

Review

Dietary D-Amino Acids as Context-Dependent Cononymic Molecules in Health and Oxidative Stress

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Abstract

Recent advances in chiral analytical chemistry have revealed that fermented and natural foods contain substantial amounts of D-amino acids (D-AAs), the mirror-image counterparts of L-amino acids, leading to their recognition as nutraceutical components with potential health relevance. Although clinical evidence provides only limited support for their therapeutic efficacy, commercial expectations have outpaced scientific validation, and recent safety concerns emphasize the need for critical evaluation. In this review, we integrate findings from food chemistry, microbiology, biochemistry, physiology, and clinical research to provide a critical overview of dietary D-AAs. We examine how dietary exposure, microbial metabolism, host clearance capacity, and redox status collectively shape their context-dependent biological effects. We highlight the mechanistic linkage between D-amino acid oxidase (DAAO)-mediated hydrogen peroxide (H₂O₂) generation and organ-specific vulnerability, thereby clarifying the molecular basis of their “double-edged sword” actions. Within this interdisciplinary framework, we propose that D-AAs function as context-dependent “cononymic” molecules in cellular communication. By distinguishing physiological regulation, experimental modulation, and clinical application, this review aims to support evidence-based nutraceutical strategies and safety assessments that harness the potential benefits of D-AAs while minimizing associated risks.

Keywords: CKD; D-amino acids; fermented foods; gut microbiota; oxidative stress; seafood

1. Introduction

1.1. Biological Homochirality to Nutraceutical Science

All living organisms on Earth share a striking and still unresolved biochemical feature: proteins are synthesized almost exclusively from L-amino acids (L-AAs), whereas their mirror-image counterparts, D-amino acids (D-AAs), are largely excluded from ribosomal translation [1]. This phenomenon, known as biological homochirality, is one of the most fundamental asymmetries of life [2]. Why living organisms select L-AAs for protein biosynthesis, despite the chemical equivalence of their D-forms, remains an enigma in evolutionary biology and origin-of-life research [3]. Although numerous hypotheses have been proposed, ranging from physicochemical constraints to environmental selection [4,5], no consensus has yet been reached [6].

For much of the twentieth century, this apparent exclusivity reinforced the view that D-AAs were biologically insignificant in higher organisms and merely represented minor



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by-products of enzymatic reactions or experimental artifacts. Early studies primarily associated D-AAs with bacterial cell walls [7] and fermentation processes [8], further supporting their presumed irrelevance to mammalian physiology. However, advances in chiral analytical chemistry and molecular biology have fundamentally altered this perspective.

The last two decades studies have revealed that D-AAs participate in diverse biological processes across kingdoms, including neurotransmission [9], host–microbe interactions [10], and redox regulation [11], and are closely associated with various physiological and pathological conditions [12]. Because humans are continuously exposed to substantial amounts of D-AAs through natural and fermentation-derived foods, evaluating their nutraceutical properties has become increasingly important. Accordingly, D-AAs are now recognized as key molecules at the interface of nutrition, metabolism, and clinical physiology, raising fundamental questions regarding how amino acid homochirality is maintained under persistent dietary exposure. In particular, it remains unclear how dietary sources, gut microbiota, and host metabolism jointly regulate D-AA homeostasis, and under what conditions D-AAs shift from physiological modulators to potential toxins.

To explore these fundamental questions, in this review, we go beyond a conventional descriptive survey of D-AAs and propose an integrative conceptual framework linking their evolutionary background, microbial ecology, dietary intake, host metabolism, and redox-mediated signaling. We argue that D-AAs should be viewed as context-dependent regulatory molecules whose biological significance emerges from their dynamic interactions with nutritional, microbial, and stress-related networks in living systems. By positioning this review at the interface of nutraceutical science and redox toxicology, we highlight hydrogen peroxide (H_2O_2) generated during D-amino acid oxidase (DAAO)-mediated degradation of D-AAs as a source of oxidative stress, as well as outline a balanced conceptual framework to support future research and safety evaluation.

1.2. Historical Overview of D-Amino Acid Research

Before reviewing recent advances in D-AA research across multiple disciplines, it is instructive to trace the historical development of scientific perspectives on molecular chirality and D-AAs. Such a retrospective approach provides essential context for understanding how D-AAs evolved from being regarded as biochemical curiosities to being recognized as biologically and nutritionally relevant molecules. In this historical framework, Louis Pasteur is widely credited as a pioneer in the discovery of molecular chirality and the foundations of modern fermentation science [13]. Following his pioneering work, research on D-AAs in biological systems has undergone a profound transformation, particularly over the past several decades (Figure 1). In 1935, Hans Krebs identified D-amino acid oxidase (DAAO) as an enzyme that degrades D-AAs via oxidative deamination [14]. This biochemical reaction produces hydrogen peroxide (H_2O_2), a reactive oxygen species (ROS) that has the potential to exert both physiological and pathological effects [15,16]. Despite this early biochemical insight, the biological significance of D-AAs and DAAO (especially the implications of DAAO-derived ROS generation as will be discussed later) remained poorly understood for many years [14].

A breakthrough came in 1949 when pioneering studies by Park and Johnson reported that treatment of bacterial cells with the antibiotic penicillin led to accumulation of unknown precursors of phosphate nucleotide derivatives [17]. In 1957, Park and Strominger revealed that the precursors contain amino acids in both L- and D-stereoisomers [18], establishing a foundation that D-Ala and D-glutamate (D-Glu) are fundamental structural components of bacterial peptidoglycan cell walls [7]. This discovery not only revolutionized understanding of bacterial structure and antibiotic mechanisms but also provided the first evidence for biological relevance of D-AAs reported by Krebs (Figure 1).

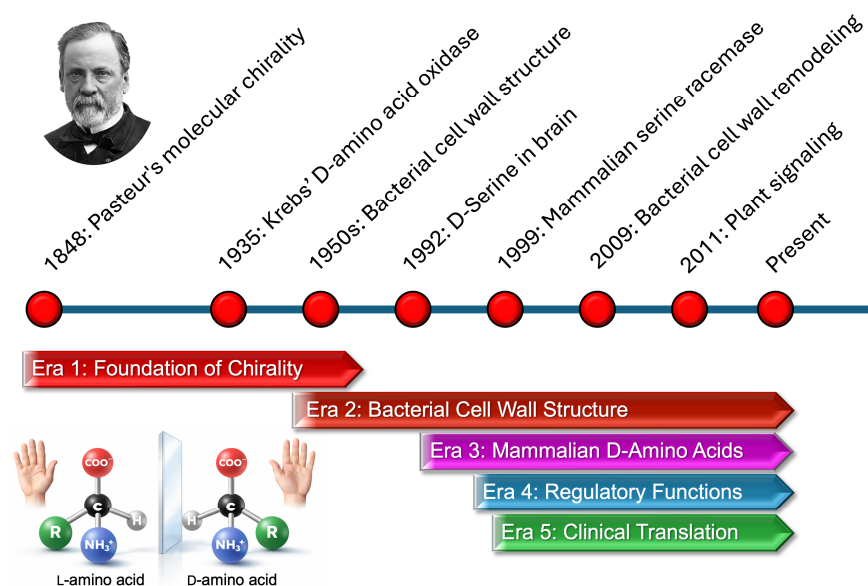


Figure 1. Paradigm shifts in D-amino acid research. In 1848, Louis Pasteur, at the age of 26, discovered molecular chirality through his observation of chiral crystal structures in tartaric acid derived from wine [19], thereby pioneering the field of biomolecular chirality. Pasteur is also widely recognized as a founder of modern fermentation science [20]. In 1935, Hans Krebs, who was later awarded the Nobel Prize for elucidating the tricarboxylic acid (TCA) cycle, reported the enzymatic activity of DAAO, which degrades D-AAAs via oxidative deamination [14]. However, the biological relevance of this discovery remained unclear for many years. Subsequent identification of D-AAAs as essential components of bacterial cell wall structures provided the first definitive evidence that D-AAAs function as biomolecules [18]. A third paradigm shift emerged with the discovery of regulatory roles of D-Ser in the mammalian brain [21]. More recent studies have established that diverse organisms, including bacteria [22], plants [23], and animals [24], actively synthesize and utilize D-AAAs as signaling and regulatory molecules. Inset images were generated using ChatGPT 5.2 (OpenAI) for illustrative purposes and were reviewed and edited by the authors.

After the discovery of D-AAAs as structural components of bacterial cell walls, D-AAAs were long regarded primarily as bacterial molecules and were thought to be absent from healthy mammals [25]. This paradigm shifted dramatically in 1992, when Hashimoto and colleagues demonstrated the presence of substantial amounts of D-serine (D-Ser) in rodent and human brains, at concentrations far exceeding those of other D-AAAs, thereby fundamentally challenging the long-standing dogma that D-AAAs are absent from mammals [21]. Subsequently, in 1999, Wolosker, Blackshaw, and Snyder identified serine racemase (SR) in mammals, indicating that they can actively synthesize D-AAAs rather than obtaining them solely from dietary sources or intestinal bacteria [24]. These groundbreaking discoveries led to the recognition that D-Ser serves as an endogenous co-agonist of *N*-methyl-D-aspartate receptors (NMDARs), playing crucial roles in neurotransmission, synaptic plasticity, and cognitive function [26–28].

In 2009, Lam and colleagues revealed that bacteria produce diverse non-canonical D-AAAs that accumulate at millimolar concentrations and govern stationary phase cell wall remodeling, establishing D-AAAs as environmental signals [22].

In plants, D-Ser was found to regulate glutamate receptor-like channels (GLRs) that are homologues of the NMDARs of mammals [23], implying a universal significance of D-AAAs across kingdoms. Together, these findings have paved the way for the idea that D-AAAs could serve as primary signaling molecules in cellular communications rather than mere structural components, establishing a new paradigm for their biological significance.

2. Fermented Food Products as D-Amino Acid Sources

2.1. Health Benefits of the Intake of Fermentation Products

Advances in nutrition science and microbiome research have promoted fermented foods—such as yogurt, kefir, and cheese—as functional foods [29] with potential contributions to metabolic, immune, and gut–brain health [10,30,31]. Recent human intervention and observational studies have provided additional clinical support for these proposed benefits (Table 1).

Table 1. Evidence-based health benefits of major fermented dairy products.

Product	Health Outcomes/Functional Effects	References
Yogurt	Type 2 diabetes risk reduction	Yoshinari et al., 2025 [32] Tremblay et al., 2026 [33]
	CVD risk reduction	Zhuang et al., 2025 [34] Hu et al., 2026 [35]
	Gut microbiota modulation	Mukarromah et al., 2025 [36]
	Gastrointestinal function	Bui et al., 2025 [37]
	Weight management/adiposity	Rouhani et al., 2025 [38]
	Bone health	Sharifan et al., 2025 [39]
Cheese	CVD/CHD risk reduction	Chen 2017 et al., [40] Zhang et al., 2023 [41] Zhuang et al., 2025 [34]
	Stroke risk reduction	de Goede et al., 2016 [42] Zhang et al., 2023 [41]
	Gut microbiota modulation	Black et al., 2025 [43]
Kefir	Gastrointestinal function	Bakırhan et al., 2025 [44]
	Metabolic syndrome/glycemic control, lipid profile, inflammatory status	Bellikci-Koyu et al., 2022 [45]

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.

