetic resolution; BDO, 1,3-butanediol; PED, 1-phenyl-12-ethanediol; *Cp*SADH, secondary alcohol dehydrogenase from *C. parapsilosis*; ee, enantiomeric excess; *Cp*CR, carbonyl reductase from *C. parapsilosis*; AKR, aldo-keto reductase; CPR, conjugated polyketone reductases; *Cp*rCR, (*R*)-specific carbonyl reductase from *C. parapsilosis* CCTCCM203011; SCR, (*S*)-specific carbonyl reductase; RCR, (*R*)-specific carbonyl reductase; COBE, 4-chloro-3-oxobutanoate ethyl ester/ethyl-4-chloro-3-oxobutanoate; CHBE, (*S*)-4-chloro-3-hydroxybutanoate ethyl ester/ethyl-4-chloro-3-hydroxybutanoate; PNTs, pyridine nucleotide transhydrogenases; HAP, 2-hydroxyacetophenone; 4HPOEt, (*S*)-ethyl-4-hydroxypentanoate; ILs, ionic liquids; TMSB, 4-(trimethylsilyl)-3-butyn-2-one; (*S*)-TMSBOL, (*S*)-4-(trimethylsilyl)-3-butyn-2-ol; C4MIM·PF6, 1-butyl-3-methylimidazolium hexafluorophosphate; IL, ionic liquid; (*R*)-1-TMSE, (*R*)-1-trimethylsilylethanol; (C_2OHMIM·NO_3), 1-(2′-hydroxyl) ethyl-3-methylimidazolium nitrate.

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1. Introduction

Biocatalytic methods are increasingly being employed for the preparation of a variety of chiral precursors which have wide biological applications [1,2]. The yeast, *Candida* sp. is widely reported to mediate the syntheses of a broad range of chiral compounds [3] - both, as whole cells and isolated enzymes. In addition to being a common source of lipases [4,5]. *Candida* sp. is also an important source of oxidoreductases. The oxidoreductases mediated reactions reported from *Candida* sp. provide important insights into their catalytic mechanisms during biotransformations. This opens up the possibilities of developing novel biocatalytic applications using the purified enzymes or whole cells. For instance, the whole cells of *Candida viswanathii* are reported for the reduction of hetero aryl methyl ketones to the (*S*)-alcohols with high enantiomeric excess (ee) [6]; *Candida chilensis* are used to produce enantiomerically pure (*R*)-allylic alcohols from the respective α,β-unsaturated ketones [7]. The carbonyl reductase enzymes from *Candida viswanathii* [8–10] and *Candida boidinii* [11–14] have also been reported in a number of biotransformations. Other species of *Candida*, such as *C. macedoniensis* [15,16], *C. utilis* [17,18], *C. tropicalis* [19,20], *C. floricola* [21,22] and *C. magnolia* [23,24] are also known to biocatalyze redox reactions. Xylose reductase from *C. tenuis* shows a broad substrate acceptance and in addition to xylitol, it reduces a number of aromatic carbonyl substrates [25–28]. Xylose reductases are also reported from *C. intermedia* [29], *C. guilliermondii* [30], *C. boidinii* [31] and *C. tropicalis* [32,33]. In addition, another important oxidoreductase of the *Candida* sp. is the formate dehydrogenase (FDH) from *C. boidinii* which is commonly used as an enzyme in cofactor regeneration (enzyme-coupled approach) [34–36].

Isolated enzymes/whole cells from *Candida* sp. are also reported for the large scale production of pharmaceuticals and fine chemicals. *Candida sorbophila* MY 1833 was used for asymmetric reduction to produce (*R*)-N-(2-hydroxy-2-pyridin-3-yl-ethyl)-2-(4-nitrophe nyl)-acetamide, an intermediate of the drug with β-3-agonist activity used in the treatment of hypertension and coronary disease [37,38]. FDH from *Candida boidinii* was combined with phenylalanine dehydrogenase (PDH) in recombinant *E. coli* to produce (*S*)-2-amino-5-(1,3-dioxolan-2-yl)-pentanoic acid, a chiral precursor used in the synthesis of the antihypertensive drug, omapatrilat, which inhibits the angiotensin-converting enzyme (ACE) [39,40].

The availability of an enzyme in adequate amounts is a challenge when an isolated enzyme is used for biotransformation instead of whole cells. A practical solution to this problem is to clone and overexpress the desired enzyme. Oxidoreductases, particularly carbonyl reductases from different *Candida* sp. have been cloned and overexpressed [15,41–45]. Although genetic engineering techniques i.e. cloning and overexpression of enzymes have opened new avenues in biocatalysis, it is a challenge to develop newer improved and sustainable green technology to obtain the desired enzymes in large quantities, which can be used to prepare enantiomerically pure compounds in bulk quantities.

Among the known *Candida* sp., *Candida parapsilosis* is now established as a whole cell biocatalyst for organic oxidation-reduction reactions. The products are enantiomerically pure molecules which are important chiral synthons and have industrial applications [46,47]. By careful choice of reaction conditions, *C. parapsilosis* has been shown to catalyze deracemization, enantioselective reduction of prochiral ketones, kinetic resolution of racemic alcohols *via* selective oxidation to produce a host of chiral compounds e.g. aliphatic and aromatic diols, α-and β-hydroxy esters, allylic alcohols, aryl ethanols and amines. Biocatalytic reduction of imine bond to the respective enantiomerically pure amines is an important transformation. *C. parapsilosis* (ATCC 7330) can asymmetrically reduce aryl imines to give optically pure amines with good yields (55–80%) and excellent optical purity (95 to >99%) [48]. In addition, the chemical analogy between the reduction of a carbonyl group (C═O) and an imine (C═N) extends the scope of the biocatalyst, *C. parapsilosis* for biotransformations. More recently, the biocatalyst *C. parapsilosis* (ATCC 7330) has been utilized for oxidation reactions. Sivakumari et al. reported the biooxidation of aromatic (activated) primary alcohols to aldehydes in high yields (up to 86%) in mild reaction conditions using hexane: water (48:2) biphasic system [49]. Using the same biocatalyst, the enantioselective oxidation of secondary alcohols were reported to produce the corresponding ketone and the enantiomerically enriched alcohols [50,51] which are discussed in the later part of this review.

The review also presents important biocatalytic reactions mediated by *C. parapsilosis* such as deracemization, asymmetric reduction of prochiral ketones, imines, resolution of racemic alcohols through selective oxidation. The understanding of the oxidoreductases from *C. parapsilosis* at the molecular level are also discussed. The review presents a consolidated view of the different reactions catalyzed by *C. parapsilosis* with a perspective to design new biocatalytic reactions for large scale reactions and also at the lab level.