

**REVIEW****Natural Occurrence and Industrial Applications of D-Amino Acids:  
An Overview**

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Interest in D-amino acids has increased in recent decades with the development of new analytical methods highlighting their presence in all kingdoms of life. Their involvement in physiological functions, and the presence of metabolic routes for their synthesis and degradation have been shown. Furthermore, D-amino acids are gaining considerable importance in the pharmaceutical industry. The immense amount of information scattered throughout the literature makes it difficult to achieve a general overview of their applications. This review summarizes the state-of-the-art on D-amino acid applications and occurrence, providing both established and neophyte researchers with a comprehensive introduction to this topic.

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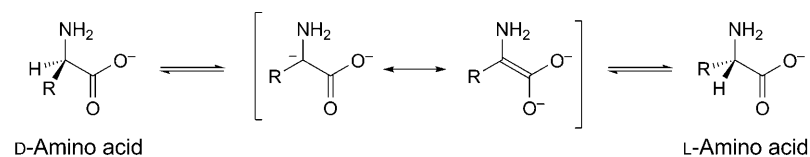
**Introduction.** – Since *Miller* established in 1953 that amino acids were most probably present in the primitive Earth's atmosphere [1], one of the largest mysteries in science has been why evolution chose the L-isomer of  $\alpha$ -amino acids for the emergence of life. While, from the chemical-physical point of view, enantiomeric enhancement in the prebiotic scenario of L-amino acids is plausible [2][3], the most broadly accepted theory is that primitive life acquired polymers by an as yet unknown mechanism. Whatever made the L-isomer so important in life, it is clear that D-isomers were of secondary importance to the scientific community for decades. However, the need to analyze D-amino acids in foodstuffs (as a result of chemical racemization by food processing [4]) to evaluate their impact in animal and human nutrition might have been the driving force behind the development of enantioselective and sensitive analytical methods. These have since allowed to demonstrate the presence of several D-amino acids in all kingdoms of life (not as contamination as was first thought). The increasing information on D-amino acids is giving rise to a new discipline of study, as can be inferred from the appearance of a monograph on this topic [5]. D-Amino acids have attracted the attention of industry, and hundreds of commercial applications are currently arising.

**How and Why Do Free D-Amino Acids Appear in Nature?** – Before considering D-amino acid production by biological/living systems, it is important to bear in mind an intrinsic chemical feature of amino acids. Carbonyl groups with a stereogenic  $\alpha$ -C-atom

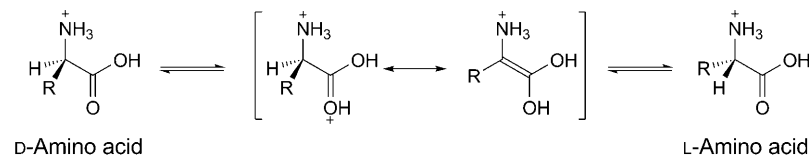
undergo base- and acid-catalyzed racemization through keto/enol tautomerisms (*Scheme*). The chemical racemization is dependent on variables such as temperature and pH [6][7], and produces D-amino acids as a cell-external process in nature (*e.g.*, in environmental samples, during food processing, *etc.*). This process might be one source of D-amino acids in nature, leading to their incorporation in the diet of several organisms [4]. Racemization also occurs *in vivo*, as has been deduced from the occurrence of D-amino acids in proteins [8]. Thus, the natural occurrence of D-amino acids in nature can be explained, and the evolution of enzymes in living organisms to use or eliminate them is understandable: D-amino acid oxidases (E.C. 1.4.3.3) and D-amino acid dehydrogenases (E.C. 1.4.99.1) would explain catabolic routes for elimination of these compounds in eukaryotes and bacteria, respectively.

*Scheme. General Scheme for Base- (a) and Acid-Catalyzed (b) Racemization of Amino Acids*

a) Base-catalyzed racemization



b) Acid-catalyzed racemization



Amino acid racemases in bacteria, but also in eukaryotes [9], can convert the D-amino acid into the L-isomer. However, amino acid racemases have been established to be mainly involved in the production of D-amino acids in biological systems [9][10]. An alternative route for D-amino acid production in bacteria would be transamination by D-amino acid transaminases, which allows the conversion of one D-amino acid into another different one [11]. An in-depth explanation of D-amino acid enzymology is beyond the scope of this work, but it is worth noting the number of enzymes classified as being involved in the metabolism of D-amino acids (*Table 1*). Indeed, based on the seminal work carried out by *Friedman* [4] on D-amino acid occurrence due to food processing, we would like to address the following question: is the increasing concentration of D-amino acids in the environment exerting some evolutionary pressure on D-amino acid metabolism?