Although fermented foods are commonly discussed in terms of probiotic effects and microbiome-mediated health benefits [46], these perspectives alone are insufficient to fully explain the marked variability in D-AA profiles observed among different fermented products [10]. Even when similar raw materials are used, substantial differences in D-AA composition and abundance have been reported [47,48], suggesting that factors beyond general microbial viability and colonization are involved.

Accumulating evidence indicates that D-AA accumulation during fermentation is strongly influenced by the metabolic characteristics of specific microbial strains, including their racemase activities and amino acid-modifying pathways. Thus, D-AA enrichment cannot be regarded merely as a secondary consequence of fermentation but rather reflects active and regulated microbial metabolism.

From a broader biological perspective, continuous dietary exposure to microbially derived D-AAs also raises important questions regarding how amino acid chirality is maintained and regulated in humans. Fermented foods sit at a major interface between microbial metabolism and host nutritional physiology, in which D-AAs are repeatedly generated, transformed, and absorbed.

Table 2 summarizes selected microbial species and strains for which direct evidence of D-AA production has been reported, providing a structured basis for comparing their contributions to D-AA accumulation across major fermented products.

Table 2. Microorganisms with direct evidence for D-AA production in fermented systems.

Microorganisms	Evidence of D-AA Production	D-AAs	References
<i>Streptococcus thermophilus</i> (LAB)	Identification and characterization of aspartate racemase responsible for D-Asp production	D-Asp	Yamauchi et al., 1992 [49]
<i>Lactococcus lactis</i> (LAB)	Functional identification of alanine racemase gene (<i>alr</i>); gene knockout abolished D-Ala synthesis	D-Ala	Bron et al., 2002 [50]
<i>Bacillus subtilis</i> var. natto (natto starter)	Chiral HPLC analysis of poly- γ -glutamate from natto	D-Glu, D-Asp, D-Ala	Ashiuchi et al., 2015 [51]
<i>Lactobacillus</i> spp. <i>Leuconostoc</i> spp. (LAB)	UHPLC analysis of D-branched-chain AAs in culture medium of 12 strains of LAB	D-Val, D-Leu, D- <i>allo</i> -Ile	Mutaguchi et al., 2018 [52]
<i>Lactobacillus</i> spp. (LAB)	Systematic quantification of D/L-AAAs with LC-MS/MS in 70 strains	D-Ala, multiple D-AAAs	Sugahara et al., 2021 [53]

2.2. Fermented Dairy Products

Fermented dairy products, including yogurt, cheese, and kefir, provide representative models for examining D-AA formation under controlled microbial conditions [30,54]. In yogurt, defined starter cultures promote proteolysis and racemization, leading to moderate but reproducible D-AA accumulation [55,56]. Cheese ripening represents a more complex and time-dependent system, in which prolonged enzymatic activity and microbial persistence result in progressive increases in D-AA content, particularly in long-aged varieties [57–59]. Kefir, characterized by its highly diverse microbial consortium, typically exhibits broader and more heterogeneous D-AA profiles than yogurt [60–62].

2.3. Asian Fermented Foods

Traditional Asian fermented foods, such as miso, natto, kimchi, and doubanjiang, exemplify long-term, multi-stage fermentations that generate distinctive D-AA signatures [63–66]. These products commonly involve sequential participation of molds, lactic acid bacteria (LAB), and *Bacillus* species, creating environments conducive to extensive proteolysis and racemization [67–69]. As a result, they are generally enriched in D-Ala, D-Glu, and D-Asp, with additional variation arising from differences in raw materials, salt concentrations, and aging periods [70,71].

Despite their cultural diversity, these foods share common biochemical principles, in which prolonged fermentation and mixed microbial communities promote sustained D-AA accumulation [47,48,72,73].

2.4. Alcoholic Fermentations

Alcoholic beverages, including wine, beer, and sake, represent another major category of fermented products containing D-AAAs [48,57,74]. In these systems, yeast-driven primary fermentation is often followed by bacterial activity during maturation or aging, providing opportunities for D-AA formation [75,76]. Wine aging is characterized by progressive accumulation of D-Pro and other D-AAAs, whereas beer and sake typically contain D-Ala, D-Glu, and D-Asp, with concentrations influenced by secondary fermentation and storage conditions [47,77,78]. Across alcoholic beverages, D-AA profiles reflect the balance between yeast metabolism, bacterial contributions, and post-fermentation processing.

2.5. Fermentation as a Biological Amplifier of D-Amino Acids

Fermented foods have been part of the human diet for over 9000 years, with archeological evidence showing that early alcoholic and dairy fermentations emerged independently in multiple ancient cultures [74,79]. Fermentation represents one of the oldest biotechnological processes and functions as a biological amplification system that enriches D-AAs through microbial proteolysis, racemization, and secondary metabolism [48,80–82]. Compared with raw materials, fermented foods consistently exhibit higher concentrations and more diverse profiles of D-AAs, reflecting the metabolic capacities of resident microorganisms and cumulative processing effects [54,65,83,84]. From a conceptual perspective, D-AA accumulation during fermentation is primarily governed by microbial community structure, substrate availability, and fermentation duration [66,85].

Taken together, fermented foods and beverages can be viewed as dynamic biochemical systems in which D-AA profiles emerge from the interplay of microbial diversity, substrate composition, and fermentation time [48,54]. Products based on simple and short fermentations tend to display limited D-AA diversity, whereas long-aged and multi-microbial systems generate more complex and abundant D-AA patterns. This comparative framework emphasizes that D-AA accumulation reflects general principles of microbial ecology and metabolic adaptation rather than product-specific properties.

3. Biology of Bacterial D-Amino Acid Production

3.1. Enzymatic Pathways and Molecular Mechanisms

Bacterial D-AA production relies on a diversity of enzymatic pathways that have evolved to serve multiple physiological functions. The most extensively characterized pathway involves amino acid racemases, enzymes that catalyze the stereospecific interconversion of L- and D-amino acid enantiomers. Alanine racemase, essential for bacterial survival, represents the archetypal enzyme in this class. It utilizes a pyridoxal phosphate (PLP) cofactor, derived from vitamin B₆, to facilitate the stereochemical inversion of alanine [86].

Beyond alanine racemase, bacteria express a diverse array of amino acid racemases with varying substrate specificities. Racemases individually specific for glutamate (Glu), aspartate (Asp), and serine (Ser) vary in their requirement for PLP. Members of a family of PLP-independent broad spectrum amino acid racemases identified in many Gram-negative bacteria have been found to interconvert ten of the 19 chiral proteogenic amino acids along with some amino acids that do not occur in proteins [87]. D-amino acid transaminases (DAAT) are another class of enzymes, evolutionarily distinct from their L-amino acid transaminase counterparts, that contribute to the diversity of D-AAs found in microbial communities. These PLP-dependent enzymes transfer an amino group from a donor molecule, usually a D-AA, to an α -keto acid acceptor to generate a D-AA product [88].

Additional pathways for D-AA synthesis have been engineered into bacteria, including dehydrogenase-mediated routes and novel enzymatic cascades. These alternative pathways expand the repertoire of D-AAs that bacteria can produce and provide metabolic flexibility under different environmental conditions [89] (Figure 2).

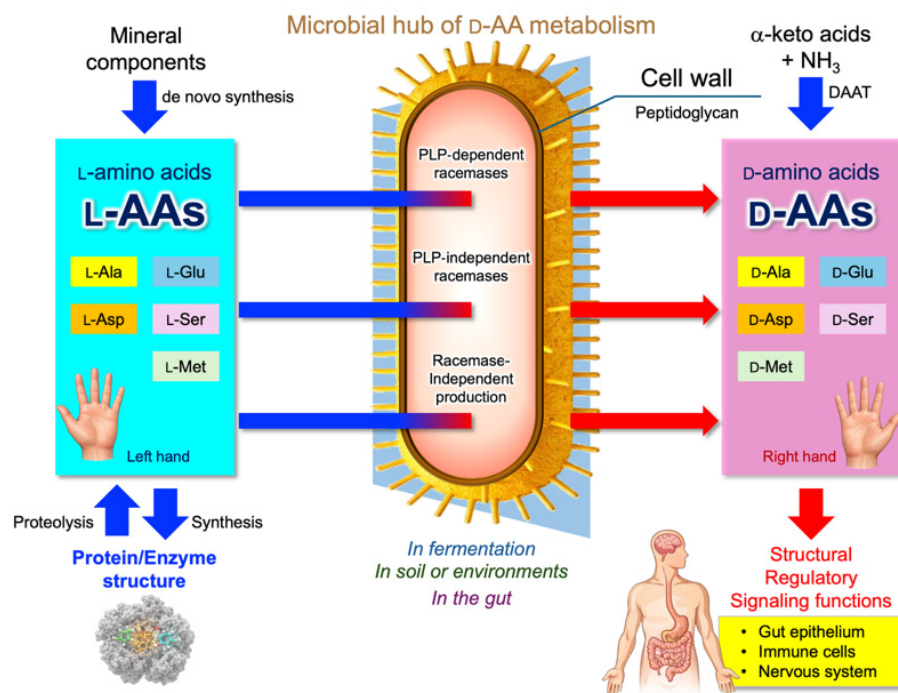


Figure 2. Microbial hub of D-amino acid metabolism. This schematic illustrates the central role of microorganisms in the production of D-amino acids (D-AAs) and their biological functions. L-AAs from proteolysis or de novo synthesis are converted into D-AAs via multiple enzymatic routes, including PLP-dependent and PLP-independent racemases as well as racemase-independent pathways, and many bacteria can produce D-AAs directly from α -keto acids and ammonia using D-AA transaminases (DAATs). D-Ala and D-Glu are structural components of bacterial peptidoglycan, whereas other D-AAs (e.g., D-Ser, D-Asp, and D-Met) exert regulatory and signaling functions. Microbially produced D-AAs act in diverse contexts, including fermentation, natural environments, and the gastrointestinal tract, where they influence host epithelial, immune, and nervous systems. Hand icons indicate the mirror-image chiral relationship between L- and D-AAs. Inset images were generated using ChatGPT 5.2 (OpenAI) for illustrative purposes and were reviewed and edited by the authors.

3.2. Phylogenetic Distribution and Evolutionary Perspectives

The capacity for D-AA production is broadly but unevenly distributed across the bacterial kingdom. While nearly all species possess the core racemases required to synthesize D-Ala and D-Glu for peptidoglycan assembly, the production of “non-canonical” D-AAs appears to serve general to specific functions. For example, diverse bacteria release D-AAs upon entry into stationary phase, eliciting cell envelope remodeling events across species lines [22]. More specifically, *Bacillus* species (phylum Firmicutes) produce D-Ala via alanine racemase late in endospore development to inhibit premature germination [90,91].

