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Chirality across scales

A look at *D*-Amino Acids in living beings

Una mirada a los *D*-aminoácidos en los seres vivos

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Abstract

The predominance of L-amino acids in biological systems has long been considered a defining feature of life. However, accumulating evidence over the past decades has demonstrated that D-amino acids are not merely biochemical anomalies, but biologically relevant molecules with diverse and essential functions across all domains of life. This review summarizes current knowledge on the distribution, biosynthesis, metabolism, and physiological roles of D-amino acids, highlighting their significance in microbial, animal, and evolutionary contexts. In bacteria, D-amino acids such as D-alanine and D-glutamate are integral components of peptidoglycan, contributing to cell wall integrity and resistance to proteolytic degradation. Beyond structural roles, several noncanonical D-amino acids act as signaling molecules to biofilm formation and microbial community dynamics. In eukaryotes, particularly in mammals, D-serine and D-aspartate have emerged as key neuromodulators involved in synaptic plasticity, neurodevelopment, and endocrine regulation, with growing implications in neurological and psychiatric disorders. Furthermore, the coexistence of functional D-amino acids with the largely L-based proteome raises fundamental questions about the origin and maintenance of biological homochirality. Mechanisms such as stereospecific aminoacyl-*tRNA* synthetases and D-aminoacyl-*tRNA* deacylases actively preserve proteomic homochirality while allowing selective utilization of D-amino acids in specialized pathways. Overall, D-amino acids represent a crucial yet historically underappreciated dimension of biological chemistry, with implications ranging from microbial physiology to neuroscience and the origin of life.

Keywords: Enantiomers, amino acids' evolution, homochirality, biofilm, racemase, peptidoglycan.

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Resumen

La predominancia de los L-aminoácidos en los sistemas biológicos se ha considerado durante mucho tiempo como una característica definitoria de la vida. Sin embargo, la evidencia acumulada en las últimas décadas ha demostrado que los D-aminoácidos no son solo anomalías bioquímicas, sino moléculas biológicamente relevantes con funciones diversas y esenciales en todos los dominios de la vida. Esta revisión resume el conocimiento actual sobre la distribución, biosíntesis, metabolismo y funciones fisiológicas de los D-aminoácidos, destacando su importancia en contextos microbianos, animales y evolutivos. Los D-aminoácidos como la D-alanina y el D-glutamato en las bacterias son componentes integrales del peptidoglicano, contribuyendo a la integridad de la pared celular y a la resistencia a la degradación proteolítica. Más allá de sus funciones estructurales, varios D-aminoácidos actúan como moléculas de señalización para la formación de *biofilms* y la dinámica de las comunidades microbianas. En los eucariontes, particularmente en los mamíferos, han surgido la D-serina y el D-aspartato como neuromoduladores clave implicados en el neurodesarrollo y la regulación endocrina, con implicaciones crecientes en trastornos neurológicos y psiquiátricos. Además, la coexistencia de D-aminoácidos funcionales con un proteoma mayoritariamente basado en L-aminoácidos plantea preguntas fundamentales sobre el origen y el mantenimiento de la homoquiralidad biológica. Los mecanismos como las D-aminoacil-*tRNA* desaciclasas preservan activamente la homoquiralidad del proteoma, al tiempo que permiten la utilización selectiva de D-aminoácidos en rutas especializadas. En conjunto, los D-aminoácidos representan una dimensión crucial, aunque históricamente subestimada, de la química biológica, con implicaciones que van desde la fisiología microbiana hasta la neurociencia y el origen de la vida.

Palabras clave: Enantiómeros, evolución de aminoácidos, homoquiralidad, biofilm, racemasa, peptidoglicano.

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Introduction

Proteins constitute one of the most abundant biomolecules in living organisms. The protein system performs structural, catalytic, signaling, storage, and immune defense functions (Sasabe and Suzuki, 2018). All proteins are composed of basic units known as amino acids, which are linked together to form chains called peptides. Upon folding, these peptides acquire a three-dimensional conformation that often corresponds to the active form known as protein. However, in most instances, several polypeptide chains associate through oligomerization to achieve the fully active state. These building blocks comprise a set of 20 α-amino acids, all sharing a common structure consisting of a central carbon atom (α-carbon) bonded to four substituents: an amino group, a carboxyl group, a hydrogen atom, and a variable side chain known as the R group (Alberts et al., 2015).

The α-carbon forms a chiral center, except in glycine, because the four substituents can adopt two possible spatial arrangements, giving rise to the *L*- (left-handed) and *D*- (right-handed) optical isomers, commonly referred to as enantiomers. The *D*- or *L*- nomenclature is assigned by comparing the Fischer projection of these molecules with that of glyceraldehyde: if the $-$OH group (or $-NH_3^+$ in amino acids) is positioned on the right, the molecule is classified as the *D*-enantiomer, whereas if it is located on the left, it is classified as the *L*-enantiomer.