**D-Amino Acids *in vivo*.** – Information on the occurrence of D-amino acids *in vivo* have been already compiled by several authors [4][5][8][12]. Once the basic notions on the natural occurrence of D-amino acids in nature have been recognized, the question is how important they are for living systems. Here, the idea proposed by *da Silva* and *da Silva* [12] on the natural sequence followed in the evolutionary process by

Table 1. *Several Enzymes Acting on D-Amino Acid Metabolism*. Metabolic pathways are based on KEGG pathway database (<http://www.genome.jp/kegg/pathway.html>). 1: Alanine and aspartate metabolism (ec00252); 2: glycine, serine, and threonine metabolism (ec00260); 3: penicillin and cephalosporin biosynthesis (ec00311); 4: arginine and proline metabolism (ec00330); 5: D-arginine and D-ornithine metabolism (ec00472); 6: metabolic pathways (ec01100); 7: D-glutamine and D-glutamate metabolism (ec00471); 8: phenylalanine metabolism (ec00360); 9: nitrogen metabolism (ec00910); 10: one-carbon pool by folate (ec00670); 11: lysine degradation (ec00310); 12: D-alanine metabolism (ec00473); 13: peptidoglycan biosynthesis (ec00550); 14: vitamin B6 metabolism (ec00750); 15: cysteine metabolism (ec00272); 16: glutamate metabolism (ec00251).

Enzymes	E.C. No	Pathway
D-Aspartate oxidase	1.4.3.1	1
D-Amino acid oxidase	1.4.3.3	2–6
D-Glutamate oxidase	1.4.3.7	7
D-Glutamate (D-aspartate) oxidase	1.4.3.15	1, 7
D-Amino acid dehydrogenase	1.4.99.1	8, 9
D-Proline reductase (dithiol)	1.21.4.1	4
D-Alanine 2-hydroxymethyltransferase	2.1.2.7	6, 10
D-Glutamyltransferase	2.3.2.1	7
D-Alanine $\gamma$ -glutamyltransferase	2.3.2.14	–
D-Tryptophan <i>N</i> -acetyltransferase	2.3.1.34	–
D-Amino acid <i>N</i> -acetyltransferase	2.3.1.36	8
D-Tryptophan <i>N</i> -malonyltransferase	2.3.1.112	–
D-Alanine transaminase	2.6.1.21	4–6, 8, 11–13
D-Methionine transaminase	2.6.1.41	12
Pyridoxamine phosphate transaminase	2.6.1.54	14
Cephalosporin C transaminase	2.6.1.74	3
D-Ala-D-Ala dipeptidase	3.4.13.22	–
Muramoylpentapeptide carboxypeptidase	3.4.17.8	13
D-Glutaminase	3.5.1.35	7
<i>N</i> -Acyl-D-glutamate deacylase	3.5.1.82	–
<i>N</i> -Acyl-D-aspartate deacylase	3.5.1.83	–
D-Arginase	3.5.3.10	5, 6
D-Threonine aldolase	4.1.2.42	–
D-Glutamate cyclase	4.2.1.48	7
D-Serine dehydratase	4.3.1.18	2
D-Cysteine lyase	4.4.1.15	15
Amino acid racemases	5.1.1.x	
Alanine racemase	5.1.1.1	1, 12, 6
Methionine racemase	5.1.1.2	–
Glutamate racemase	5.1.1.3	6, 7, 16
Proline racemase	5.1.1.4	4
Lysine racemase	5.1.1.5	–
Threonine racemase	5.1.1.6	–
Arginine racemase	5.1.1.9	5–7, 11
Amino acid racemase	5.1.1.10	2, 5–7, 15
Phenylalanine racemase	5.1.1.11	8
Ornithine racemase	5.1.1.12	5
Aspartate racemase	5.1.1.13	1
Serine racemase	5.1.1.18	2
D-Lysine 5,6-aminomutase	5.4.3.4	11
D-Ornithine 4,5-aminomutase	5.4.3.5	5
D-Alanine-poly(phosphoribitol) ligase	6.1.1.13	12
D-Aspartate ligase	6.3.1.12	–
D-Alanine-D-alanine ligase	6.3.2.4	12, 13
UDP- <i>N</i> -Acetylmuramoylalanine-D-glutamate ligase	6.3.2.9	6, 7, 13
D-Alanine-alanyl-poly(glycerolphosphate) ligase	6.3.2.16	–

a toxic product is interesting. The ‘toxic’ or ‘usable’ feature of a compound evolves approximately in the following sequence: toxicity, protection, rejection, signaling, integration, and utilization. As will be discussed below, the D-amino acids known *in vivo* are in almost all cases related to toxic/protective/signaling features, and we may, therefore, be dealing with an as yet unfinished evolutionary process for D-amino acid utilization.

The best described and understood use of D-amino acids might be their involvement in the formation of the peptidoglycan of eubacteria (Fig. 1). D-Alanine and D-glutamate have a central role, and the enzymes involved in their metabolic routes have been thoroughly studied [13][14]. The peptidoglycan is intimately related to cellular division, and thus enzymes involved in its formation became important targets to avoid cell propagation in infections. Natural occurrence of antibiotics containing D-amino acids acting on this or other metabolic pathways have been extensively studied (*cf.* Table 2). Natural  $\beta$ -lactam antibiotics are analogs of the terminal residues of N-acetylmuramic acid/N-acetylglucosamine peptide subunits (D-alanyl-D-alanine; Fig. 1), which are precursors of the nascent peptidoglycan layer. This similarity facilitates their binding to the active site of penicillin-binding proteins, and prevents the final cross-linking (transpeptidation) of the nascent peptidoglycan layer, disrupting cell-wall synthesis [59].