3.3. Peptidoglycan Components

D-AAs have served as key structural components of bacterial peptidoglycan for billions of years, making them one of the most ancient and conserved uses of these stereoisomers in biology. The peptidoglycan layer, often referred to as the “cell wall” although it is more of a meshwork, relies on D-AAs for structural integrity, resistance to enzymatic degradation, and protection against osmotic lysis.

Peptidoglycan structure consists of glycan chains composed of alternating *N*-acetylglucosamine and *N*-acetylmuramic acid residues, with stem peptides attached to the *N*-acetylmuramic acid units that contain D-AAs at specific positions. The canonical structure of the exported stem pentapeptide has D-Glu at the second position and D-Ala at the fourth and fifth positions.

The terminal D-alanyl-D-alanine residues are the recognition site for transpeptidases, the enzymes responsible for cross-linking adjacent peptidoglycan strands. The transpeptidation reaction couples the exergonic terminal D-Ala cleavage reaction to the formation of a peptide bond that links the remaining D-Ala to an amino group on an adjacent stem peptide [92]. The breakage of the D-alanyl-D-alanine linkage provides the required energy for the overall reaction in the ATP-free extracellular environment of the peptidoglycan layer. This process, combined with the action of D,D-carboxypeptidases, which cleave the terminal D-Ala from uncrosslinked pentapeptides, explains why D-Ala is the most abundant D-AA released by bacteria [93].

Peptide crosslinking helps to form the covalently bound three-dimensional peptidoglycan network that defines bacterial cell shape and provides mechanical strength, while still allowing for diffusion of molecules through it and accommodation of multi-protein complexes that span the cell envelope [93].

The specificity of this recognition system has made it an attractive target for antimicrobial development. Transpeptidases (which are sometimes referred to as Penicillin Binding Proteins, PBPs) are inhibited by β -lactam antibiotics that mimic the D-alanyl-D-alanine structure and form covalent adducts, effectively preventing peptidoglycan synthesis. Similarly, vancomycin binds specifically to the D-alanyl-D-alanine terminus, preventing transpeptidase access and blocking cross-linking reactions [94].

The incorporation of D-AAs into peptidoglycan serves multiple protective functions. Most importantly, the use of D-AAs renders the peptide side chains resistant to degradation by environmental and host proteases (or peptidases), which have evolved specifically for L-amino acid sequences [95], helping to ensure survival in enzyme-rich environments such as soil and host tissues.

Antibiotic resistance and stress tolerance mechanisms frequently involve modifications to classical D-AA components. Vancomycin-resistant enterococci replace the terminal D-Ala with D-lactate or D-Ser, dramatically reducing antibiotic binding affinity while maintaining cell wall function [96]. In *Lactobacillus lactis*, incorporation of D-methionine (D-Met) at the fifth position or D-phenylalanine (D-Phe) at the fourth or fifth position of the pentapeptide confers increased tolerance to acid conditions [97]. These modifications demonstrate the plasticity of bacterial peptidoglycan systems and their ability to evolve resistance while preserving essential structural functions [98].

3.4. Roles of D-Amino Acids in Biofilms

After the initial excitement that arose from reports that mixtures of D-AAs at nanomolar concentrations could inhibit formation or even disassemble biofilms [99], subsequent research revealed D-AA effects to be more nuanced, depending on the nutritional status and genetic background of the bacteria (reviewed by Aliashkevich et al., 2018 [100]). While D-AAs may not act as universal biofilm-interfering signals, they can disrupt biofilm stability and potentiate susceptibility to antimicrobial agents [101–103]. These effects are driven by the incorporation of exogenous D-AAs into peptidoglycan, replacing the canonical D-Ala and D-Glu [95], as well as the inhibition of enzymes that maintain the integrity of the extracellular matrix [104].

Taken together, current evidence suggests that D-AAs act as conditional modulators of biofilm dynamics rather than as broadly applicable biofilm-disassembly agents. Further systematic investigations are therefore required to delineate the species-specific mechanisms, concentration ranges, and environmental contexts under which D-AAs influence bacterial biofilm formation and dispersal.

3.5. D-Amino Acid Production by Gut Bacteria and Influence on the Intestinal Environment

The human gut microbiota harbors numerous bacterial species capable of producing diverse D-AAs, each contributing distinct metabolic profiles to the overall intestinal environment. Evidence for the bacterial origin of D-AAs is seen in colonic D-Ala levels, with germ-free mice having minuscule concentrations compared to conventional mice [105].

Beyond their roles in the bacteria that produce them, D-AAs are one of several metabolite classes released into the intestinal environment that influence host physiology. Their role in intestinal function was recently reviewed by Miyamoto and Sujino, 2026 [106]. D-AAs modulate host epithelial barrier integrity, stimulate antimicrobial peptide secretion, regulate innate and adaptive immune responses, and influence the composition of the microbial community. These effects are mediated in part by D-AAs acting as substrates for epithelial cell DAAO and as regulatory factors for T-cell NMDAR. Declines in gut D-AA levels are consistently among the dysbiotic indicators of Inflammatory Bowel Disease (IBD) [106].

Understanding species-specific contributions by gut bacteria would aid in developing interventions to modulate D-AA levels for therapeutic benefit. Proof-of-concept studies have already demonstrated this potential; for example, supplementation with D-tryptophan (D-Trp)-producing *Lactobacillus* strains has been shown to attenuate allergic airway inflammation in murine models [107], suggesting that targeted modulation of bacterial D-AA output could serve as a strategy for treating host immune and metabolic disorders.

4. Biology of Natural Food Sources Rich in D-Amino Acids

4.1. Marine Invertebrates as Natural Sources Rich in D-Amino Acids

In the context of natural food sources of D-AAs, marine invertebrates—particularly bivalves (shellfish) and crustaceans (e.g., shrimps and crabs)—are among the richest dietary sources of free D-AAs, often accumulating D-Ala at unusually high (millimolar) levels compared with most unprocessed foods [108–111]. In general, D-Ala found in such marine invertebrates is considered to function as osmolytes that contribute to adaptation to high salinity in seawater [108]. The marine environment may have promoted the evolution of sophisticated systems for D-AA production and utilization, which appear more complex than those found in terrestrial invertebrates.

4.1.1. Cephalopods: Discovery of D-Aspartate Linking to Neural Science

Cephalopods, including squid and octopus, have attracted attention from researchers due to their exceptional D-Asp concentrations and potential neurological significance. The identification of D-Asp in the brain of *Octopus vulgaris* by D'Aniello and Giuditta in 1977 was a seminal milestone in D-AA research, providing the first clear evidence that free D-AAs are intrinsic components of the nervous system of higher invertebrates rather than microbial contaminants [112]. Subsequent studies extended this finding to other cephalopod neural tissues, including squid axoplasm, demonstrating that D-Asp is widely distributed throughout the cephalopod nervous system [113].

During the 1990s, analyses of tissue distribution and enzymatic metabolism further demonstrated that D-Asp is preferentially enriched in neural tissues in both vertebrates and invertebrates, suggesting physiological relevance rather than incidental accumulation [114]. In the 2000s, the research focus shifted from distribution to function, as D-Asp was shown to be developmentally regulated, actively released, and involved in neuroendocrine signaling in both invertebrates and vertebrates [114,115]. More recent studies further proposed that D-Asp acts as an endogenous signaling or neurotransmitter-like molecule, interacting with NMDAR-related pathways and contributing to neural and sen-

sory functions [116]. Thus, the D-AA research of cephalopods has kept a strong relevance to mammalian neuroscience to date.

4.1.2. D-Amino Acids in Bivalve Mollusks

Bivalve mollusks are one of the most intensively studied groups of marine invertebrates with respect to D-AA biology. Early biochemical surveys revealed that bivalve tissues—particularly muscle and mantle—accumulate unusually high concentrations of free D-AAs, most notably D-Ala, often reaching millimolar levels that far exceed those observed in terrestrial organisms or vertebrate tissues [109,111]. Pioneering studies by Abe and colleagues demonstrated that D-Ala constitutes a major fraction of the free amino acid pool in bivalves, and that its accumulation is strongly influenced by environmental salinity [108–110]. These findings established D-Ala as a key osmolyte in bivalves, contributing to cellular volume regulation and osmotic balance under fluctuating seawater conditions rather than representing a simple metabolic byproduct [108].

Interestingly, little or negligible amounts of D-Ala are observed in bivalves belonging to the subclass Pteriomorpha, including oysters (*Crassostrea gigas*), scallops (*Patinopecten yessoensis*), and ark shells (*Scapharca broughtonii*). In contrast, bivalve mollusks of the subclass Heterodonta, such as the hard clam (*Meretrix lusoria*), short-necked clam (*Ruditapes philippinarum*), Sakhalin surf clam (*Pseudocardium sachalinense*), and otter shell (*Tresus keenae*), accumulate abundant D-Ala together with other D-AAs [110]. This clear taxonomic difference suggests that D-AA metabolism in bivalves is closely linked to evolutionary lineage and ecological adaptation.

From a nutritional perspective, the exceptional accumulation of D-Ala and other D-AAs in bivalve mollusks implies that these organisms constitute highly concentrated natural dietary sources of D-AAs for humans.

4.2. Plant Sources: Hidden D-Amino Acid Reservoirs

The D-AA content of terrestrial plants has long been underestimated. Even though early studies in the 1970s indicated abundant contents of D-Ala in plant tissues such as roots of sunflower (*Helianthus annuus*) [117], plant D-AAs were historically regarded either as rare biochemical curiosities or as growth-inhibitory compounds. Consequently, evidence for their occurrence was fragmentary, and a coherent mechanistic framework for D-AA metabolism in plants was largely lacking [117].

A major conceptual shift began in the 2000s when plant nutrition studies recognized that soils contain both L- and D-AAs and asked whether plants can actually use D-AAs as nitrogen sources for their growth; work in the model plant *Arabidopsis thaliana* showed that utilization is possible but strongly constrained by uptake and internal metabolism, and that engineering D-AA-metabolizing enzymes can alter these constraints [118]. In parallel, molecular enzymology provided the first clear demonstration of a plant enzyme dedicated to D-AA metabolism: the cloning and functional characterization of an *Arabidopsis* D-AA aminotransferase (involved in the transitory peak in D-Asp levels during germination) established that higher plants possess specific catalytic capacity to transform D-AAs [119]. Building on these foundations, quantitative chiral profiling demonstrated active uptake and conversion of multiple exogenously supplied D-AAs in *Arabidopsis*, firmly moving the field from “toxic effects” toward definable transport-metabolism pathways [120].

A second wave of turning points reframed plant D-AAs as components of signaling and rhizosphere interaction. In reproductive tissues, D-Ser emerged as a physiologically relevant regulator of GLRs in pollen tubes, placing a D-AA directly within plant amino acid signaling networks [23]. At the whole-plant/soil interface, it was shown that *Arabidopsis* roots can exude D-AAs into the rhizosphere after uptake, implying bidirectional flux

and potential ecological roles beyond internal detoxification [121]. Recent studies on At-DAT1 as a key enzyme mediating D-AA-stimulated ethylene production in *Arabidopsis* have suggested a mechanistic link between D-AA metabolism and hormonal signaling in plants [122,123].