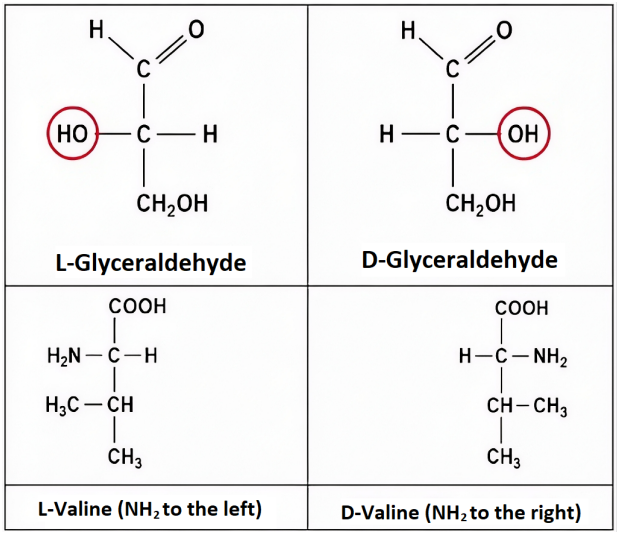


Figure 1. *D/L* designation of chiral molecules using Fischer projections. In glyceraldehyde (top), the *L* configuration is assigned when the hydroxyl group ($-$OH) attached to the chiral carbon is located on the left side of the Fischer projection, whereas the *D* configuration corresponds to its location on the right. This criterion constitutes the historical reference for the relative *D/L* nomenclature used for carbohydrates and amino acids. Using valine as an example (bottom), the *L* configuration has the amino group ($-NH_2$) positioned on the left side of the α-carbon, whereas in the *D* configuration this group is located on the right. Note that the $-$OH and $-NH_2$ groups exhibit the same relative orientation in their respective Fischer projections. Thus, the *D/L* designation expresses a structural relationship to glyceraldehyde and does not necessarily indicate the direction of optical rotation of plane-polarized light.

Only one of the two enantiomers is incorporated into proteins: *L*-amino acids. Consequently, proteins are considered a homochiral system (Du et al., 2023; Sasabe and Suzuki, 2018). For many years, it was widely assumed that homochirality extended to all biological functions involving amino acids, leading to the belief that *D*-amino acids lacked biological relevance (Blackmond, 2010). However, advances in analytical techniques, particularly enantioselective chromatography (Kobayashi, 2019), enabled the detection of *D*-amino acids in bacterial cultures. These findings demonstrated that *D*-amino acids are naturally present in living organisms, where they perform physiological functions distinct from those associated with proteins (Pollegioni et al., 2025).

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Since their initial discovery, *D*-amino acids have also been identified in eukaryotes, ranging from yeasts to the mammalian nervous system (Fuchs et al., 2005), considerably expanding the range of biological functions attributed to these molecules. Their roles at multiple biological levels continue to be investigated, and although much of their metabolism remains poorly understood, they have attracted considerable interest in fields such as microbiology, neuroscience, endocrinology, and biotechnology (Du et al., 2023).

D-amino acids in bacteria

The first compelling evidence for the biological role of *D*-amino acids emerged from studies of the bacterial cell wall, a structure shared by all bacteria. The bacterial cell wall consists of peptidoglycan, a polymeric network composed of glycosidic linkages between *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM), cross-linked by peptides containing primarily *D*-alanine (*D*-Ala) and *D*-glutamate (*D*-Glu) residues (Cava et al., 2011). These amino acids serve as anchoring points for adjacent peptidoglycan strands by forming short peptide bridges between *D*-Ala residues. The extensive cross-linking of these chains provides the bacterial cell wall with remarkable mechanical rigidity (Figure 2). In addition to their structural role, *D*-amino acid residues protect bacteria against proteases and other components of the host immune system that are unable to recognize these enantiomers as substrates. Consequently, *D*-amino acids have become attractive targets for the development of novel antibodies and antimicrobial agents (Sanchez et al., 2014).

The establishment of bacterial colonies is frequently accompanied by the formation of extracellular multicellular structures known as biofilms. These structures are composed primarily of amyloid protein fibers and polysaccharides, providing a protective environment that supports the multicellular proliferation of bacteria such as *Bacillus subtilis* (Kolodkin-Gal et al., 2010), where they are shielded from host immune defenses during infection. *D*-amino acids within the peptidoglycan also contribute to biofilm attachment, providing mechanical stability and facilitating bacterial movement through the extracellular matrix (Su et al., 2022).