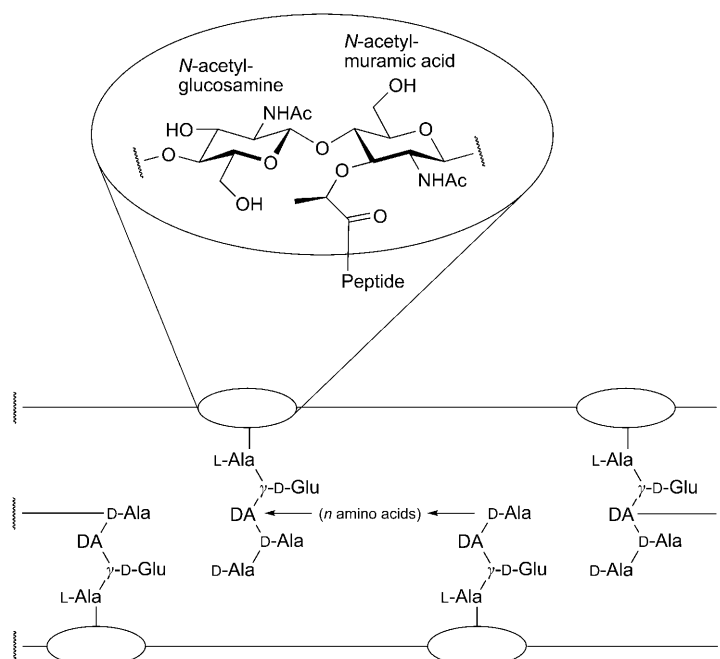


Fig. 1. *Bacterial peptidoglycan* (adapted from [14]). DA: diamino acid (generally diaminopimelic acid or L-lysine); *n*: number of amino acids in the cross-bridge, which differs depending on the organism.

Despite the widespread appearance of D-amino acid residues in natural antibiotics, their existence is not limited to bacteria (Table 2). They are also known to occur in

fungi [28], microalgae and macroalgae [60][61], higher plants [62][63], marine invertebrates [21–26][64], amphibians [15–19][65], and mammals [8][20][66], both in free and/or in complex form. D-Aspartic acid has also been detected in several proteins in different tissues from elderly humans [8] (e.g., phosphophoryn, osteocalcin, type-I collagen C-terminal telopeptide, myelin,  $\beta$ -amyloid, crystallin, and elastin).

Among the most studied free D-amino acids, we should include D-alanine, D-aspartic and N-methyl-D-aspartic acid (NMDA), and D-serine. D-Alanine levels in aquatic invertebrates increase when submitted to osmotic stress, and so this amino acid has been proposed to be an effective osmolyte [64]. D-Alanine levels also increase during anaerobiosis in crustaceans, suggesting that it might be an anaerobic end product under anoxia [64]. ‘Excitatory amino acids’ are known to mediate synaptic excitation and, therefore, nerve signal transmission in the mammalian central nervous system by binding to several receptors [67]. In this sense, D-aspartic acid and NMDA are widely known for being agonists of the L-glutamate receptor of NMDA type in vertebrates and invertebrates, and they are involved in hormone synthesis and release [68]. Recently, D-serine has also been shown to be an agonist of NMDA receptors, mediating several important physiological and pathological processes [9][69][70]. *Moloney* has reviewed other D-amino acids which have been established to bind some class of receptors [67], such as (*R*)-2-amino-3-(3-hydroxy-5-phenylisoxazol-4-yl)propanoic acid (R-APPA; competitive antagonist of the quisqualate receptor); 3,5-dihydroxyphenylglycine (3,5-DHPG; agonist of metabotropic glutamate receptor class I), and several derivatives of D-phenylglycine (D-PG; agonists of metabotropic glutamate receptor class II and III).

Several D-amino acids (such as D-tyrosine, D-aspartic acid, D-tryptophan, D-histidine, and D-lysine) are substrates for aminoacyl-tRNA synthetases, which have been related to the impairment of bacterial growth through the accumulation of D-aminoacyl-tRNA molecules [71]. This would explain the toxicity of D-amino acids detected in several organisms, as protein translation would be avoided. However, as peptidyl D-amino acids have been detected in soluble fractions not only in bacteria, the general assumptions on post-translational racemization do not seem to suffice to explain all the cases where they are detected. The same D-aminoacyl-tRNA molecules have been proposed as precursors of peptidyl D-amino acids, allowing D-amino acid incorporation during protein synthesis [72]. Further studies are necessary to draw definitive conclusions, although *in vitro* incorporation during translation of D-methionine and D-phenylalanine has been observed in mutated ribosomes [73].