As discussed in Section 3.3, peptidoglycan containing D-AAs were long considered to be exclusive to bacterial cell walls. However, accumulating evidence over the past decade has demonstrated the presence of peptidoglycan-like structures in plant chloroplasts or plastids across the green plant lineage, likely owing to their cyanobacterial evolutionary origin [124]. Despite this discovery, the biosynthetic pathways, regulation, and functional significance of plastidial peptidoglycan in plants remain incompletely understood [124].

Unlike mammalian systems, physiological experiments investigating D-AA functions in terrestrial plants faces practical challenges, particularly with respect to controlled administration and intervention strategies. In this context, the water-floating fern *Azolla* has provided a useful experimental model. Using *Azolla pinnata*, D-cysteine (D-Cys), but not L-Cys, was shown to induce spontaneous root detachment, a striking physiological response that parallels the effects exogenous donors of the gasotransmitter hydrogen sulfide (H₂S) [125]. This finding highlights the potential for D-AAs to act as triggers of specific physiological processes in plants via redox- and gasotransmitter-mediated signaling pathways [126].

Research on D-AAs in plants is an emerging and rapidly evolving field. Many fundamental questions remain unresolved, including the quantitative contribution of plant-derived D-AAs to human diets, their ecological roles in the rhizosphere, and their integration into broader plant metabolic and signaling networks. Addressing these questions will be essential for fully understanding the significance of plants as hidden reservoirs of dietary D-AAs [127].

4.3. D-Amino Acids as Ubiquitous Biomolecules Across Biological Kingdoms

Contrary to the traditional view presented in earlier textbooks, it is now evident that D-AAs are widely distributed across biological kingdoms and represent ubiquitous biomolecules in living organisms on Earth. Advances in analytical chemistry, genomics, and molecular biology have revealed that D-AAs are not restricted to microbial cell walls or fermentation products but are actively involved in diverse physiological processes in microbes, plants, and animals [12].

In humans, D-AAs originate from multiple sources (Figure 3). In addition to endogenous production by amino acid racemases and microbial synthesis by the gut microbiota, substantial amounts of D-AAs are continuously supplied through dietary intake. Although comprehensive and standardized datasets on D-AA contents in foods remain limited, several food categories—including fermented foods, seafoods, and root vegetables—have been identified as particularly rich sources of free D-AAs. Furthermore, dietary supplements containing D-AAs, provide additional routes.

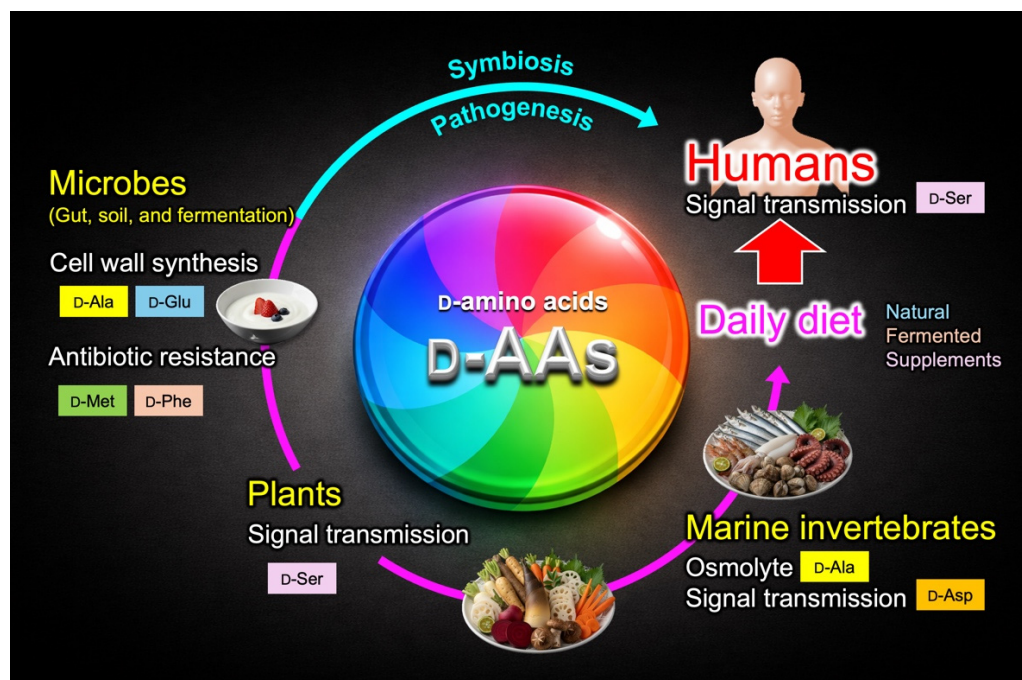


Figure 3. Biological functions of D-AAs across biological kingdoms. In humans, D-AAs are derived not only from dietary sources but also from gut microbial consortia, thereby influencing host physiology through mechanisms that shape the balance between symbiosis and pathogenesis and may have clinical relevance. In bacteria, D-AAs serve essential structural roles as integral components of the peptidoglycan cell wall and contribute to antibiotic resistance. In marine invertebrates, D-AAs function as osmolytes, facilitating adaptation to salinity fluctuations in aquatic environments. Emerging evidence further highlights signaling roles of D-AAs in both intra- and intercellular communication across taxa, bridging microbiology, plant biology, and animal physiology. Inset images were generated using Google Gemini (Nano Banana, version 2.5 Flash; Google) for illustrative purposes and were reviewed and edited by the authors.

5. Therapeutic Potentials of D-Amino Acids

It is evident that humans ingest D-AAs daily through diverse dietary sources, including fermented and natural products, via multiple intake routes (Figure 3). This observation raises the important question of whether dietary D-AAs confer measurable health benefits when considered as nutraceuticals. To avoid conceptual ambiguity, it is essential to distinguish among three major levels at which the biological effects of D-AAs have been evaluated: (i) physiological functions under endogenous production and typical dietary exposure, (ii) experimentally observed effects under high-dose or disease-model conditions, and (iii) clinical and nutraceutical relevance in humans. These levels differ substantially in their experimental contexts and translational significance and should not be conflated when assessing therapeutic potential [12,128].

5.1. Involvement of D-AAs in Neural Functions and Diseases

Due to the historical background of discoveries (Figure 1), the primary focus was the association of D-AAs with neural functions and diseases. Neuropsychiatric and neurodegenerative disorders—including schizophrenia, dementia (particularly Alzheimer's disease), Parkinson's disease, and amyotrophic lateral sclerosis (ALS)—remain major unmet challenges in modern medicine. This is largely because their etiologies are heterogeneous and incompletely understood, and truly disease-modifying therapies are still limited [129–131]. These conditions impose a substantial and growing global health burden, comparable in societal impact to cancer and metabolic diseases [129].

From a pharmacokinetic perspective, D-AAs have attracted increasing attention as a novel class of endogenous signaling molecules involved in neural development, synaptic plasticity, and redox regulation [12,128]. Among psychiatric disorders, schizophrenia has been a central focus of D-AA research since the discovery of abundant D-Ser in the mammalian brain in the 1990s [21,26]. This finding stimulated decades of research spanning fundamental molecular mechanisms to clinical exploration [9,12,128].

Schizophrenia is a chronic and severe neuropsychiatric disorder characterized by disturbances in perception, cognition, emotion, and behavior, and is typically associated with positive symptoms, negative symptoms, and cognitive impairment [132]. Accumulating evidence indicates that multifactorial neurodevelopmental mechanisms involving glutamatergic dysregulation and NMDAR hypofunction contribute to disease pathogenesis [9].

5.2. D-AAs as Agonists and Co-Agonists of NMDARs

NMDARs are among the most extensively investigated strategic targets through which interactions with D-AAs have been elucidated at a molecular level. NMDARs are tetrameric ionotropic glutamate receptors (iGluRs), typically composed of two GluN1 and two GluN2 subunits [133], that transduce glutamatergic signals throughout the central nervous system (CNS) and spinal cord [134].

Their activation always requires the binding of a co-agonist that was initially thought to solely be glycine. However, research over the past decades has identified D-Ser and D-Ala as endogenous co-agonists, while D-Asp has been found to act as an agonist at the glutamate site to regulate NMDAR-dependent Ca^{2+} influx into the cytosol [133,135]. These findings provide a mechanistic basis for the proposed involvement of D-AAs in a broad spectrum of neuropathologies, including schizophrenia [9,12,128].

5.3. D-Serine

The exploration of the physiological roles of D-Ser has gained particular attention as a co-agonist of synaptic NMDARs, apparently supplanting the classic co-agonist glycine (Figure 4). Because NMDAR hypofunction has been strongly implicated in the pathophysiology of schizophrenia, alterations in D-Ser availability and metabolism have attracted considerable attention as potential mechanistic contributors to disease onset and symptom expression.

Clinical and postmortem studies have reported reduced D-Ser levels in the serum and cerebrospinal fluid of patients with schizophrenia [136], supporting the hypothesis that impaired D-Ser-mediated NMDAR signaling contributes to cognitive and negative symptoms [137]. At the molecular level, D-Ser homeostasis is regulated by a balance between synthesis by serine racemase (SR) and degradation by DAAO [137].

Accordingly, increased DAAO protein expression and activity have been reported in postmortem brains of patients with schizophrenia [138,139], and genetic association studies have identified polymorphisms in the *DAAO* gene and its regulatory partner *DAOA* (formerly *G72*) that are linked to schizophrenia susceptibility [140,141]. These findings suggest that excessive degradation of D-Ser by DAAO may lower synaptic D-Ser availability, thereby exacerbating NMDAR hypofunction [133,134,142].