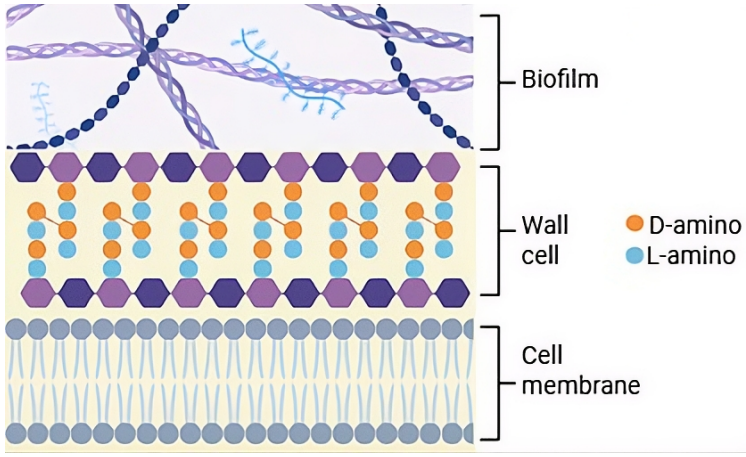


Figure 2. Structure of the bacterial peptidoglycan cell wall composed of sugar chains cross-linked by peptides containing *D*-Ala and *D*-Glu residues. The incorporation of *D*-amino acids enhances cell wall rigidity and promotes adhesion to extracellular biofilm structures, including TasA amyloid proteins (Sasabe and Suzuki, 2018).

Beyond their structural function, *D*-amino acids also exert regulatory roles within biofilms (Roesch et al., 2003), promoting cyst dispersal (exit from the dormant phase) and accelerating bacterial proliferation. Although these regulatory mechanisms remain under investigation, studies on *Staphylococcus aureus* and *Pseudomonas aeruginosa* have demonstrated that increasing the concentration of *D*-amino acids such as *D*-leucine (*D*-Leu), *D*-methionine (*D*-Met), *D*-tryptophan (*D*-Trp), and *D*-tyrosine (*D*-Tyr)

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promotes the disassembly of TasA amyloid fibers, one of the principal structural components of bacterial biofilms (Kolodkin-Gal et al., 2010).

The replacement of *D*-Ala residues in peptidoglycan has been extensively investigated and can be readily achieved by enriching the culture medium with alternative *D*-amino acids. This substitution reduces or inhibits the anchoring of the peptidoglycan cell wall to TasA proteins within the biofilm matrix (Ramón-Pérez et al., 2014). Among these compounds, *D*-Leu, *D*-Met, *D*-Trp, and *D*-Tyr exhibit the greatest inhibitory effects on bacterial biofilm formation and are currently being investigated as potential therapeutic agents against bacterial infections (Su et al., 2022). Furthermore, supplementation with *D*-amino acids such as *D*-Met and *D*-Trp has been shown to enhance the efficacy of antibiotics, including ciprofloxacin and vancomycin by increasing bacterial permeability and improving molecular recognition (Cava et al., 2011; Sanchez et al., 2014).

Lactic Acid Bacteria and D-Amino Acid Metabolism

The primary biological source of *D*-amino acids is their synthesis through racemases (Radkov and Moe, 2014), a family of enzymes whose function is to recognize an *L*-amino acid and convert it into its corresponding *D*-enantiomer. However, these enzymes have also been shown to catalyze the reverse reaction, converting *D*-amino acids into their *L*-enantiomers (Mutaguchi et al., 2018). Racemases are not exclusive to bacteria, as they have been identified in several animal groups (Fuchs et al., 2005; Ollivaux et al., 2014). Nevertheless, bacteria remain the group in which the enzymes involved in *D*-amino acid metabolism have been most thoroughly characterized. The best-studied enzyme of this family is alanine racemase (*AlaR*) (Kobayashi et al., 2015; Rubinstein and Major, 2010), which serves as the primary source of *D*-alanine (*D*-Ala) for the peptidoglycan cell wall. Enzymes capable of racemizing other amino acids have also been identified, including aspartate racemase (*AspR*) and glutamate racemase (*GluR*) (Glavas and Tanner, 1999).

Lactic acid bacteria comprise a large group of sugar-fermenting microorganisms of considerable industrial importance and are also natural members of the intestinal microbiota (Kobayashi, 2019; Sasabe and Suzuki, 2018). This group of bacteria has been shown to release large amounts of *D*-amino acids into the surrounding medium, predominantly *D*-Ala, but also *D*-leucine (*D*-Leu), *D*-valine (*D*-Val), and *D*-methionine (*D*-Met) (Mutaguchi et al., 2016). Owing to their high production of racemic amino acids during fermentation processes, lactic acid bacteria have attracted considerable interest for industrial applications and large-scale production (Kato et al., 2011).

