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REVIEW

Application and microbial preparation of D-valine

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Abstract D-Valine is an important organic chiral source and has extensive industrial application, which is used as intermediate for the synthesis of agricultural pesticides, semi-synthetic veterinary antibiotics and pharmaceutical drugs. Its derivatives have shown great activity in clinical use, such as penicillamine for the treatment of immune-deficiency diseases, and actinomycin D for antitumor therapy. Fluvalinate, a pyrethroid pesticide made from D-valine, is a broad-spectrum insecticide with low mammalian toxicity. Valnemulin, a semi-synthetic pleuromutilin derivative synthesized from D-valine, is an antibiotic for animals. Moreover, D-valine is also used in cell culture for selectively inhibiting fibroblasts proliferation. Due to its widespread application, D-valine is gaining more and more attention and some approaches for D-valine preparation have been investigated. In comparison with other approaches, microbial preparation of D-valine is more competitive and promising because of its high stereo selectivity, mild reaction conditions and environmental friendly process. So far, microbial preparation of D-valine can be mainly classified into three categories: microbial asymmetric degradation of DL-valine, microbial stereoselective hydrolysis of *N*-acyl-DL-valine by D-aminoacylase, and microbial specific hydrolysis of DL-5-isopropylhydantoin by D-hydantoinase coupled with D-carbamoylase. In this paper, the industrial application of D-valine and its microbial preparation are reviewed.

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Introduction

It was once assumed that only L-amino acids were selected during evolution for formation of proteins and that all living organisms were composed exclusively of L-amino acids (Fuchs et al. 2005; Fujii 2005). With the development of analytical technologies, D-amino acids were detected in microbes, plants and animals (Hamase et al. 2009; Lupoli et al. 2011; Vranova et al. 2012). Recently D-amino acids are gaining considerable importance as valuable intermediates for the production of pharmaceuticals, agrochemicals and food additives (Yagasaki and Ozaki 1998; Martínez-Rodríguez et al. 2010; Gao et al. 2015).

D-Valine is an important organic chiral source and has extensive industrial applications, which is used as intermediate for the synthesis of agricultural pesticides, semi-synthetic veterinary antibiotics and pharmaceutical drugs (Zhang et al. 2015). Due to its wide application, D-valine is gaining more and more attention. Some approaches for D-valine preparation have been investigated, including stereo asymmetric synthesis, induced crystallization, chemical resolution and microbial preparation. However, stereo asymmetric synthesis costs much due to expensive chiral auxiliaries (Lucet et al. 1999). Induced crystallization is not feasible due to long production cycle and low optical purity and yield of D-valine (Susumu et al. 1965). Chemical resolution is an important method of D-amino acids preparation, but chiral resolving agents are hard to obtain (Yoshioka et al. 1994). In comparison with above approaches, microbial preparation of D-valine is more

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competitive and promising because of its high stereo selectivity, mild reaction conditions and environmental friendly process. In this paper, the industrial application of D-valine and its microbial preparation are reviewed.

Application of D-valine

Synthesis of agricultural pesticides

D-Valine is used as chiral intermediate for agrochemical synthesis, which is irreplaceable in the skew symmetric synthesis of agricultural pesticides such as pyrethroids. Henrick et al. (1980) synthesized a group of substituted 2-anilino-3-methylbutyrates with L- or D-valine as raw material, and found that the esters of (R)-2-anilino-3-methylbutyric acids derived from D-valine were far more active than the (S)-enantiomers derived from L-valine, indicating the absolute stereochemical requirement (at C-2, in the acid portion) for insecticidal activity. Fluvalinate [α-cyano-3-phenoxybenzyl 2-[2-chloro-4-(trifluoromethyl)anilino]-3-methylbutanoate], a synthetic pyrethroid pesticide prepared from D-valine and commercially known as Maurik, Klartan or Apistan, was selected from the numerous synthetic analogues for commercialization by Zoecon Corporation due to its broad spectrum, high insecticidal activity and low mammalian toxicity (Quistad et al. 1982; Anderson et al. 1985). Fluvalinate can effectively prevent and cure crop diseases caused by lepidoptera and diptera insects (Yang et al. 2004). Moreover, Fluvalinate is widely used in beekeeping industry to control varroa mite, the most devastating parasite of honeybees (Elzen et al. 1999; Haarmann et al. 2002).