**Industrial Applications of D-Amino Acids.** – Due to the large number of natural antibiotics containing D-amino acids isolated mainly from bacteria, the majority of applications of these compounds are related to antimicrobial activities. Unquestionably, antibiotics constitute one of the mankind’s most relevant medical breakthroughs. The Ancient Egyptians used moldy bread to treat wounds, and thousands of years later we learned that this cure was due to the antibiotic effect of penicillin. It was not until 1888 that *E. de Freudenreich* discovered pyocyanin/pyocyanase, a bacterial secretion from *Bacillus pyocyaneus* which retarded the growth of other bacteria. However, the toxicity of the antibiotic compounds isolated during the first decades of the 1900s delayed their widespread use in human treatment. In this sense, tyrothricin (mixture of

gramicidin (20%) and tyrocidine (80%)) became the first commercially available antibiotic. Since then, a huge amount of different natural antibiotics have been isolated from various microorganisms. *Table 2* shows some examples of natural antibiotics containing D-amino acids. In many cases, these antibiotics have been approved for clinical use, and have become commercially available, thereby increasing their economic importance. Some examples are tyrothricin (tyrozets), D-cycloserine (seromycin), polymyxin (polytrim), daptomycin (cubicin), or penicillin G, among others.

Based on the structure of naturally occurring antibiotics, one of the strategies that researchers followed was to modify them synthetically to create new drugs. The most prominent examples are the  $\beta$ -lactam penicillins and cephalosporins [74–77]. On the basis of their respective core structure (6-aminopenicillanic (6-APA) and 7-aminocephalosporanic acid (7-ACA)), modifications at certain positions led to the preparation of a wide range of semisynthetic penicillins and cephalosporins, which are or have been used clinically (*Fig. 2* and *Table 3*). Thereby, D-*para*-hydroxyphenylglycine and D-phenylglycine have played a key role. On the other hand, all derivatives of 6-APA contain at least one D-amino acid, D-valine. Some of these compounds are considered as ‘essential medicines’ by *World Health Organization* [91] (amoxicillin, ampicillin, benzylpenicillin, cloxacillin, phenoxymethylpenicillin). Other examples of ‘essential medicines’ containing D-amino acids are: D-cycloserine, bacitracin, and D,L-methionine. The same strategy used more than 50 years ago to modify natural antibiotics is currently used to overcome what *Levy* has named ‘*the antibiotic paradox*’ [92]. As this author sadly foretold, the misuse of antibiotics is creating antibiotic-resistant strains. Many important antibiotics (*e.g.*, vancomycin or methicillin [93] are not acting on some strains isolated in hospitals). Some of the ‘new’ compounds being tested for their antibiotic effects are again semisynthetic penicillins and cephalosporins (mezlocillin, piperacillin, azlocillin, bacampicillin; *Table 3*). However, other strategies have been followed, such as converting natural antibiotic L-peptides into their partial or total D isomers [94][95] (cecropin A, B, and D, melittin, magainin I and II, or cecropin A–melittin hybrids; *Table 4*).

On the other hand, some of the antibiotics described have been applied clinically or commercially for other tasks (*Table 4*), such as deodorants (D-cycloserine [103]), spermicides (gramicidin S [141]), chemotherapeutics (actinomycin D or dactinomycin, magainin derivatives [116][125]), fluorescent markers of DNA (7-aminoactinomycin D [126]), or immunosuppressives to prevent organ rejection (cyclosporin and derivatives [142]). Other compounds of commercial interest for whose synthesis D-amino acids are used are sweeteners (being alitame the most representative [117–120]), fluvalinate (a pyrethroid pesticide [115]), tadalafil and analogs (cialis as the most widely known, used in treatment of erectile dysfunction [121][122]), or the analog dipeptides thymodepressin and SCV-07 [123][124]. Whereas thymodepressin ( $\gamma$ -D-Glu-D-Trp) has applications in psoriasis treatment, SCV-07 ( $\gamma$ -D-Glu-L-Trp) is a potent immunomodulator with antimicrobial activity, which enhances the immune system and has also been used in the treatment of chronic hepatitis C.

We should also consider the fact that D-amino acid exploitation is intimately related to their slower rate of incorporation/assimilation compared to the L-isomer, both in free or peptide-bound form. Peptides composed partially of D-amino acids are more