Enzymatic studies on *D*-amino acid production in lactic acid bacteria have revealed that several racemases are not specific to a single R side chain, as many of them recognize more than one substrate, thereby synthesizing multiple *D*-amino acids from their corresponding *L*-enantiomers. For example, isoleucine racemase (*IsoR*) isolated from *Lactobacillus* sp. (Mutaguchi et al., 2018) exhibits low specificity toward aliphatic amino acids and is capable of racemizing not only *L*-isoleucine (*L*-Ile) but also *L*-leucine (*L*-Leu), *L*-valine (*L*-Val), *L*-norvaline (*L*-Nva), and *L*-norleucine (*L*-Nle). A similar case is lysine racemase (*LysR*) isolated from *Oenococcus oeni* (Kato et al., 2012), which has been shown not only to catalyze the racemization of lysine to *D*-lysine (*D*-Lys), but also to synthesize *D*-arginine (*D*-Arg) and *D*-ornithine (*D*-Orn), two other positively charged amino acids.

Racemases are not the only enzymes involved in *D*-amino acid synthesis. *D*-amino acid aminotransferases (DAATs) constitute another family of enzymes that synthesize *D*-amino acids by transferring an amino group to sugar (Kobayashi, 2019; Martinez-Carrion and Jenkins, 1965). The reaction mechanism begins with the recognition of an α-keto acid; during transamination, the carbonyl group is replaced by an amino group. These enzymes are considered to exhibit a certain degree of substrate specificity through the recognition of R side chains (Shilova et al., 2023). Nevertheless, it has been widely demonstrated that several DAATs can catalyze the transamination of amino acids bearing different types of R side chains, enabling bacteria to produce multiple *D*-amino acids using a single enzyme, including *D*-Val, *D*-Leu, *D*-Nva, and *D*-Met (Tanizawa et al., 1989). An even more remarkable example is the DAAT characterized in the hyperthermophi-

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lic bacterium *Thermotoga maritima*, whose DAAT is capable of catalyzing the synthesis of *D*-alanine (*D*-Ala), *D*-glutamine (*D*-Gln), *D*-aspartate (*D*-Asp), and *D*-cysteine (*D*-Cys) (Yu et al., 2024), thereby recognizing substrates with R side chains of markedly different chemical characteristics.

Archaea and D-Amino Acids

The case of Archaea, the second major domain of prokaryotes and the lineage from which eukaryotes originated, should also be considered (Stevens and Warnecke, 2023). Archaea are unicellular organisms that possess a cell wall less dense than that of bacteria, known as pseudopeptidoglycan. This structure also consists of a matrix of short peptides linked to polysaccharides; however, very few of these peptides contain *D*-amino acids (Sasabe and Suzuki, 2018; Yu et al., 2024). The incorporation of *D*-alanine (*D*-Ala) and *D*-glutamate (*D*-Glu) into pseudopeptidoglycan may occur; however, these additions are considered to result from the availability of these molecules in the surrounding environment. Detection of these *D*-amino acids is infrequent and is thought to originate primarily from microbial communities, such as those inhabiting marine sediments (Imachi et al., 2024).

Because they are considered metabolic anomalies, enzymes associated with *D*-amino acids in archaea are generally regarded as catabolic. Several enzymes capable of recognizing *D*-amino acids have been identified, including alanine racemase (*AlaR*) and an amino acid dehydrogenase exhibiting activity toward *D*-alanine (*D*-Ala) and *D*-proline (*D*-Pro) as substrates (Nagata et al., 1999). These enzymes are believed to function in the elimination of *D*-amino acids that may accumulate because of the coexistence with *D*-amino acid-producing bacteria, such as lactic acid bacteria. Within archaeal metabolism, there is little evidence supporting the endogenous production of *D*-enantiomers. More recently, a possible pathway for the synthesis of α-keto acids has been described. These molecules are precursors of sugars and serve as substrates for DAAT enzymes in the biosynthesis of *D*-amino acids (Sasabe and Suzuki, 2018; Yu et al., 2024).

D-Amino Acids in Eukaryotes

Following the discovery of *D*-alanine (*D*-Ala) in bacteria, evidence of other *D*-amino acids was gradually found in numerous biological processes in eukaryotes as well. In the mid-1960s, *D*-amino acids were identified in several animal species. *D*-serine (*D*-Ser) was first isolated in *Bombyx mori* (Srinivasan et al., 1962), the silkworm, where it promotes chrysalis formation and moth metamorphosis. During the following decades, amino acids such as *D*-Ala, *D*-methionine (*D*-Met), and *D*-glutamate (*D*-Glu) were isolated from numerous marine invertebrates (Preston, 1985). *D*-Ala and *D*-aspartate (*D*-Asp) were detected in the muscle tissues of mollusks such as *Octopus vulgaris* (Abe et al., 2005), and during embryonic development in echinoderms such as *Paracentrotus lividus* (D'Aniello et al., 1990).