Synthesis of veterinary drugs

Berner and Vyplel (1987) synthesized a group of pleuromutilin derivatives by chemical modification at C-14 of tricyclic skeleton of pleuromutilin. Valnemulin, a semi-synthetic pleuromutilin derivative prepared from D-valine, was selected from these derivatives for its prominent biological activity and high water solubility (Macher 1992). Valnemulin can be synthesized as follows: pleuromutilin reacts with *p*-toluenesulfonyl chloride and dimethyl cysteamine hydrochloride to prepare cysteamine-substituted pleuromutilin, meanwhile D-valine and methyl acetoacetate reacts with potassium hydroxide, then anhydridisation with isobutyl chloroformate, followed by amidation with cysteamine-substituted pleuromutilin (Feng et al. 2010). Valnemulin can inhibit protein synthesis by binding to 50S ribosomal subunit of bacteria and has effective antimicrobial activities against *mycoplasma* and *brachyspira*, such as *Mycoplasma hyopneumoniae* and *Brachyspira hyodysenteriae* (Poulsen et al. 2001). Nowadays, Valnemulin is often used as an antibacterial agent in veterinary medicine for the treatment and prevention of swine dysentery, porcine proliferative enteropathy, porcine colonic and swine enzootic pneumonia (Huang et al. 2010; Yuan et al. 2010).

Manufacturing of pharmaceutical drugs

Compounds and peptides containing D-valine, such as D-penicillamine, actinomycin D, fungisporin and valinomycin, have received much attention as pharmaceutical drugs in clinical use due to their significant biological activities (Wakayama et al. 2003). D-Penicillamine (3-mercapto-D-valine) is used for the treatment of immune-deficiency diseases such as rheumatoid arthritis and Wilson's disease (van Rijthoven et al. 1991; Durand et al. 2001). Actinomycin D is well known for its effective inhibition of DNA transcription and is employed clinically as chemotherapeutics for the treatment of highly malignant tumors (Mondick et al. 2008). In the biosynthesis of actinomycin D by *Streptomyces*, the multifunctional actinomycin synthetase II catalyzes the formation of peptide bond between L-threonine and L-valine and then epimerizes L-valine to D-valine (Stindl and Keller 1994). D-Valine residues in actinomycin D play an important role in the antitumor activity by increasing the water solubility of the antibiotic. Replacements of D-valine residues with other D-amino acids reduced drastically the water solubility of actinomycin D analogues and consequently decreased their capacities of DNA binding (Chu et al. 1994). Based on the structure–activity relationship of actinomycin D, novel actinomycin D analogues were designed and chemically synthesized with D-valine as raw material, and the analogues retaining D-valine but with long side chains at the fifth position showed greater antitumor activity than actinomycin D itself (Zhang et al. 2010).

Cell culture

The application of cell culture to the analysis of mammalian development has been severely limited because of the proliferative advantage of fibroblasts over the epithelial cells. A selective culture medium was developed to enable the growth of normal epithelial cells while selectively inhibiting fibroblasts proliferation, in which D-valine was substituted for L-valine (Gilbert and Migeon 1975). Since L-valine is essential for cell growth, only those cells containing D-amino acid oxidase could convert D-valine into L-valine and thereby proliferate. Fibroblasts could not grow in this selective medium due to lacking D-amino acid oxidase. Thus, D-valine could be used as a selective agent in medium to inhibit the proliferation of contaminating fibroblasts, such as the culture of astrocyte

from rat spinal cord (Cholewinski et al. 1989) and the culture of smooth muscle cells from human myometrium (Hongpaisan 2000). The effects of D-valine on pulmonary artery endothelial cell morphology and function in cell culture were also investigated (Picciano et al. 1984). The results showed that endothelial cells grown in D-valine medium did not become contaminated by fibroblasts, and D-valine-treated endothelial cells grew in cobblestone array, exhibited contact inhibition and strongly expressed factor-VIII antigen.