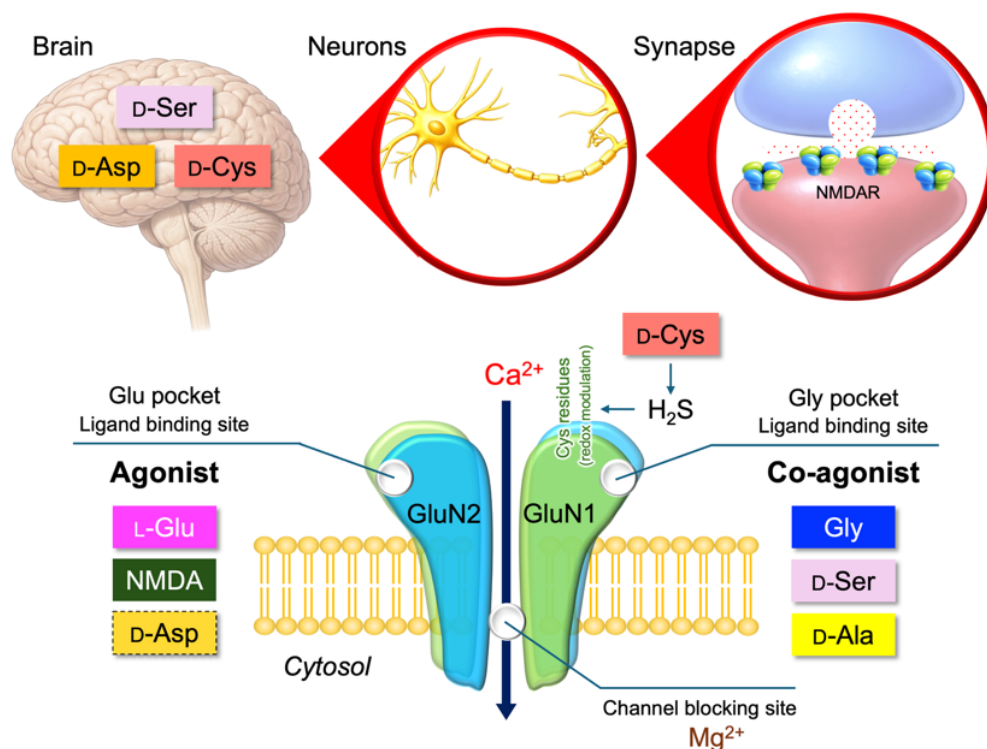


Figure 4. D-AAAs regulate NMDAR function through distinct mechanisms. NMDARs, historically referred to as NRs (*N*-methyl-*D*-aspartate receptors) in earlier literature, are heterotetrameric ionotropic glutamate receptors (iGluR) composed of two GluN1 (glutamate receptor, ionotropic, NMDA-type subunit 1) and two GluN2 (glutamate receptor, ionotropic, NMDA-type subunit 2), which together form the functional receptor complex. D-Asp acts as an endogenous agonist at the GluN2 glutamate-binding site, whereas Gly, D-Ser, and D-Ala serve as co-agonists at the GluN1 glycine-binding site. NMDAR activity is further modulated by Mg^{2+} channel block and redox-sensitive cysteine residues on GluN1, with D-Cys acting indirectly via H_2S -mediated redox regulation. NMDA, *N*-methyl-*D*-aspartate; NMDAR, *N*-methyl-*D*-aspartate receptor; Glu, glutamate; Gly, glycine. Inset images on the upper panel were generated using ChatGPT 5.2 (OpenAI) for illustrative purposes and were reviewed and edited by the authors.

On this basis, therapeutic strategies aimed at enhancing NMDAR function—either through D-Ser supplementation or inhibition of DAAO—have been explored in clinical trials. In schizophrenia, D-Ser has been evaluated in randomized, placebo-controlled trials and in evidence syntheses, with some studies reporting modest symptomatic improvement but substantial heterogeneity across trials [143,144]. D-Ser has also been explored in individuals at clinical high risk for schizophrenia [145]. However, among double-blind augmentation trials conducted in patients receiving antipsychotic treatment, a clozapine add-on study [146] and a separate add-on trial in chronic schizophrenia [147] reported no significant advantage of D-Ser over placebo in the primary analyses, underscoring the likelihood that background antipsychotic regimens and study design meaningfully influence outcomes. The overall clinical signal to date remains modest and context-dependent.

Beyond schizophrenia, exploratory human studies suggest that acute D-Ser dosing may improve selected cognitive measures in healthy young and older adults [148], and a small pilot crossover trial in chronic post-traumatic stress disorder (PTSD) reported reductions in symptoms [149]. In major depressive disorder, an adjunctive randomized controlled trial found no overall difference versus placebo but suggested potential benefit in more severe subgroups [150]. In Alzheimer's disease, elevated circulating D-Ser levels and an increased D/total serine ratio have been proposed as candidate early-stage biomarkers of disease progression [151].

Taken together, current evidence clearly distinguishes three analytical levels in D-Ser research: (i) tightly regulated endogenous control of synaptic D-Ser under physiological conditions, (ii) experimentally induced modulation of D-Ser/DAAO pathways in cellular and animal models, and (iii) limited and context-dependent clinical applicability in human intervention studies. Failure to separate these levels has contributed to inconsistent interpretations of therapeutic potential.

5.4. D-Asp

D-Asp is also recognized as an endogenous agonist of NMDARs [152,153], acting at the glutamate/NMDA (agonist) binding site (Glu pocket) on GluN2 subunits. This mode of action contrasts with that of co-agonists such as glycine and D-Ser, which occupy the GluN1 glycine modulatory site (Gly pocket), and the efficacy of D-Asp is generally lower than that of L-Glu and NMDA [153].

In neuropsychiatric research, post-mortem analyses have described reduced D-Asp levels in the prefrontal cortex of individuals with schizophrenia, accompanied by findings consistent with increased D-aspartate oxidase (DDO) activity [154,155]. In addition, lower circulating D-Asp concentrations have recently been reported in patients with schizophrenia, further suggesting dysregulation of D-Asp metabolism in this disorder [156].

Beyond neuropsychiatric research, D-Asp is detectable in seminal plasma and sperm, and lower D-Asp levels, or a reduced D-Asp/L-Asp ratio, have been reported in infertile males, supporting its consideration as a candidate biomarker associated with male reproductive status [157]. In males, supplementation with D-Asp has been reported in some studies to increase luteinizing hormone (LH) and testosterone levels [158].

In recent years, D-Asp has been widely marketed as a dietary supplement, particularly as a component of “testosterone boosters” and male performance products, with major commercial presence in North America and Europe. Its popularity largely stems from early animal and human studies suggesting stimulatory effects on steroidogenic pathways and testosterone production [158]. However, subsequent randomized controlled trials and systematic reviews in healthy or resistance-trained men have reported inconsistent or minimal effects on circulating testosterone levels [159–162]. The gap between the commercial use of D-Asp and the strength of current clinical evidence emphasizes the need for cautious interpretation of its nutraceutical claims.

Thus, D-Asp research similarly spans three distinct levels: physiological roles in neural and endocrine regulation, experimentally induced hormonal and metabolic effects, and nutraceutical applications that remain insufficiently supported by robust clinical evidence. Clear separation of these levels is essential for balanced interpretation.

5.5. D-Cys

In redox biology and biochemistry, both L- and D-Cys occupy unique positions due to the presence of a thiol (–SH) group, which confers high chemical reactivity toward a wide range of oxidants [163]. In mammals, a metabolic pathway in which D-Cys is converted by DAAO to 3-mercaptopyruvate, and subsequently by 3-mercaptopyruvate sulfurtransferase (3MST) to H₂S, has been well characterized, including in kidney- and brain-relevant contexts [11,164,165]. Despite these promising physiological roles, D-Cys has no established therapeutic benefit in humans to date, and putative cytoprotective or neuroprotective effects remain supported predominantly by preclinical evidence rather than by controlled clinical trials [128,165,166].

Accordingly, the biological significance of D-Cys should be interpreted across physiological redox signaling, preclinical cytoprotective mechanisms, and currently unvalidated

clinical applications. At present, translational evidence remains largely confined to experimental systems.

5.6. Other D-AAs

5.6.1. D-Met

In patients undergoing chemoradiotherapy for head-and-neck cancer, oral D-methionine (D-Met) has been evaluated as a supportive care intervention and has shown signals of reduced oral mucositis and/or oral pain across several secondary assessments. However, the prespecified primary endpoint (grade 3–4 oral mucositis) did not reach conventional statistical significance, and increased body odor was reported more frequently in the D-Met group [167].

In a separate clinical context, among patients receiving cisplatin (a platinum-based chemotherapeutic agent), oral D-Met protected against high-frequency hearing loss in an exploratory, double-blind, placebo-controlled Phase II trial [168]. Nevertheless, confirmatory evidence from larger, adequately powered studies is needed.

5.6.2. D-Asn

In pediatric chronic kidney disease (CKD), plasma D-asparagine (D-Asn) shows robust associations with established renal markers, including creatinine and cystatin C, and has been suggested as a potentially useful endogenous marker for CKD detection [169]. However, since D-Asn concentrations are strongly influenced by renal handling and excretion, the observed disease associations likely reflect altered clearance rather than a causal role [170]. Beyond CKD, exploratory evidence in glioblastoma indicates that blood and urinary D-Asn levels may be lower than in controls and may increase following tumor resection, with urinary D-Asn demonstrating good discriminatory performance in one report [171]. In addition, asparagine (L-Asn) residues in long-lived human proteins can undergo age-related non-enzymatic racemization to D-forms [172].

5.6.3. D-Arg

L-Arg is the substrate for nitric oxide synthase (NOS) in both vertebrate and invertebrate animals, where it is enzymatically converted to the gasotransmitter nitric oxide (NO) [173]. In contrast, for its D-enantiomer, no therapeutic benefit of supplementation has been established to date [174,175]. Most proposed benefit- or risk-related claims for D-Arg are derived primarily from preclinical and cell-based studies [176].

5.6.4. D-Glu

Although D-Glu is detectable in human biospecimens, no therapeutic benefit of D-Glu supplementation has been confirmed [174,177]. Consistent with a potential microbiota-related contribution, human fecal samples contain a multitude of D-AAs, including D-Glu, which has also been detected in human urine [174,178].

5.6.5. D-Trp

In humans, D-tryptophan (D-Trp) has no established therapeutic benefit, and human outcome data remain sparse. Classic metabolic studies indicate that D-Trp is absorbed and subsequently excreted largely as metabolites within tryptophan-related pathways [179], whereas proposed immunomodulatory effects are supported mainly by preclinical and microbiome-focused studies rather than by controlled clinical trials [107]. Mechanistically, D-Trp may undergo enzymatic D → L conversion (stereoinversion), potentially involving DAAO and aminotransferase activities [180], situating D-Trp within broader tryptophan biology.

For most minor D-AAs, available data are dominated by detection studies and mechanistic experiments, whereas convincing evidence at the level of clinical efficacy is generally lacking. This imbalance emphasizes the importance of distinguishing descriptive biochemistry from therapeutic relevance.

5.7. Summary of Clinical Perspective

Despite compelling preclinical evidence demonstrating diverse physiological functions, only a limited number of naturally occurring D-AAs have been evaluated in human interventional clinical trials (Table 3): D-Ser for schizophrenia and cognitive disorders, D-Asp for reproductive function and athletic performance, and D-Met for a supportive care in chemoradiotherapy. This stark contrast between the breadth of preclinical D-AA research and the narrowness of clinical translation represents a significant translational gap in the field.

Table 3. Human interventional clinical trials for specific D-AAs.