The presence of free *D*-amino acids in the blood of marine organisms serves as a buffering system against the osmotic pressure of seawater, since the protonatable groups of amino acids such as *D*-Ala have been shown to function as physiological buffers (D'Aniello et al., 1990). This buffering activity is regulated by *D*-amino acid oxidases (DAAO), which catalyze the conversion of *D*-amino acids into α-keto acids (Yoshimura et al., 2016), thereby regulating the concentration of these molecules within tissues. DAAOs exhibit high specificity toward *D*-Ala. DAAOs with affinity for *D*-Asp and *D*-Met have also been described; however, this affinity does not appear to be exclusive, as they are capable of catabolizing other *D*-amino acids to a lesser extent (Preston, 1985).

Plants have also been shown to incorporate *D*-amino acids into multiple physiological and developmental processes. Within the glaucophyte algae, a group associated with the origin of the kingdom Plantae, the physiology includes several *D*-amino acids, among which *D*-Ala and *D*-Glu have been identified (Palmer et al., 2004). The presence of *D*-amino acids in plants was originally attributed to the rhizosphere microenvironment, where coexistence with bacterial communities enriches the surrounding medium with these molecules, representing approximately 3–5 % of the total amino acid content (Pollegioni et al., 2025).

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The study of the physiology of these molecules began with their detection in most fruits, where *D*-Ala, *D*-arginine (*D*-Arg), *D*-Asp, and *D*-Glu were isolated (Pollegioni et al., 2025), and subsequently associated with seed development. In the early 1990s, *D*-Met was found not to be restricted to the roots; rather, it undergoes active transport to other plant tissues, suggesting its involvement in physiological functions (Du et al., 2023). Receptors for *D*-Asp and *D*-Ala have been identified that promote ethylene production, a phytohormone responsible for radicle development during germination and root maturation (Du et al., 2023; Kolukisaoglu, 2020). Finally, the production of peptidoglycan within chloroplast cell walls has been associated with an ancestral trait shared between cyanobacteria and the chloroplasts of angiosperms, providing evidence supporting the endosymbiotic theory of this organelle (Tran et al., 2023).

Within the fungal kingdom, *D*-amino acids are generally not synthesized. A particular case is that of yeasts, which, by coexisting with lactic acid-fermenting bacteria, have evolved metabolic pathways that exploit the abundance of these molecules in their environment (Kato et al., 2011; Mutaguchi et al., 2016). In *Saccharomyces cerevisiae*, enzymatic complexes of amino acid dehydratases (AmDH) have been described. These enzymes are lyases that convert amino acids such as *D*-threonine (*D*-Thr) and *D*-serine (*D*-Ser) into sugars (Gogami et al., 2011). One of these enzymes is serine dehydratase (*SerDH*), which recognizes both *D*- and *L*-serine as substrates and converts them into trioses, exhibiting a preferential affinity for *D*-Ser (Ito et al., 2008).

This affinity suggests an ecological adaptation. As discussed previously, fermentative environments typically contain high concentrations of *D*-amino acids due to the activity of lactic acid bacteria. In environments where both microorganisms coexist, yeasts, like some archaea, can utilize *D*-amino acids as substrates for the production of pyruvate and oxaloacetate, which subsequently enter the Krebs cycle (Mutaguchi et al., 2016) (Figure 3).