Microbial preparation of D-valine

In view of the economic importance of D-valine as a chiral synthon, it is an urgent task to establish economical, efficient and environmental friendly production methods for D-valine. Microbial preparation can yield D-valine with high optical purity, high productivity and green process, and is therefore the most promising method for manufacturing of D-valine. So far, microbial preparation of D-valine can be mainly classified into three categories based on the starting materials: microbial asymmetric degradation of DL-valine, microbial stereoselective hydrolysis of *N*-acyl-DL-valine by *N*-acyl-D-amino acid amidohydrolase (D-aminoacylase), and microbial specific hydrolysis of DL-5-isopropylhydantoin by D-hydantoinase coupled with *N*-carbamoyl-D-amino acid amidohydrolase (D-carbamoylase). The strategy for microbial preparation of D-valine is shown in Fig. 1, and the production methods reported in literature are summarized and compared in Table 1.

Microbial asymmetric degradation of DL-valine

DL-Valine is commercially produced by racemization of L-valine on a large scale at low cost (Zhang et al. 2015). Thus, its use as raw material for D-valine production would be advantageous if the D-isomer could be efficiently isolated from the racemic compound. Some microorganism strains showed asymmetric degrading activity against DL-amino acids and degraded the L-isomers enantioselectively (Senuma et al. 1989; Umemura et al. 1992). Takahashi et al. (1997) described D-valine production from DL-valine by microbial asymmetric degradation. The ability to degrade L-valine was screened among 1000 strains, and *Proteus vulgaris* IAM 12003, having the ability of selective degradation of L-isomer in DL-valine, was selected as the most suitable strain. The cells harvested were used to eliminate L-isomer from DL-valine, and D-valine was isolated from the reaction mixture at a yield of 36 % after 72 h.

To develop a practical process for D-valine preparation from DL-valine, L-valine was used as a sole source of carbon and nitrogen in basal minimal medium to isolate L-valine-degrading microorganism, and a yeast strain DLPU-zpb was obtained, which showed asymmetric degrading activity against DL-valine (Zhang et al. 2015). Based on the morphology, physiological and biochemical characteristics, and 26S rDNA D1/D2 domain sequence, the strain DLPU-zpb was identified as *Candida maltosa*. The cells of *C. maltose* DLPU-zpb were used as a biocatalyst for elimination of the L-isomer out of DL-valine, and the L-isomer was completely degraded within 72 h at 30 °C, pH control at 6.0 and 50 g/L DL-valine, and then remaining D-valine

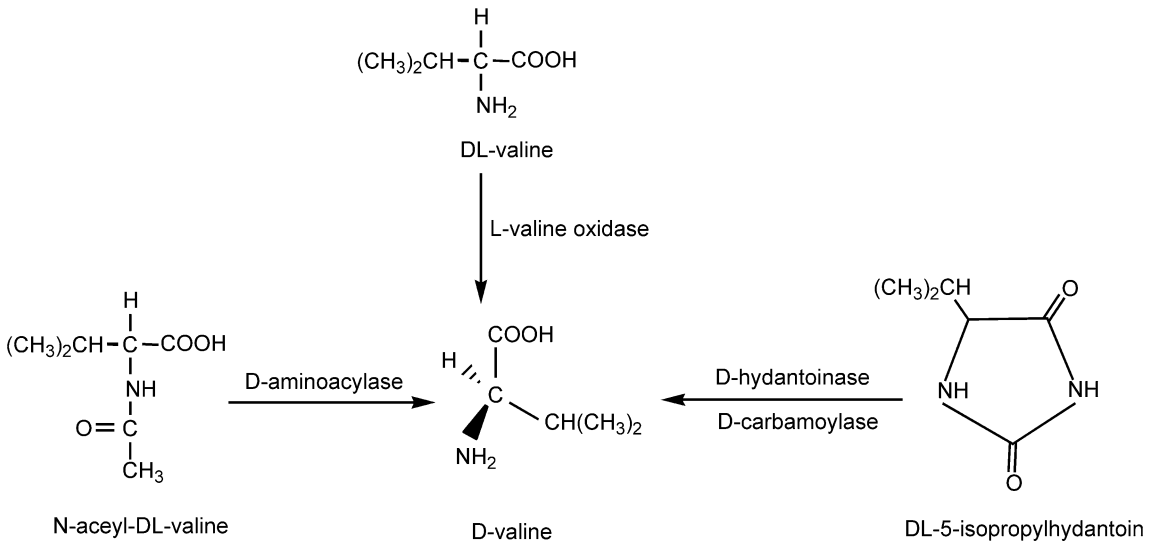

Fig. 1 Routes for microbial preparation of D-valine from different starting materials