D-AA	Target Population <i>n</i> (Randomized)	Dosage Duration	Main Outcomes	Study Design	Level of Evidence *	References
D-Ser	Schizophrenia spectrum patients on stable antipsychotics <i>n</i> = 195	2 g/day 16 weeks	Primary: NS (SANS <i>p</i> = 0.32 MATRICS <i>p</i> = 0.39)	MC DB RCT PLA Add-on	Level II	Weiser et al., 2012 [181]
	Clinical high-risk patients for schizophrenia <i>n</i> = 44	60 mg/kg/day 16 weeks	Primary: significant (SOPS-negative ↓ <i>p</i> = 0.03) Secondary: NS	Pilot DB RCT PLA	Level II	Kantrowitz et al., 2015 [145]
	Inpatient MDD patients <i>n</i> = 52	2 g/day 6 weeks	Primary: NS (HDRS-17 <i>p</i> = 0.82) Secondary: NS Subgroup: significant (severe MDD) Anhedonia: borderline	DB RCT PLA Add-on	Level I	Sempach et al., 2025 [150]
D-Asp	Resistance-trained men <i>n</i> = 22	6 g/day 12 weeks	Primary: NS (TT <i>p</i> = 0.614 FT <i>p</i> = 0.543) Secondary: significant (E2 ↓)	DB RCT PLA	Level I	Melville et al., 2017 [160]
	Male boxers (normobaric hypoxia camp) <i>n</i> = 16	6 g/day 14 days	Primary: NS (T, FT, C, T/C, LH) Secondary: NS (Hematology)	SB RCT PLA	Level II	Płoszczyca et al., 2024 [161]
D-Met	HNSCC patients receiving cisplatin chemoradiation <i>n</i> = 60	100 mg/kg BID 6–7 weeks (RT days only)	Primary: borderline (G3–4 mucositis <i>p</i> = 0.058) Secondary: significant (↓ ulcer/erythm) AEs: odor ≥ G2 ↑	MC DB RCT PLA Phase II	Level II	Hamstra et al., 2018 [167]
	Cancer patients receiving cisplatin chemotherapy <i>n</i> = 50	100 mg/kg 5 cycles (precisplatin)	Primary: significant (↓ hearing loss 11.2 kHz L ear <i>p</i> = 0.016) AEs: NS	DB RCT PLA Phase II	Level II	Campbell et al., 2022 [168]

* A hierarchical rating based on the updated assignment of level of evidence [182]. Abbreviations: AEs, adverse events; Add-on, adjunctive to standard treatment; BID, twice daily (bis in die); C, cortisol; DB, double-blind; E2, estradiol; FT, free testosterone; HDRS-17, Hamilton depression rating scale; HNSCC, head and neck squamous cell carcinoma; LH, luteinizing hormone; MATRICS, measurement and treatment research to improve cognition in schizophrenia; MC, multicenter; MDD, major depressive disorder; NS, not significant; PLA, placebo; RCT, randomized controlled trial; RT, radiotherapy; SANS, scale for the assessment of negative symptoms; SB, single-blind; SOPS, scale of prodromal symptoms; T, testosterone; T/C, testosterone-to-cortisol ratio; TT, total testosterone.

Overall, although multiple D-AAs have been detected in human tissues, urine, and plasma and have been investigated for potential therapeutic applications, there is currently no clear or consistent clinical evidence demonstrating that supplementation with any specific D-AA confers a definitive therapeutic benefit in humans [10]. Importantly, the increasing commercial availability and consumption of D-AA-containing supplements such as “testosterone boosters” have substantially outpaced the strength of supporting clinical evidence, raising concerns regarding their indiscriminate use.

One plausible explanation for the limited and inconsistent outcomes observed in intervention studies is the marked inter-individual variability in the metabolic capacity of the gut microbiota and host clearance systems, including DAAO activity, which can effectively buffer or neutralize exogenously administered D-AAs. As a result, supplemental D-AAs may fail to achieve sustained or biologically meaningful elevations in target tissues, thereby obscuring potential therapeutic effects in controlled trials.

Moreover, several D-AAs, including D-Ser, D-Ala, and D-Asp, serve as endogenous agonists or co-agonists of NMDARs, which are central regulators of Ca^{2+} -dependent cellular signaling, particularly in neuronal and synaptic contexts. Given the critical physiological roles of NMDAR signaling, endogenous levels of these D-AAs are expected to be under strict homeostatic control, involving coordinated regulation of synthesis, compartmentalization, enzymatic degradation, and renal excretion. Consequently, excessive intake of D-AAs from supplements or unregulated clinical use is likely to be rapidly counteracted by these homeostatic mechanisms and ultimately eliminated, most commonly via urinary excretion, rather than producing sustained therapeutic effects.

6. Oxidative Stress Induced by D-Amino Acids

6.1. H_2O_2 Generation by D-Amino Acid Oxidase (DAAO): The Double-Edged Sword

D-amino acid oxidase (DAAO, EC 1.4.3.3) is a key flavoprotein enzyme responsible for the catabolism of a wide range of neutral and basic D-AAs in mammals and plays a central role in maintaining D-AA homeostasis [183–185]. DAAO catalyzes the oxidative deamination of D-AAs to their corresponding α -keto acids, producing ammonia (NH_3) and H_2O_2 as reaction products [183] (Figure 5). Through this activity, DAAO contributes to the regulation of endogenous D-AA levels, including D-Ser and D-Ala, thereby modulating physiological processes such as NMDAR-mediated neurotransmission and amino acid signaling [26].

However, DAAO also represents a biochemical “double-edged sword.” While its enzymatic activity is essential for preventing excessive accumulation of bioactive D-AAs, the concomitant generation of H_2O_2 introduces a potential source of oxidative stress. In tissues with high DAAO expression—most notably the kidney, liver, and certain brain regions [184]—DAAO-derived H_2O_2 can contribute to local redox imbalance leading to oxidative damage if antioxidant defenses are insufficient [186,187]. This dual role is particularly relevant under conditions of increased D-AA availability, such as high dietary intake, altered gut microbiota composition, impaired renal clearance, or aging (Figure 5).

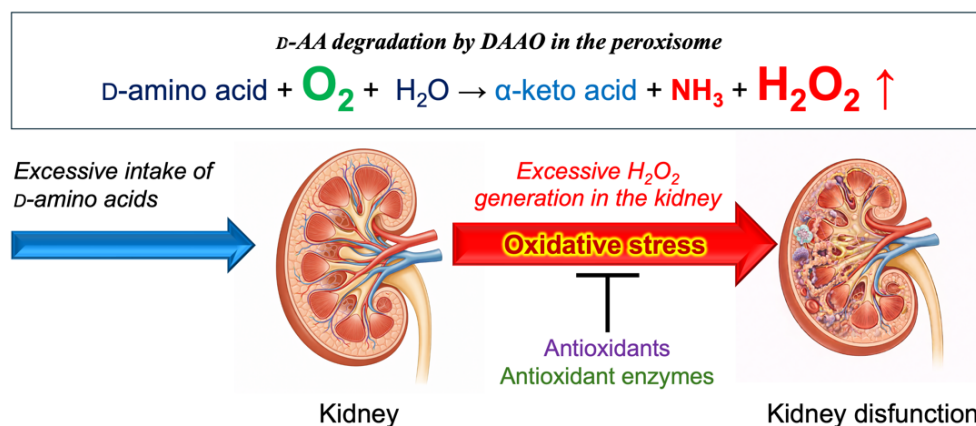


Figure 5. Oxidative stress induced by D-AAs in the kidney. Schematic illustration of a proposed mechanism by which excessive intake of D-AAs, particularly from high-dose supplements or unbalanced fermented products, may induce renal oxidative stress. D-AAs are degraded by D-amino acid oxidase (DAAO) and D-aspartate oxidase (DDO) in peroxisomes, both of which generate the reactive oxygen species (ROS) H_2O_2 as a byproduct. In the kidney, excessive H_2O_2 production may overwhelm antioxidant defenses, leading to oxidative damage and tubular dysfunction. Antioxidants and antioxidant enzymes counteract this process, emphasizing the context-dependent balance between D-AA metabolism, redox homeostasis, and renal susceptibility. Inset images were generated using ChatGPT 5.2 (OpenAI) for illustrative purposes and were reviewed and edited by the authors.

6.2. Liver as a High-Capacity “Detox” Organ with Potential Overload Scenarios

The liver is a principal site of amino-acid handling and xenobiotic metabolism and expresses D-AA-catabolizing activities consistent with a first-pass clearance role after intestinal absorption [188]. In this context, hepatic DAAO and its paralog DDO [189] viewed as redox-relevant “gatekeepers”: they limit systemic exposure to circulating D-AAs but generate H_2O_2 during clearance. Because hepatocytes possess robust antioxidant and peroxisomal H_2O_2 -detoxifying capacity, liver DAAO activity is often interpreted as being physiologically compatible with redox homeostasis under ordinary dietary exposure [15,190]. Nevertheless, conceptually, hepatic D-AA oxidation becomes more likely to contribute to oxidative stress when (i) exposure to a single D-AA is unusually high (e.g., high-dose supplementation), (ii) antioxidant capacity is impaired (aging, metabolic disease), or (iii) peroxisomal/mitochondrial redox balance is already strained by parallel metabolic stressors [15,191,192]. Thus, compared with the kidney, the liver may have greater buffering capacity, but it also receives higher substrate flux; both factors should be considered when interpreting D-AA-linked oxidative signals systemically [15,190].

6.3. Brain as a Low Baseline Antioxidant Reserve

In the brain, D-AA biology intersects with neurotransmission because D-Ser (and D-Ala in some contexts) functions as an endogenous co-agonist system for NMDARs, and D-AA levels are regulated by DAAO/DDO and transport processes [193,194]. This creates a distinct organ logic: D-AA metabolism in the CNS is not only “clearance” but can influence synaptic function, while DAAO-mediated oxidation can contribute to local H_2O_2 production and thereby potentially modulate redox-sensitive pathways. Experimental evidence supports the possibility of DAAO involvement in ischemic brain injury, consistent with a model in which D-AA oxidation contributes to oxidative stress during ischemia/reperfusion—an established ROS-intensive setting in the CNS [195,196]. At the same time, D-AA effects in the brain are context dependent; for example, D-Ser has been discussed both as a functional neuromodulator [26] and, under some experimental conditions, as capable of promoting oxidative damage markers in brain tissue [197]. Collectively, these findings suggest that the CNS may be more vulnerable to shifts in D-AA metabolism—

redox coupling than the liver because neuronal tissue has high oxidative demand and comparatively limited antioxidant reserve, and because D-AA pathways converge with excitatory neurotransmission [15,193–196].

6.4. DAAO-Derived H_2O_2 in Renal Oxidative Stress

Among mammalian organs, the kidney exhibits the highest levels of DAAO and DDO expression [184,188], with particularly strong localization in proximal tubular epithelial cells [184,187]. This renal enrichment indicates that the kidney functions as the principal organ for systemic clearance of circulating D-AAs, thereby placing renal tubular cells at the center of D-AA metabolism. While this system likely contributes to physiological detoxification under normal dietary exposure, excessive substrate availability may shift DAAO activity from a homeostatic process toward a source of oxidative burden [198,199].

These observations indicate that DAAO-mediated H_2O_2 generation contributes to physiological redox regulation under normal exposure conditions, but may shift toward pathological oxidative stress when substrate availability exceeds buffering capacity.

H_2O_2 is increasingly recognized as a dual-function redox molecule that participates in physiological signaling at low concentrations but induces oxidative damage when produced excessively [15]. In the kidney, proximal tubular cells are especially susceptible to oxidative stress due to their high mitochondrial density and dependence on oxidative phosphorylation, which together confer elevated oxygen consumption and an increased propensity for mitochondrial ROS production under physiological and pathological conditions [200,201].

DAAO-dependent metabolism of D-AAs provides a localized intracellular source of H_2O_2 in renal tubular epithelial cells, thereby mechanistically linking D-AA load to the magnitude of oxidative stress [184,202]. Experimental and mechanistic studies indicate that excessive H_2O_2 can impair mitochondrial function, promote lipid peroxidation, and activate redox-sensitive inflammatory and cell death pathways in renal tubular epithelium [202–204].