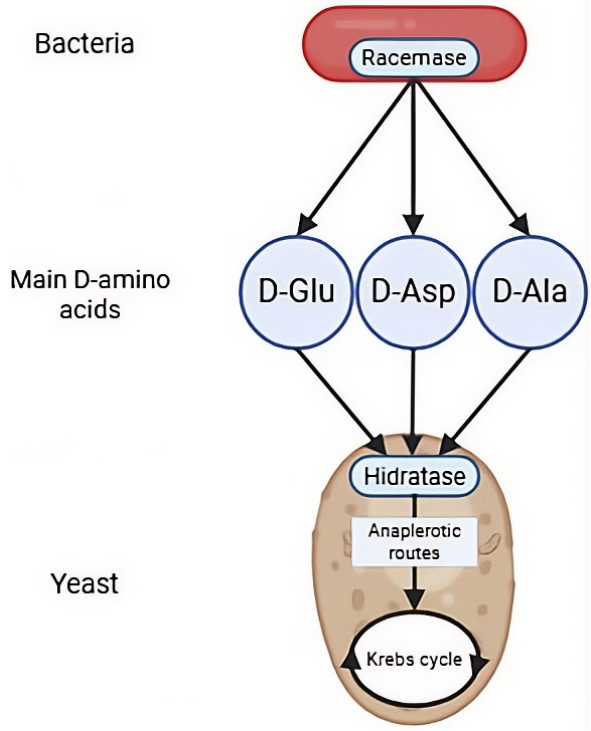


Figure 3. Anabolism of *D*-amino acids by racemase enzymes (AAr) in lactic acid bacteria. *D*-amino acids are released into the extracellular medium as regulators of biofilm formation. Catabolism of *D*-amino acids by yeasts for the synthesis of Krebs cycle metabolites (anaplerotic pathways) (Mutaguchi et al., 2016).

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Mammalian Nervous System and D-Amino Acids

D-amino acids have been identified in the nervous and endocrine systems of mammals. These animals possess highly complex nervous systems, from which amino acids such as *D*-serine (*D*-Ser) and *D*-aspartate (*D*-Asp) have been isolated (Fuchs et al., 2005), and enzymatic complexes involved in their metabolism have also been described (Sasabe and Suzuki, 2018). *D*-Ser has been demonstrated to act as a promoter of synaptic transmission as well as dendrite formation. Deficiency in the production of this molecule has been associated with impaired cognitive abilities and linked to diseases such as Alzheimer's disease (Li-Zhen and Xing-Zu, 2003; Ni et al., 2023).

The production of this amino acid is highly concentrated in the brain, particularly in astrocytes. These cells contain enzymatic complexes composed of serine racemase (*SerR*) and *SerDH* (Suzuki et al., 2015), thereby regulating local *D*-Ser levels while simultaneously producing energy. This amino acid plays a central role in the development of motor and spatial abilities. During embryonic development of the cerebellum, *D*-Ser is present at high concentrations, which decline to minimal levels in adulthood (Nagata et al., 1994). Regulation of *D*-Ser levels is mediated by *D*-amino acid oxidase (DAAO). This enzyme exhibits low expression at birth and during postnatal development, with its activity increasing during adulthood, thereby maintaining *D*-Ser concentrations at minimal levels. DAAO activity has been reported to be concentrated in the base of the cerebellum and the spinal cord, maintaining *D*-Ser production localized within the central nervous system (Sasabe et al., 2014).

D-Asp is another amino acid widely found in the mammalian nervous system and has been attributed several endocrine functions, particularly during cellular differentiation (Furuchi and Homma, 2005). Its presence in glandular tissue stimulates the production of testosterone in the testes and of oxytocin, vasopressin, and prolactin in the pituitary gland (Wang et al., 2000). As observed for *D*-Ser, *D*-Asp is associated with neuronal plasticity, displaying peak activity during embryonic development followed by a marked decline after birth. Dietary supplementation with *D*-Asp has been shown to provide benefits for neuronal plasticity (Errico et al., 2011). This amino acid has also been incorporated into the cosmetic industry as an anti-aging additive, as its absorption through the skin has been associated with an antioxidant effect on collagen in dermal cells (Mutaguchi et al., 2016).

As in the case of *D*-Ser, *D*-Asp production is associated with the enzyme aspartate racemase (*AspR*), which has been shown to catalyze the racemization reaction in both directions, from *L*- to *D*- and from *D*- to *L*- (Matsuda et al., 2015). However, *D*-Asp production cannot be attributed exclusively to this enzyme. Studies employing targeted mutagenesis have successfully inactivated the *AspR* enzyme, resulting in reduced *D*-Asp levels in mice without completely abolishing its production (Kobayashi, 2019), thereby demonstrating the existence of additional biosynthetic pathways. The explanation for these alternative pathways was found in the low substrate specificity of certain racemases, such as *SerR*, whose activity has also been shown to synthesize *D*-Asp from the corresponding *L*-enantiomer (Ito et al., 2016).

Several enantioselective enzymes for *D*-amino acids are present in the nervous system. In the case of *SerR*, several of these enzymes are capable of recognizing multiple *D*-amino acids. Another example is the ionotropic *L*-glutamate receptors (NMDARs), which have been shown to exhibit affinity for *D*-Ser, *D*-Asp, and glycine (*Gly*) (Mothet et al., 2000). Consequently, maintaining tight regulation of *D*-amino acid levels is essential. Excessive activation of NMDARs or the inactivation of DAAO enzymes results in the accumulation of *D*-amino acids, which has been shown to induce cytotoxicity that, within the brain, may ultimately lead to schizophrenia (Sasabe et al., 2007).