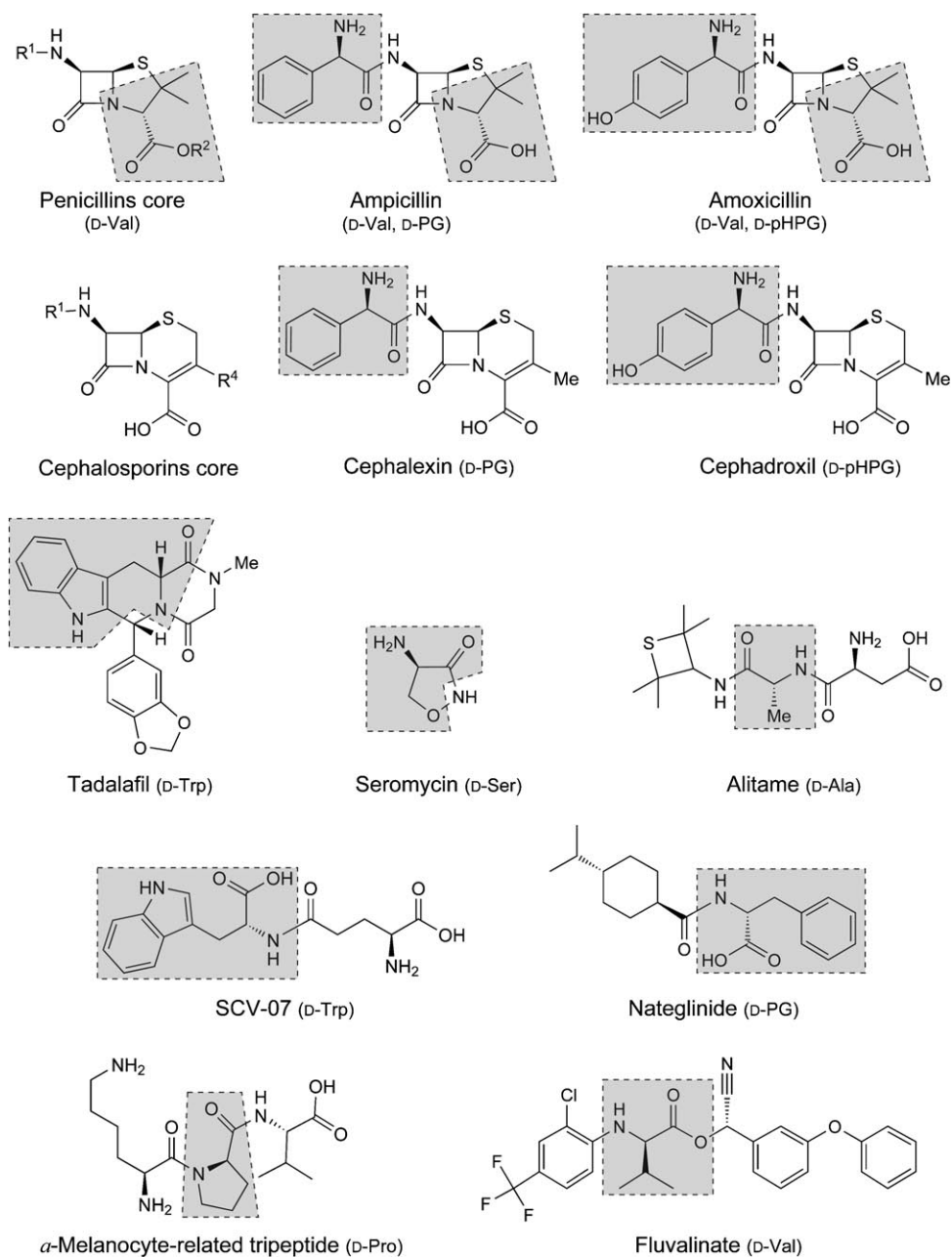


Fig. 2. Selected compounds with economical value containing D-amino acids. The gray background shows the D-amino acid contained in the structure.

Table 2. Several D-Amino Acid-Containing Compounds Described in the Literature. It is remarkable to highlight that, due to the huge number of antibiotics isolated, classification is difficult, and some of the compounds in the table might be structurally related among them. cHH: Crustacean hyperglycemic hormone; D-Aba: D-aminobutanoic acid; D-diAba: D- $\alpha,\gamma$ -diaminobutanoic acid; D-Aaa: D- $\alpha$ -aminoadipic acid; D-pHPG: D-*para*-hydroxyphenylglycine; D-oCTyr: D-*ortho*-chlorotyrosine; D-oC $\beta$ HTyr, D-*ortho*-chloro- $\beta$ -hydroxy-tyrosine; 4HnPro: *allo*-4-hydroxy-n-proline; m-D-Leu: *N*-methyl-D-leucine; D-Thr: D-*allo*-threonine; D-avCys: S-(2-aminovinyl)-D-cysteine; D-avmCys: S-(2-aminovinyl)-(3S)-3-methyl-D-cysteine.

Compound	D-Amino acid	Function	Source	Ref.
Dermorphins	D-Ala and others	Opioid peptide	Frogs	[15]
Dermenkephalins	D-Met	Enkephalin-like activity	Frogs	[16]
Deltorphin I and II	D-Ala	Opioid peptides	Frogs	[17]
Bombinins	D- <i>allo</i> -Ile	Antibiotic	Frogs	[18]
Conotoxins	D-Phe, D-Leu	Repetitive activity in motor nerve	Frogs	[19]
C-Type natriuretic peptides	D-Leu, D-Met	Venom (defensin-like)	Platypus	[20]
FMRMamide-related peptide	D-Leu	Excitation of the anterior byssus retractor muscle	Mytilus	[21]
Ocp-1	D-Phe	Cardioactive peptide	Octopus	[22]
cHH	D-Phe	Regulation of endogenous blood glucose metabolism	Octopus	[23]
Achatin I	D-Phe	Enhances cardiac activity	Snails	[24]
Fulcin and derivatives	D-Asn, D-Ala	Contraction of the penis retractor muscle	Snails	[25]
Contryphans	D-Trp or D-Leu	Venom	Snails	[26]
$\omega$ -Agatoxin	D-Ser	Calcium channel blocker	Spider	[27]
Several peptibiotic analogs	D-Isovaline (Iva)	Secondary metabolites, some with antibiotic activity	Filamentous fungi	[28]
Cyclosporines and derivatives	D-Ala	Antibiotic	<i>Tolyposcladium inflatum</i>	[29]
HC-Toxin	D-Pro, D-Ala	Inhibitor of root growth of maize	<i>Helminthosporium carbonum</i>	[30]
Peptidoglycan	D-Ala, D-Glu	Structural support/protection	Eubacteria	[13][14]
Seromycin	D-Cycloserine	Antibiotic	<i>Streptomyces orchidaceus</i>	[31]
Bacteriocins type I (epidermin, mersacidin, gallidermin)	D-avCys or D-avmCys	Antibiotic	<i>Staphylococcus</i> strains	[32][33]
Etamycin and derivatives	D-Leu, 4HnPro	Antibiotic	<i>Streptomyces</i> strains	[34]
Monamycins	D-Val, m-D-Leu, D-Ile	Antibiotic	<i>Streptomyces</i> strains	[35]