Table 1 Summary of the microbial preparation of D-valine using different starting materials

Starting materials	Microorganism strain	Enzyme involved	Relative activity (%)	Substrate concentration	Reaction time (h)	D-Valine yield (%)	References
DL-Valine	*Proteus vulgaris* IAM 12003	L-Valine oxidase	NA	100 g/L	72	36	Takahashi et al. (1997)
	Candida maltose DLPU-zpb	L-Valine oxidase	NA	50 g/L	72	NA	Zhang et al. (2015)
N-acyl-DL-valine	*Alcaligenes denitrificans* MI-4	D-Aminoacylase	1	20 mmol/L	NA	NA	Sakai et al. (1991)
	Alcaligenes faecalis DA1	D-Aminoacylase	6	20 mmol/L	NA	NA	Yang et al. (1991)
	Alcaligenes xylosoxydans A-6	D-Aminoacylase	8	20 mmol/L	0.5	NA	Moriguchi et al. (1993)
	Variovorax paradoxus Iso1	D-Aminoacylase	18	25 mmol/L	0.5	NA	Lin et al. (2002)
	Defluvibacter sp. A 131-3	D-Aminoacylase	100	150 g/L	72	NA	Kumagai et al. (2004)
	Microbacterium natoriense TNJL143-2	D-Aminoacylase	6	10 mmol/L	1	NA	Liu et al. (2012)
DL-5-isopropylhydantoin	*Agrobacterium radiobacter*	D-Hydantoinase, D-carbamoylase, hydantoin racemase	NA	100 g/L	48	60	Battilotti and Barberini (1988)
	Recombinant *E. coli*	D-Hydantoinase, D-carbamoylase, hydantoin racemase	NA	15 mmol/L	5	NA	Martinez-Rodriguez et al. (2002)
	Recombinant *E. coli*	D-Hydantoinase, D-carbamoylase, hydantoin racemase	NA	50 g/L	48	88	Nozaki et al. (2005)
	Recombinant *E. coli*	D-Hydantoinase, D-carbamoylase, hydantoin racemase	NA	15 mmol/L	5	NA	Martínez-Gómez et al. (2007)

NA Not available

could be easily isolated from the resultant reaction mixture, which provides a new method for D-valine preparation from DL-valine.

Candida maltose DLPU-zpb degrades the L-isomer in DL-valine enantioselectively, but the assimilation pathway of L-valine in vivo is still unclear. Umemura et al. (1996) studied L-alanine assimilation in *C. maltosa* JCM1504 and found that alanine aminotransferase functioned as the first enzyme. L-Alanine is converted into pyruvic acid, which is then metabolized via tricarboxylic acid cycle. Another product of this reaction, glutamic acid, is deaminated to α–ketoglutaric acid by glutamate dehydrogenase. Ammonia formed is partially metabolized as a nitrogen source and most of it is excluded to the medium, which causes the rapid increase of pH value of reaction mixture. It is assumed that L-valine degradation in *C. maltosa* DLPU-zpb is similar to that of L-alanine and L-valine aminotransferase functions as the first enzyme. Additionally, it should be noted that the theoretical yield of D-valine using this method is only 50 % at maximum.