Homochiral Proteins in a Heterochiral System

In the absence of sources of asymmetry, the products of an abiotic chemical reaction generate a racemic mixture: chiral molecules such as amino acids are produced in equivalent amounts. This does not occur in protein systems because of the active function of enzymes themselves, which synthesize, recognize, and are composed of *L*-amino acids. There-

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fore, the exclusive use of *L*-amino acids in proteins can be considered the result of a dynamic equilibrium (Du et al., 2023).

As discussed throughout this review, the presence of *D*-amino acids in living organisms is strictly regulated by enzymes, including racemases, *D*-amino acid aminotransferases, *D*-amino acid oxidases, and *D*-amino acid dehydratases (Molla et al., 2020; Ollivaux et al., 2014). Because of these regulatory mechanisms, *D*-amino acids are rarely found in proteins. Their occurrence is generally associated with post-translational modifications that take place in the polypeptide chain, since they are only exceptionally incorporated by the ribosome during the elongation process (Alberts et al., 2015). Amino acids reach the ribosome attached to a transfer RNA (*tRNA*), which recognizes the nucleotide sequence that determines the identity of each amino acid.

To prevent the incorporation of *D*-amino acids into *tRNAs*, two regulatory mechanisms, or chirality checkpoints, have been described (Kuncha et al., 2019). The first is the stereoselectivity of aminoacyl-*tRNA* synthetases (*aaRS*s), the enzymes responsible for attaching amino acids to their corresponding *tRNAs*. These enzymes exhibit a chiral preference for *L*-amino acids; however, substrate recognition may occasionally fail, resulting in the attachment of *D*-enantiomers (Prathapan, 2025). These errors are corrected by the second checkpoint, the *D*-aminoacyl-*tRNA* deacylases (*DTD*) (Bhatt et al., 2016; Jani and Pappachan, 2022). These enzymes recognize the chirality of amino acids attached to *tRNAs* and hydrolyze the ester bond when *D*-amino acids have been mistakenly charged, thereby eliminating aminoacylation errors.

DTD activity is enantiospecific and therefore acts exclusively on *D*-amino acids. It has been demonstrated, however, that this recognition is biased in the particular case of glycine, an achiral amino acid (Calendar, 2017). Because glycine lacks chirality, *DTD* can recognize glycyl-*tRNA* ($tRNA^{Gly}$) as a substrate and hydrolyze the aminoacyl bond despite the correct amino acid being attached. Evidence indicates that this bias is prevented by the elongation factor *EF-Tu*, which forms a complex with $tRNA^{Gly}$, thereby shielding glycine from recognition and hydrolysis by *DTD* (Kuncha et al., 2019).

Evolution Toward Homochirality

Life is intrinsically linked to planet Earth; its origin and evolution modified the Earth's crust so profoundly that the planet cannot be understood without considering the intervention of the biosphere (Cintas, 2013). Biological activity is the reason why *D*-amino acids are scarce in nature, as enzymatic activity continuously recycles these molecules into other metabolites. However, such enzymatic barriers did not exist on the primitive Earth. During the first millions of years, the formation of organic molecules under abiotic conditions produced racemic mixtures of *D*- and *L*-amino acids, making both enantiomers available during the processes of chemical evolution.

Two major abiotic mechanisms have been proposed to explain the selection of one enantiomer before the emergence of life on Earth. On the one hand, deterministic hypotheses attribute chiral preference to physical and chemical biases analogous to those occurring throughout the universe and within Earth's geochemistry. On the other hand, stochastic hypotheses propose that symmetry breaking originated from local fluctuations or contingencies, whose effects were subsequently amplified until significant enantiomeric differences were established (Malloy et al., 2025).

Within the deterministic framework, parity violation in the electroweak interaction predicts minimal energy differences between enantiomers, suggesting a systematic bias favoring *L*-amino acids and *D*-sugars (Malloy et al., 2025). Although these differences are far too small to account for homochirality by themselves, they may have been reinforced in environments where heavy metal centers generated chiral coordination complexes capable of discriminating between *L*- and *D*-enantiomers during the abiotic formation of peptides. One example of this mechanism involves Cu(II) and the oxygen-evolving complex (OEC), in which intrinsically chiral copper structures promote spin polarization during electron transfer in hydrogen production, thereby benefiting from the chirality of the material (Cintas, 2013; Garcés-Pineda et al., 2025).

In this context, the salt-induced peptide formation (SIPF) mechanism, proposed as a general pathway for amino acid condensation in primitive

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oceans rich in NaCl and Cu(II), not only overcomes the thermodynamic and kinetic barriers associated with peptide formation in aqueous environments, but also provides a scenario in which the structure of metal complexes could slightly favor the incorporation of *L*-amino acids, thereby offering a plausible explanation for the origin of biological homochirality (Cintas, 2013).