Within the broader framework of redox biology [163], D-AA metabolism can therefore be positioned as part of the O_2 –ROS axis that intersects with renal stress responses rather than as a neutral nutritional process [163,205].

6.5. Experimental Evidence for D-Amino Acid-Induced Nephrotoxicity

The nephrotoxic potential of D-AAs has been most clearly demonstrated in experimental studies using D-Ser, which induces acute tubular necrosis and renal dysfunction in rodents [206]. Crucially, these pathological changes are markedly reduced by pharmacological inhibition of DAAO or in DAAO-deficient models, strongly implicating DAAO-mediated H_2O_2 generation as the causal mechanism for cytotoxicity of D-AAs [207].

In vitro studies using renal proximal tubular cell lines further demonstrate that exposure to D-AAs elevates intracellular ROS levels and compromises cell viability in a DAAO-dependent manner [208]. The protective effects of catalase and other H_2O_2 -scavenging systems in these models provide additional support for the central role of H_2O_2 rather than alternative metabolic by-products [203].

Collectively, these experimental findings indicate that nephrotoxicity arises not from the chirality of amino acids per se but from their enantiomer-specific oxidative metabolism within renal tubular cells [203,206].

6.6. Clearance of DAAO-Derived H_2O_2 in Renal Peroxisomes

Peroxisomes are equipped with antioxidant enzymes that both generate and eliminate H_2O_2 , with catalase traditionally considered the primary detoxifying system [209]. Catalase is characterized by a very high catalytic capacity but relatively low affinity for H_2O_2 ,

suggesting that it functions most effectively when intraperoxisomal H_2O_2 levels are elevated rather than at low basal concentrations [210,211]. Recent studies have emphasized the role of thiol-based peroxidases, particularly peroxiredoxin 5 (PRDX5), which is localized to peroxisomes and displays higher affinity for H_2O_2 than catalase [212,213]. This has led to a model in which catalase and PRDX5 act cooperatively, with catalase serving as a high-capacity scavenger and PRDX5 contributing to fine control of lower H_2O_2 concentrations generated during continuous oxidase activity such as that of DAAO [15,205,209,212].

The pathological relevance of this detoxification system is underscored by experimental evidence showing that D-Ser-induced nephrotoxicity is strongly dependent on DAAO activity and is attenuated by DAAO inhibition or genetic deficiency [184,187,206,207]. These findings indicate that the antioxidant capacity of renal peroxisomes can be exceeded under conditions of excessive D-AA exposure, consistent with DAAO-mediated oxidation generating ROS in the S_3 segment of proximal tubules [214].

Modulation of the antioxidant glutathione (GSH) status has also been reported to influence the severity of D-Ser-induced renal injury, implying involvement of thiol-dependent peroxide detoxification pathways in shaping susceptibility to DAAO-derived oxidative stress [214].

An additional complexity is that the peroxisomal membrane is permeable to small molecules such as H_2O_2 , allowing a fraction of DAAO-derived H_2O_2 to diffuse into the cytosol and engage extra-peroxisomal antioxidant systems, including cytosolic peroxiredoxins and glutathione peroxidases (GPx) [209,215].

Although peroxisome-derived H_2O_2 has been proposed to participate in redox signaling under certain conditions, its contribution to pathological oxidative stress in renal tubular cells remains incompletely defined [15,205,209,216]. Notably, quantitative data delineating the relative contributions of catalase, PRDX5, and diffusion-mediated cytosolic detoxification to the clearance of DAAO-derived H_2O_2 in the kidney are still lacking.

6.7. Risk Populations and Safety Concerns

In humans, circulating and urinary levels of several D-AAs increase with aging and are significantly altered in patients with CKD, reflecting impaired renal clearance and altered amino acid metabolism [170].

CKD is also characterized by diminished antioxidant capacity and heightened basal oxidative stress, conditions that may sensitize the kidney to additional H_2O_2 burdens arising from DAAO activity [217]. From this perspective, D-AAs may function as conditional stressors whose adverse effects become apparent primarily in susceptible populations rather than in healthy individuals [217].

In 2024, health hazards associated with the consumption of health food products containing red yeast rice (beni-koji; *Monascus* spp.), characterized primarily by renal dysfunction, were reported in Japan [218]. Recent investigations of the Japanese beni-koji-associated kidney injury outbreak have increasingly implicated unintended contaminants, particularly puberulic acid, as candidate nephrotoxics [218–220]. Toxicological studies published in 2025 further support direct proximal tubular toxicity of puberulic acid in vivo and in mechanistic models, consistent with the clinical manifestations of Fanconi syndrome and acute tubulointerstitial injury [218].

Free D-AAs have been detected in red yeast rice powder, including 29.6 mg/kg of D-Ala and 129 mg/kg of D-Glu [221]. From a D-AA perspective, a speculative (but currently untested) link is that primary tubular injury induced by such toxicants may secondarily perturb D-AA handling, thereby enhancing DAAO-dependent H_2O_2 generation in susceptible hosts (e.g., individuals with CKD or advanced age). This process could amplify oxidative tubular stress rather than serve as the initiating insult [218,220]. Accord-

ingly, the possibility of atypical D-AA accumulation arising from unintended fermentation processes, including bacterial contamination or altered microbial consortia, should be considered as a contributing factor warranting further investigation.

6.8. Need of Standardized Analytical Workflows for D-AAs

Current regulations for food supplements and food ingredients generally treat amino acids as a single class and do not routinely distinguish between D- and L-enantiomers in specifications for use, purity standards, or safety assessments [222]. This regulatory gap may be particularly relevant for fermented foods and supplements that are consumed chronically or in concentrated forms, especially by individuals with CKD or age-related decline in renal function.

Advances in D-AA research have been closely linked to developments in chiral analytical chemistry. In principle, two major strategies are employed for chiral separation: direct methods based on enantioselective separation, and indirect methods using chiral derivatization reagents (CDRs) that convert enantiomers into diastereomers for separation on achiral columns (Li et al., 2025 [223]).

Current mainstream approaches for D-AA analysis can be broadly classified into LC–MS/MS combined with chiral separation, chiral LC/HPLC, and chiral derivatization followed by reversed-phase LC [224,225]. Each platform presents distinct advantages and limitations. LC–MS/MS offers the highest sensitivity and selectivity for trace analysis but requires costly instrumentation and careful management of matrix effects [225–227]. Chiral LC/HPLC enables direct D/L discrimination without derivatization but often demands extensive optimization depending on the target D-AAs and sample matrix [228–230]. In contrast, CDR-based approaches are particularly suitable for multi-component profiling of multiple D-AAs in a single run [224,228,231].

Among available CDRs, (S)-NIFE has been widely applied in pre-column derivatization HPLC–MS/MS workflows for profiling D-AAs in diverse biological and food matrices [225,232,233]. More recently, Harada et al. developed a novel CDR, (R)-BiAC, enabling rapid and high-resolution simultaneous determination of multiple D-AAs within 11.5 min [234]. Nevertheless, the simultaneous and efficient resolution of multiple chiral analytes remains a central challenge in analytical chemistry [223]. In addition, issues related to reproducibility, matrix effects, and inter-laboratory standardization persist.

To facilitate knowledge sharing across food and nutritional sciences, biology, physiology, medical research, and clinical studies, the establishment of standardized analytical workflows integrating sampling, extraction, separation, quantification, and quality control is essential. Future efforts toward validated reference materials, unified protocols, and inter-laboratory ring trials will be critical for generating reliable and comparable D-AA datasets, thereby supporting evidence-based nutritional and safety assessments.

7. D-Amino Acids as Stressors in Eukaryotes

7.1. Eukaryotes Sensitive to D-Amino Acids

It is generally accepted that D-AA uptake in plants [127] and mammals [235,236] is mediated largely by broad-specificity amino acid transport systems, whereas D-AA-specific transporters have been reported primarily in bacteria (e.g., DsdX for D-Ser [237]). Consequently, excessive accumulation of D-AAs in the extracellular space may lead to their inadvertent cellular uptake, thereby disturbing metabolic, translational, and redox homeostasis in L-AA-optimized cellular systems in eukaryotes.

At the organismal level, mammals appear to maintain systemic homochirality primarily through the predominant biosynthesis of L-enantiomeric amino acids (e.g., SR) and the efficient elimination of D-AAs via enzymatic degradation with broad specificity (e.g.,

DAAO) and urinary excretion [238]. In contrast, there is currently no convincing evidence that mammals actively regulate amino acid chirality at the intracellular level. This may suggest that chiral balance is controlled primarily at the whole-body scale rather than within individual cells, implying that intracellular environments in eukaryotes may be potentially vulnerable to excess D-AA influx [238].

7.2. D-Amino Acids as Stressors

An overview of recent publications makes it clear that D-AAs exhibit both potential health benefits and tissue-damaging effects that may contribute to therapeutic outcomes and pathophysiology, although definitive evidence and further validation are still required. This dual nature does not align well with the conventional view of biomolecules. Such characteristics have been described in the literature using expressions such as “double-edged sword [239]”, “Janus-faced [240]”, “two sides of the same coin [241]”, or “Yin–Yang [242]”, and are also central to the concept of stress theory [163].

According to Hans Selye’s stress concept, stressors can exert both beneficial (“eustress”, adaptive stress) and detrimental (“distress”, maladaptive stress) effects on living organisms, depending on their context, intensity, and duration [243].

Within this framework, D-AA-induced H_2O_2 potentially function as a signaling molecule under eustress conditions [15], implying that the ROS generation can be involved in the signaling functions of D-AA in an indirect manner. In contrast, excessive ROS generation promotes cellular oxidative damage (distress conditions) through complex interactions with the nitric oxide–reactive nitrogen species (NO–RNS) axis and the hydrogen sulfide (H_2S)–reactive sulfur species (H_2S –RSS) axis [163,164,203]. From this perspective, the negative effects of excessive D-AA intake may be mitigated by ROS-scavenging activities and antioxidant systems as demonstrated in CKD.

8. Future Perspectives

8.1. Molecular Targets of D-Amino Acids in Eukaryotes

Table 4 summarizes the confirmed and emerging molecular targets of D-AAs identified to date in plants and animals. Notably, many of these candidates are functionally linked, directly or indirectly, to intracellular Ca^{2+} signaling pathways (Table 4), highlighting Ca^{2+} -dependent processes as a recurring theme in D-AA-mediated regulation. Among them, ionotropic glutamate receptors (iGluRs) including NMDARs and GLRs have been the most extensively studied targets in both mammals and plants, where D-AAs such as D-Ser and D-Asp modulate receptor activity and downstream signaling.

Beyond iGluRs, recent studies have identified additional and seemingly disparate D-AA-responsive targets, including sweet taste receptors expressed in the gastrointestinal tract and airways. It is well known that many D-AAs possess distinct taste properties as well as G-protein-coupled receptor-linked pathways involved in neutrophil function (Table 4). At first glance, these receptor systems appear functionally unrelated, operating in distinct tissues and physiological contexts such as nutrient sensing, epithelial defense, and immune cell behavior. However, their shared sensitivity to D-AAs raises the possibility that these targets represent components of a broader, distributed D-AA-responsive signaling network rather than isolated exceptions.