Microbial stereoselective hydrolysis of *N*-acyl-DL-valine by D-aminoacylase

D-Aminoacylase catalyzes enantioselective hydrolysis of *N*-acyl-D-amino acid to its corresponding D-amino acid and fatty acid, which is recognized as a convenient method to produce D-amino acid (Gao et al. 2015). Recently much attention has been paid on using microbial D-aminoacylase for the production of D-amino acids from *N*-acyl-DL-amino acids. D-Aminoacylase from *Alcaligenes denitrificans* MI-4 (Sakai et al. 1991), *Alcaligenes faecalis* DA1 (Yang et al. 1991), *Alcaligenes xylosoxydans* A-6 (Moriguchi et al. 1993), *Variovorax paradoxus* Iso1 (Lin et al. 2002) and *Microbacterium natoriense* TNJL143-2 (Liu et al. 2012) have been reported, but their relative activities towards *N*-acyl-D-valine were low (Table 1). Kumagai et al. (2004) screened for a microorganism capable of producing D-aminoacylase with high activity on *N*-acyl-D-valine and isolated *Defluvibacter* sp. A 131-3 using a medium containing *N*-acetyl-DL-valine. D-Aminoacylase from this strain showed higher activity on *N*-acetyl-D-valine than that of other *N*-acetyl-D-amino acids. Resolution of *N*-acetyl-DL-valine by this enzyme was performed at 30 °C, pH 8.0 and 150 g/L of substrate, and D-valine was efficiently resolved from *N*-acetyl-DL-valine, indicating the enzyme has great potential for D-valine production on industrial scale.

D-Aminoacylase from *A. xylosoxydans* A-6 (AxD-NAase) has been produced and sold as a commercial enzyme for the manufacture of neutral D-amino acids (Wakayama et al. 2003). However, the enzyme acts ineffectively on *N*-acyl-D-valine. To construct mutant AxD-NAase with substrate specificity different from that of wild-type enzyme, the substrate recognition site of AxD-NAase was rationally manipulated by site-directed mutagenesis based on computational structural analysis and comparison of its primary structure with other D-aminoacylase (Yano et al. 2011). The amino acid residues, F191, V297, L298, and M346 located in the substrate-binding pocket of AxD-NAase were substituted with W191, F297, A298, and F346, respectively. For the resultant mutant enzymes, both F191W and L298A showed higher catalytic efficiency towards *N*-acetyl-D-trptophan than the wild-type enzyme, and the activity of F191W on *N*-acetyl-D-alanine was improved, but the catalytic efficiency of all the mutant enzymes towards *N*-acetyl-D-valine was still low.

Microbial specific hydrolysis of DL-5-isopropylhydantoin

The "hydantoinase process" is a well-established method for industrial production of D-amino acids from chemically synthesized DL-5-substituted hydantoin. In this cascade process, the D-isomer of DL-5-substituted hydantoin is hydrolyzed by a stereoselective D-hydantoinase to *N*-carbamoyl-D-amino acid, followed by the hydrolysis of *N*-carbamoyl-D-amino acid to D-amino acid by D-carbamoylase. At the same time, the remaining *non*-hydrolyzed L-5-substituted hydantoin is racemized by the hydantoin racemase (Yokozeki and Kubota 1987; Rodríguez-Alonso et al. 2015). This process has evolved over the years from the isolation of microorganisms capable of producing above enzymes to the construction of recombinant systems for industrial application (Liu et al. 2008).

As shown in Fig. 2, "hydantoinase process" could be applied for D-valine production from DL-5-isopropylhydantoin. Battilotti and Barberini (1988) described the preparation of D-valine from DL-5-isopropylhydantoin using the resting cells of *Agrobacterium radiobacter*, which are high producers of D-hydantoinase, D-carbamoylase and hydantoin racemase. In this process, DL-5-isopropylhydantoin was chemically synthesized from isobutyraldehyde, sodium cyanide and ammonium carbonate. Microbial specific hydrolysis of D-5-isopropylhydantoin to D-valine by D-hydantoinase coupled with D-carbamoylase was carried out at 40 °C, pH control at 7.5 and 100 g/L DL-5-isopropylhydantoin. At the same time that D-hydantoinase enantioselectively hydrolyzed D-5-isopropylhydantoin, the remaining L-5-isopropylhydantoin was racemized by the hydantoin racemase. After 48 h of reaction, almost all DL-5-isopropylhydantoin was converted to D-valine and only 6.8 % of the hydantoin was left in the reaction mixture.