Another deterministic perspective shifts the origin of chirality to interstellar space and early meteoritic bombardment. The synthesis of amino acids in interstellar ice analogs exposed to ultraviolet radiation has been documented, as has their presence in comets and meteorites. In meteorites such as *Murchison*, mixtures containing dozens of amino acids with small enantiomeric excesses have been identified, suggesting a possible extraterrestrial source of molecular asymmetry (Jakschitz and Rode, 2012). These imbalances may have resulted from circularly polarized radiation in star-forming regions, capable of inducing photochemical asymmetry in previously racemic mixtures. Consequently, the primitive Earth may have inherited a slight chiral bias in the organic material delivered from space (Jakschitz and Rode, 2012).

In contrast, stochastic hypotheses argue that the universe does not inherently "prefer" one handedness over the other, and that the choice between *L*- and *D*-enantiomers may ultimately have been a historical accident (Malloy et al., 2025). The so-called chance hypothesis envisions a scenario in which a slight imbalance between enantiomers, arising from random fluctuations, stochastic crystal nucleation, or spontaneous resolution within a particular microenvironment, became fixed because that specific molecular ensemble participated in the earliest cycles of chemical self-organization and replication (Malloy et al., 2025).

However, without an amplification mechanism, such fluctuations would tend to return to a racemic state. This is where the autocatalytic models with mutual antagonism proposed by Frank (1953) and subsequently developed in recent studies become relevant. In these models, each enantiomer catalyzes its own formation while simultaneously reacting with its mirror image to produce an inactive compound, allowing even a minute initial excess to grow until an almost enantiopure population is achieved. The Soai reaction (Soai et al., 1995), an autocatalytic alkylation capable of amplifying minimal enantiomeric excesses to values approaching optical purity, has become the experimental paradigm of this behavior (Jakschitz and Rode, 2012; Hanopolskyi et al., 2021).

From a physical perspective, crystallization processes and phase behavior provide alternative pathways for symmetry breaking and amplification. In systems that crystallize as conglomerates, the combination of dissolution, recrystallization, and mechanical attrition may lead to the complete disappearance of one enantiomer from the solid phase. Conversely, in systems forming racemic crystals, eutectic models demonstrate that the coexistence of racemic solids and pure enantiomorphic crystals establishes very high enantiomeric excesses in solution (Malloy et al., 2025). Experiments involving amino acids and copolymerization models have further shown that these dynamics can interact with surface self-assembly processes to generate highly non-random oligomer distributions from racemic mixtures, thereby providing a bridge between phase chemistry and the emergence of homochiral peptide structures.

Finally, these physicochemical processes are complemented by biological fixation mechanisms. Modern protein biosynthesis exhibits extremely high chiral selectivity: the molecular machinery composed of aminoacyl-*tRNA* synthetases and the ribosomal peptidyl transferase center discriminates very efficiently against *D*-amino acids, making their incorporation into proteins through natural biosynthetic pathways virtually impossible (Jakschitz and Rode, 2012). This suggests that, once a certain degree of enrichment in *L*-amino acids and *D*-sugars had been achieved through the combined action of deterministic and stochastic mechanisms, evolution fixed this preference by integrating chirality into the very core of translation and replication (Blackmond, 2010). Thus, current theories regarding the emergence of homochirality converge on the view that small initial asymmetries, whether dictated by physical laws, statistical chance, or the intrinsic dynamics of chemical networks, were progressively amplified and channeled by increasingly complex chemical systems until they became encoded within the molecular machinery of life as it exists today.

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Conclusions

The statement that living organisms constitute a homochiral system is not entirely accurate. Amino acid homochirality is a condition that applies to proteins, but it is not a universal rule for organisms. As highlighted throughout this review, *D*-amino acids perform multiple biological functions, among which hormonal functions are particularly noteworthy, providing a high degree of specificity within these systems owing to the stereoselectivity of these molecules. The homochiral nature of proteins and the use of *D*-enantiomers in other biological systems are tightly regulated by proteins themselves, which actively function as stereoselective determinants, directing the use of *L*-amino acids as the basis for protein synthesis and *D*-amino acids as signaling molecules.

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Declaration on the Use of Artificial Intelligence

The authors DECLARE that, during the preparation of the article entitled " A look at *D*-Amino Acids in living beings", no generative artificial intelligence tools or automated assistance systems were used for the writing, analysis, data interpretation, content generation, translation, or editing of the manuscript.

The authors assume full responsibility for the content, originality, integrity, and final version of the article.

Author Contributions

J.F.D.A.: Conceptualization, investigation, project administration, resources, supervision, visualization, writing–original draft, writing–review and editing. **M.I.H.A.:** Conceptualization, investigation, resources, software, visualization, writing–original draft, writing–review and editing.

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