Table 2 (cont.)

Compound	D-Amino acid	Function	Source	Ref.
Bacteriocins type II (Lactacin 3147, Lactocin S)	D-Ala	Antibiotic	<i>Lactobacillus</i> strains	[36]
Poly- $\gamma$ -D-glutamate	D-Glu	Capsule for toxins	<i>Bacillus anthracis</i>	[37]
Gramicidin D	D-Leu, D-Val	Antibiotic	<i>Bacillus brevis</i>	[38]
Gramicidin S	D-Phe	Antibiotic	<i>Bacillus brevis</i>	[39]
Tyrocidines A, B	D-Phe	Antibiotic	<i>Bacillus brevis</i>	[39]
Tyrocidines C, D	D-Phe, D-Trp	Antibiotic	<i>Bacillus brevis</i>	[40]
Fengycin	D-Orn, D- <i>allo</i> -Thr, D-Ala, D-Tyr	Antibiotic	<i>Bacillus subtilis</i>	[40]
Iturins (iturins, bacillomycins, mycosubtilin)	D-Tyr, D-Asn, D-Ser	Antibiotic	<i>Bacillus subtilis</i>	[41]
Surfactin and derivatives	D-Leu	Antibiotic	<i>Bacillus subtilis</i>	[42]
Bacitracin	D-Asp, D-Glu, D-Orn, D-Phe	Antibiotic	<i>Bacillus brevis</i>	[43]
Mycobacillin	D-Asp, D-Glu	Antibiotic	<i>Bacillus subtilis</i>	[44]
Polymyxins	D-Phe, D-Leu, D-Ser, D-diAba	Antibiotic	<i>Bacillus polymyxa</i>	[45]
Cereulide	D-Ala	Food poisoning (toxin, valinomycin related)	<i>Bacillus cereus</i>	[46] [47]
Valinomycins	D-Val	Antibiotic	<i>Streptomyces</i> strains	[48] [49]
Actinomycins	D-Val, D- <i>allo</i> -Ile	Antibiotic	<i>Streptomyces</i> strains	[50]
Streptogramins B	D-Aba or D-Ala	Antibiotic	<i>Streptomyces</i> strains	[51]
Quinoxalines (echinomycin, triostin A)	D-Ser	Antibiotic	<i>Streptomyces</i> strains	[52]
Daptomycin and derivatives	D-Ala, D-Ser, D-Asn	Antibiotic	<i>Streptomyces</i> and other <i>Actinomycetes</i>	[53]
Ramoplanins	D-aThr, D-pHPG, D-Ala	Antibiotic	<i>Actinoplanes</i> strains	[54]
Penicillin G	D-Val	Antibiotic	<i>Penicillium</i> and <i>Aspergillus</i> strains	[55]
Cephalosporin C	D-Aaa	Antibiotic	<i>Penicillium</i> and <i>Aspergillus</i> strains	[55]
Tolaasin	D-Pro, D-Ser, D-Leu, D-aThr, D-Val, D-Gln, D-diAba	Antibiotic	<i>Pseudomonas tolaasii</i>	[56]
Vancomycin	D-Leu, D-pHPG, D-oC $\beta$ HTyr	Antibiotic	<i>Actinoplanes</i> strains	[57]
Teicoplanin	D-pHPG, D-oCTyr	Antibiotic	<i>Actinoplanes</i> strains	[57]
Hasadillins	D-Tyr, D-Thr, D-aThr, D-Glu	Antibiotic	<i>Hasadillia</i> sp.	[58]

Table 3. *Semisynthetic Penicillins and Cephalosporin Antibiotics Where D-para-Hydroxyphenylglycine (D-pHPG), D-Phenylglycine (D-PG), or D-2-(2,5-Dihydro)phenylglycine (D-dHPG) Are Used.* It is worth noting that all penicillin members contain a second D-amino acid, D-valine, which forms part of the nucleus of 6-aminopenicillanic acid (6-APA; see Fig. 2).