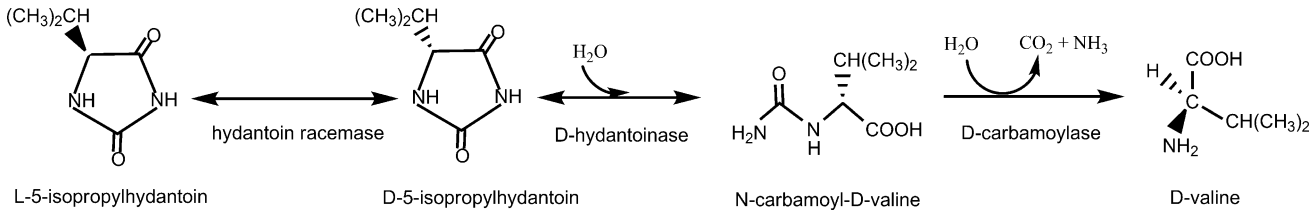

Fig. 2 Reaction scheme for D-valine preparation from DL-5-isopropylhydantoin hydantoin by the "hydantoinase process"

Recently, recombinant systems of whole cell catalysis via co-expression of three genes encoding D-hydantoinase, D-carbamoylase and hydantoin racemase in *E. coli* have been constructed. Martinez-Rodriguez et al. (2002) developed a reaction system using recombinant *E. coli* with separate expression of D-hydantoinase and D-carbamoylase from *Agrobacterium radiobacter* NRRL B11291 and hydantoin racemase from *Agrobacterium tumefaciens* C58. This whole cell system allowed complete conversion of DL-5-monosubstituted hydantoins to D-amino acids. Nozaki et al. (2005) reported the co-expression of three genes encoding D-hydantoinase, D-carbamoylase and hydantoin racemase in *E. coli* and D-amino acid production by whole cells. The genes encoding D-hydantoinase and D-carbamoylase were from *Flavobacterium* sp. AJ11199, and hydantoin racemase gene was from *Microbacterium liquefaciens* AJ3912. D-Valine yield reached 88 % in 48 h using the transformant D9 strain when 50 g/L of DL-5-isopropylhydantoin was used as the substrate. An accumulation of *N*-carbamoyl-D-valine was observed due to lower activity of D-carbamoylase on *N*-carbamoyl-D-valine. Martínez-Gómez et al. (2007) constructed the recombinant polycistronic structure of hydantoinase process genes from *Agrobacterium tumefaciens*. The three genes in one plasmid were co-expressed in *E. coli* with one promoter in a polycistronic structure, and the D-carbamoylase gene was cloned closest to the promoter to obtain the highest activity, thus avoiding the accumulation of *N*-carbamoyl-D-amino acid. The whole-cell recombinant system produced D-amino acids including D-valine from corresponding DL-5-substituted hydantoins and showed higher reaction rates for the conversion of aliphatic amino acids than for aromatic ones. However, the rate of D-valine production was low, which was not due to accumulation of the intermediate but possibly due to the substrate specificity of the D-hydantoinase.

Conclusion and future perspectives

D-Valine is an important organic chiral source and the market demand trends to increase year by year. The application of D-valine for the synthesis of agricultural pesticides, semi-synthetic veterinary antibiotics and pharmaceutical drugs is the main drive of this increase. Therefore, it is an urgent task to establish economical, efficient and environmental friendly production methods for D-valine. Microbial preparation can yield D-valine with high optical purity, high productivity and green process, and is therefore the most promising method. Among above three microbial approaches for D-valine preparation, the "hydantoinase process" is the most attractive method because the maximum theoretical yield of D-valine is 100 %.

Microbial preparation of D-valine has shown incomparable advantages over traditional chemical synthesis. With advances in genomics, computational biology and protein engineering, a combination of high-throughput screening techniques and recombinant DNA technology should benefit for obtaining new biocatalysts with high catalytic efficiency and stereoselectivity, which will greatly promote the microbial preparation of D-valine on an industrial scale.

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Compliance with ethics standards

Conflict of interest All authors declare that they have no conflict of interest.

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