Compound	Ref.	D-Amino acid
Cefadroxil	[78][79]	D-pHPG
Cefatrizine	[80]	
Cefprozil	[79]	
Cefoperazone	[81]	
Cefpiramide [SM-1652]	[82]	
Amoxicillin	[83]	
Cephalexin	[78–80][84]	D-PG
Cefaloglycin	[84]	
Cefaclor	[78][79]	
Loracarbef	[79]	
Ampicillin and derivatives:	[83]	
Pivampicillin	[85]	
Piperacillin	[86]	
Bacampicillin	[87]	
Azlocillin	[88]	
Mezlocillin	[88]	
Metampicillin	[83]	
Talampicillin	[85]	
Lenampicillin	[89]	
Cefradine	[79][84]	
Cefroxadine (CPG9000)	[78]	
Epicillin	[90]	

resistant to hydrolysis by peptidases and proteases. Therefore, potent, long-acting substitutes for naturally occurring peptides have been developed [143]. Peptide hormones fulfil several indispensable signalling processes involved in the metabolism of multicellular organisms. Therefore, the pharmacokinetic properties of peptide hormones containing D-amino acids have attracted the research community. Furthermore, based on the results of *Tugyi et al.* [144], D-amino acid-containing peptides with increased resistance to proteolytic cleavage might also retain antibody recognition, a feature of great interest from the immunological point of view. Some examples of this D-form of peptide hormones are analogs of vasopressin, GnRH, or somastatin, with very diverse applications from chemotherapeutic to fertility treatments (*Table 3*; [130–140]). Other examples of peptides containing D-amino acids have signalling features such as the opioid peptides Ac-rfwink-NH<sub>2</sub> [112] (with analgesic functions) or nateglinide [114], which stimulates insulin secretion, and is used in diabetes type-2 treatment.

Free D-amino acids are also of industrial interest. D-Methionine solutions have applications in preventing, treating, or alleviating oral mucositis, hearing loss due to chemotherapy, antibiotics, and noise, neuronal damage due to various central nervous system disorders and injuries, and anthracycline toxicity [96]. D-Phenylalanine has been used as an analgesic in warm-blooded animals and as antidepressant treatment of

Table 4. Several Uses of Free D-Amino Acids and Compounds Containing D-Amino Acids. D-Nal: D-3-(2-naphthyl)alanine; D-cit: D-citrulline; D-Hcit: D-homocitrulline; D-norVal: D-norvaline; DhArg: D-homoarginine; Pal: 3-(pyridin-3-yl)-D-alanine; D-Aba: D-aminobutanoic acid; D-Aph: 4-amino-phenylalanine; D-PG: D-phenylglycine; D-Cpa: 4-chlorophenylalanine; D-NicLys: N(sup6)-nicotinyl-D-lysine.

Compound	Amino acid	Application	Ref.
D-Methionine		Treating oral mucositis, hearing loss, neuronal damage, and anthracycline toxicity	[96]
D-Phenylalanine		Analgesic in warm blooded animals, antidepressant treatment of <i>Parkinson's</i> disease	[97]
D-Alanine or D-serine (or derivatives)		Treatment of neuropsychiatric disorders	[98][99]
D-Lysine		Reduction of renal uptake of radioactivity during scintigraphy and PRRT	[100]
D-Cycloserine (Seromycin)		Tuberculosis treatment, treatment of anxiety disorders	[101][102]
O-Carbamoyl-D-cycloserine		Antibiotic, acts sinergically with D-cycloserine	[101]
D-cycloserine/ $\beta$ -chloro-D-alanine		Deodorant	[103]
$\beta$ -Chloro-D-alanine		Antibiotic, acts sinergically with D-cycloserine	[101]
D-O- <sup>18</sup> F-Fluoromethyltyrosine	D-Tyr	Screening of cancers using positron emission tomography (PET) imaging	[104][105]
D-Proline derivatives	D-Pro	Treatment of diseases associated with amyloidosis	[106]
D-Hydroxyproline derivatives	D-Pro	Allergen-reducing composition	[107]
Poly-D-lysine	D-Lys	Enhance cell attachment to plastic and glass surfaces.	[108][109]
Poly-D-Leu	D-Leu	Asymmetric synthesis	[110][111]
Ac-rtwink-NH <sub>2</sub> (opioid peptide)	D-Arg, D-Phe, D-Trp, D-Ile, D-Asn, D-Lys	Analgesic activity	[112]
Opioid peptides	Several D-amino acids	Selective ligands for opioid receptors	[113]
Nateglinide	D-Phe	Insulin secretagogue	[114]
Fluvalinate (tau-fluvalinate)	D-Val	Pyrethroid pesticide	[115]
Cecropin, melittin, magainin derivatives	Several D-amino acids	Antibiotic	[94][95]
Magamins derivatives (MSI-78)	Several D-amino acids	Antibiotic/anticancer	[116]
Alitame (and other dipeptides)	D-Ala, D-Aba, D-norVal, D-Val, D-PG	Artificial sweeteners	[117-120]
Tadalafil (cialis) and other related peptides	D-Trp, D-2-alkyltryptophans	Treatment of erectile dysfunction and/or of pulmonary arterial hypertension	[121][122]

Table 4 (cont.)

Compound	Amino acid	Application	Ref.
Thymopressin ( $\gamma$ -D-Glu-D-Trp)	D-Glu, D-Trp	Atopic dermatitis treatment (such as Psoriasis)	[123]
SCV-07 ( $\gamma$ -D-Glu-L-Trp)	D-Glu	Potent immunomodulatory and antimicrobial activity	[124]
Dactinomycin (actinomycin D)	D-Val	Antibiotic/anticancer	[125]
7-Aminoactinomycin D	D-Val	Fluorescent markers of DNA	[126]
Luciferin and derivatives	D-Cys	Luminescent reagents	[127]
2-Alkyl-D-cysteine	D-Cys	Inhibition of aminopeptidase M	[128]
D-Version of sweet arrow peptide	D-Pro	Intracellular drug delivery vector	[129]
Analogues of peptide hormones containing D-amino acids:			
<i>GnRH Analogs:</i>			
Abarelix	D-Ala, D-Cpa <sup>8</sup> ), D-Asp	In general, GnRH analogs are used in the treatment of some hormone-dependent cancers (such as prostate cancers) and diseases and conditions which result from inappropriate sex hormone levels. GnRH Antagonists (those containing more than one D-amino acid have also applications in reproduction technologies.	[130]
Antarelix	D-Nal, D-Cpa <sup>8</sup> ), D-Pal, D-Hcit, D-Ala		[130]
Cetrorelix	D-Nal, D-Cpa <sup>8</sup> ), D-Pal, D-Cit, D-Ala		[130][131]
Ganirelix	D-Nal, D-Cpa <sup>8</sup> ), D-Pal, D-hArg, D-Ala		[130][131]
Iturelix (Antide)	D-Nal, D-Cpa <sup>8</sup> ), D-Pal, D-NicLys, D-Ala		[130][131]
Nal-Glu	D-Nal, D-Cpa <sup>8</sup> ), D-Pal, D-Glu, D-Ala		[130][131]
AzalineB	D-Nal, D-Cpa <sup>8</sup> ), D-Pal, D-Ala		[131]
Degarelix	D-Nal, D-Cpa, D-Pal, D-Aph, D-Ala		[131]
Lupron (Leuprolin)	D-Leu		[131]
Synarel (nafarelin)	D-Nal		[131]
Zoladex (Goserelin)	D-Ser (tBu)		[131]
Suprefact (busarelin)	D-Ser		[131]
Decapeptyl (triptorelin)	D-Trp		[131]
Other GnRH analogs	Several D-amino acids		[132][133]

Table 4 (cont.)

Compound	Amino acid	Application	Ref.
<i>Somatostatin Analogs:</i>			
Lanreotide	D-Nal, D-Trp	As a resume, somatostatin analogs present activities vs. processes arising from inappropriate angiogenesis, such as cancers, cardiovascular diseases, proliferative retinopathies, and rheumatoid arthritis.	[134]
Octreotide (sandostatin)	D-Phe, D-Trp		[134]
Seglitide (MK 678)	D-Trp		[134]
Vapreotide (RC-160)	D-Phe, D-Trp		[134]
KE 108	Cyclo-D-Dab, D-Trp		[134]
Hexarelin	D-Trp(2-Me), D-Phe		[135]
Other somastatin analogs	Several D-amino acids		[134–137]
$\alpha$ -Melanocyte-related tripeptide and derivatives	D-Pro	Anti-inflammatory	[138] [139]
Desmopressin (vasopressin analog)	D-Arg	Treatment of bedwetting	[140]

<sup>a)</sup> This amino acid is shown as D-Phe in [130] [131].

*Parkinson's* disease [97]. D-Alanine or D-serine have been evaluated in the treatment of neuropsychiatric disorders [98][99] (schizophrenia, *Alzheimer's* disease, autism, depression, benign forgetfulness, childhood learning disorders, close head injury, and attention deficit disorder). Recently, promising results have been published concerning *in vivo* uptake of D-amino acids in tumors [104][105], showing <sup>18</sup>F-labelled D-isomers suitable for positron emission tomography (PET) imaging of normal and tumor tissues. D-Proline derivatives are used to treat diseases associated with amyloidosis, such as *Alzheimer's* disease, maturity-onset diabetes mellitus, familial amyloid polyneuropathy, scrapie, and *Kreuzfeld–Jacob* disease [106].

Another use of D-amino acids is in the production of peptides composed entirely of these isomers. Poly-D-leucine is used in enantioselective epoxidation of chalcone I [110][111], whereas poly-D-lysine is used as a coating to enhance cell attachment to plastic and glass surfaces, and to culture a wide variety of cell types, particularly neurons, glial cells, and transfected cells [108][109]. Derived from the natural *gamma*-linked poly-D-glutamic acid (which conforms the capsule of several *Bacillus* and *Staphylococcus* strains, and is involved in causing anthrax by *Bacillus anthracis*), this polymer has been studied for its ability to translocate across biological membranes *via* the paracellular pathway. This finding may prove useful for oral delivery of therapeutic proteins and polypeptides [145].

**Conclusions.** – The mechanisms by which D-amino acids can be obtained or produced are still to be completely unraveled. Current evidence has clearly lent more importance to these compounds than was first thought. Besides their importance in natural and semisynthetic antibiotics, their slower relative rate of degradation compared to the corresponding L-isomers may be an outstanding property in the therapeutic use of peptides containing D-amino acids. Thus, D-amino acids as chiral synthons are increasingly important in the industry, and effective processes for their economic production are still of interest in the next decade.

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