This apparent convergence invites a more integrative interpretation of D-AAs as signaling molecules in eukaryotes. Specifically, it suggests that D-AAs may act as context-dependent chemical cues that interface with Ca^{2+} -dependent signaling modules across metabolic, immune, and neural systems.

Table 4. Confirmed and emerging molecular targets of D-AAs in eukaryotes.

Target	Type/Family	D-AA Ligands	Tissue/Cellular Distribution	Function/Physiological Role	References
NMDA Receptors (NMDARs)	Ionotropic glutamate receptor	D-Ser (co-agonist) D-Asp (agonist) D-Glu (agonist) D-Ala (agonist)	Brain (widespread), Spinal cord	Neurotransmission, Synaptic plasticity, Learning and memory, Neuronal excitability	[26,244]
Glutamate-like Receptors (GLRs)	Plant ionotropic glutamate-like receptors	D-Ser	Plant tissues (roots, shoots, guard cells)	Calcium signaling, Stress responses, Pollen tube growth, Wound signaling	[23,127]
Delta Glutamate Receptors (GluD1/GluD2)	Ionotropic glutamate receptor family	D-Ser	Brain (GluD2: cerebellum, Purkinje cells; GluD1: forebrain, hippocampus)	Synaptogenesis, Synaptic plasticity, Motor coordination, Neuronal signaling (controversial as direct ion channel)	[245–248]
Taste Receptor (T1R2/T1R3)	Class C GPCR heterodimer	D-Trp D-Phe D-Ser, etc.	Taste buds, Gastrointestinal tract, Pancreatic β -cells, Brain, Airways	Sweet or umami taste perception, Incretin secretion, Glucose sensing, Insulin secretion, Innate immunity	[249–253]
G-Protein Coupled Receptors	GPCR	D-Phe D-Trp	Neutrophils, Immune cells	Chemotaxis regulation, Innate immune response modulation	[10,254]

Abbreviations: GPCR, G-protein-coupled receptor.

8.2. Possible Evolutionary Integration of D-AA Sensing in Eukaryotic Systems

G protein-coupled receptors were identified in taste cells on the tongue in early studies, but these receptors were later identified in cells all over the body, demonstrating a more general chemosensory role beyond taste [255]. Accumulating evidence suggests that D-AAs in eukaryotes may function as context-dependent chemical signals linking microbial activity, nutrition, immunity, and neural regulation [12]. Because many D-AAs are preferentially produced by bacteria during growth, fermentation, and biofilm remodeling (see Sections 3.3 and 3.4), they have been proposed as potential indicators of microbial metabolic state [106]. However, the extent to which host organisms actively exploit this information remains to be fully elucidated.

In epithelial tissues, including the gut and airway, broad-specificity chemosensory receptors such as taste receptors have been shown to respond to diverse luminal ligands, including sugars and certain D-AAs (Table 4). It is therefore conceivable that these receptors were evolutionarily recruited, at least in part, to monitor microbially modified nutrients and metabolites, thereby linking luminal sensing to endocrine secretion, barrier function, and innate immune regulation [251,256]. Nevertheless, direct evidence for such an adaptive role of D-AA sensing *in vivo* is still limited.

Similarly, emerging studies indicate that D-AAs can influence immune cell behavior, including chemotaxis and inflammatory responses [10,254]. This raises the possibility that immune cells may utilize D-AA gradients as supplementary cues reflecting local microbial activity, in addition to classical pathogen-associated molecular patterns. Whether such mechanisms operate broadly under physiological conditions remains an open question.

In the nervous system, ancient amino acid-based ligand recognition motifs appear to have been refined into high-fidelity signaling modules, exemplified by the involvement of D-Ser and D-Asp in NMDAR regulation (see Section 5.2). While this specialization supports synaptic plasticity, it may also render neural circuits susceptible to certain mi-

crobial amino acid analogs, such as the neurotoxin BMAA [163,257]. This potential vulnerability points to a possible evolutionary tradeoff, although in vivo relevance is still under investigation.

Taken together, these observations support a working hypothesis that D-AA signaling pathways in eukaryotes may have emerged through long-term host–microbe co-adaptation, in which microbial metabolites were gradually integrated into metabolic, immune, and neural regulatory networks (Figure 6). Future comparative, genetic, and multi-omics studies will be required to rigorously test this hypothesis and to clarify the physiological and pathological significance of D-AA sensing systems.

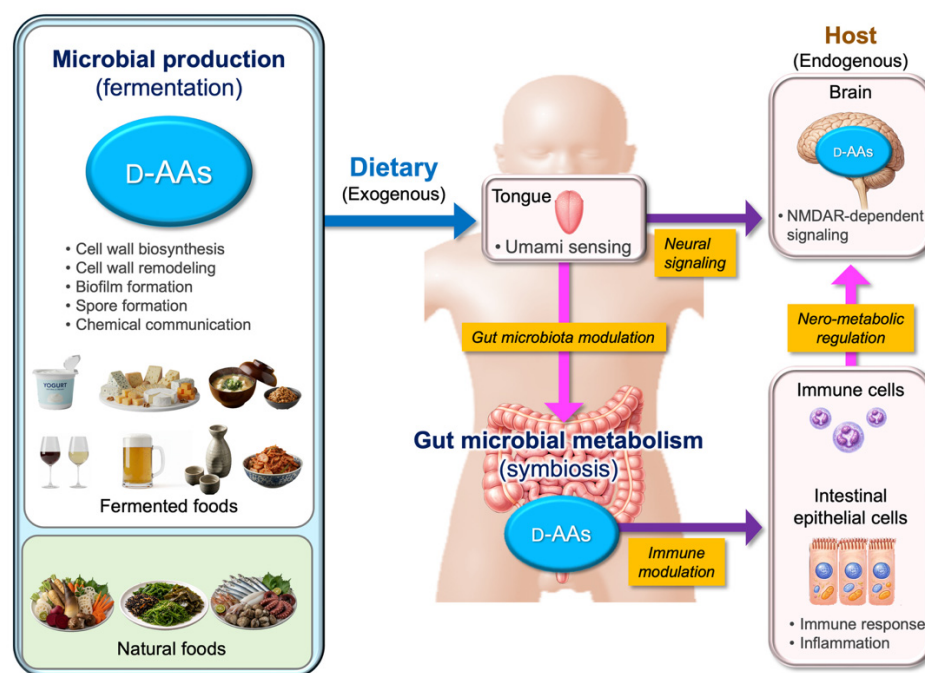


Figure 6. Schematic diagram illustrating the hypothetical functions of dietary D-AAs in humans. D-AAs are present in natural foods (plants and animals), fermented food products, and dietary supplements. Many D-AAs are perceived as umami by taste receptors (T1R family) on the tongue, thereby potentially influencing food preference. These umami receptors are also expressed in immune cells, such as neutrophils, as well as in intestinal epithelial cells, where they may contribute to the regulation of innate immune responses. Orally ingested D-AAs modulate symbiotic gut microbial communities through prebiotic effects. In this context, D-AAs may function as signaling molecules reflecting bacterial metabolic activities and may be involved in host immune regulation. In addition to this exogenous dietary pathway, neural cells in the brain can endogenously synthesize D-AAs, which contribute to the regulation of NMDAR function. Photographic-style inset images were generated using Google Gemini (Google), whereas illustrative images were generated using ChatGPT 5.2 (OpenAI), for illustrative purposes and were reviewed and edited by the authors.

8.3. D-Amino Acids as Inter-Kingdom Communication Tools: Behind Context-Dependency

The apparently opposing nature of D-AAs, characterized by both potential benefits and risks, can therefore be understood as a manifestation of the universal, context-dependent actions of stressors [163]. If D-AAs are viewed as a universal biochemical “language” shared among living organisms (Figure 3), each D-AA may be regarded as a “word” in intra- or intercellular communication. As with words in human language, the biological meanings of D-AAs can shift according to historical (evolutionary) and regional (ecological) contexts and may even convey contradictory effects under different conditions. In this sense, D-AAs can be considered “contronymic” molecules, capable of exerting opposing or context-dependent biological actions [173].

By overviewing possible molecular targets of D-AAAs (Table 4), it appears that D-AAAs in eukaryotes serve three interconnected evolutionary roles that reflect their ancient origins as inter-kingdom signaling molecules. First, they function as microbial surveillance signals: DAAO in intestinal mucosa and neutrophils oxidizes bacterial D-Ala to produce antimicrobial H_2O_2 [183,254], while the sweet taste receptor (T1R2/T1R3) and G-protein-coupled receptors detect various D-AAAs in mucosal tissues to regulate chemotaxis and innate immunity [252,254,256]. This surveillance is targeted: bacteria produce noncanonical D-AAAs (D-Met, D-Leu, D-Tyr, D-Phe) at millimolar concentrations during stationary phase to regulate peptidoglycan remodeling and biofilm dispersal [22,95], creating species-specific chemical signatures that eukaryotic immune systems evolved to detect. Second, eukaryotes co-opted this machinery for neural signaling. D-Ser, produced by SR [24,26], functions as the primary NMDAR co-agonist critical for synaptic plasticity and memory [258,259], while glutamate delta receptors may also respond to D-Ser [245–247]. Recently, Gumerov and coworkers revealed that the conserved amino acid-binding motif (dCache_1AA) from bacterial chemoreceptors to mammalian $\alpha 2\delta$ calcium channel subunits demonstrates deep evolutionary conservation of this sensory architecture [260]. Third, D-AAAs regulate metabolism and pain: $\alpha 2\delta$ subunits are therapeutic targets of gabapentin [261] and pregabalin [262], while T1R2/T1R3 in pancreatic β -cells stimulates insulin secretion [263].

The cyanobacterial neurotoxin β -N-methylamino-L-alanine (BMAA) further supports the above perspectives for ongoing molecular dialog between prokaryotes and eukaryotes through these conserved pathways [163]. BMAA, produced by diverse cyanobacteria [264,265], acts as an NMDAR and mGluR5 agonist, inducing neurotoxicity at concentrations as low as 10 μ M [266]. BMAA crosses the blood–brain barrier, becomes misincorporated into proteins in place of L-Ser, and has been detected in brains of Alzheimer’s and ALS patients [264,267]. This molecular mimicry—a “false word” in the shared chemical language—demonstrates that NMDARs retain their ancestral capacity to respond to microbial amino acid analogs, revealing these “neural” receptors as ancient, versatile amino acid sensors rather than exclusively neurotransmitter-specific proteins.

We propose that D-AA function as an ancient molecular vocabulary in biological language inherited from bacterial chemosensory systems. Eukaryotes partially retained and elaborated this system across three evolutionary layers: (1) inter-kingdom surveillance at barrier surfaces, (2) endogenous neural signaling through de novo D-AA synthesis, and (3) specialized metabolic functions. Different bacteria produce distinct D-AA profiles during different growth phases [22,95], creating context-specific chemical signatures that eukaryotic receptors decode through tissue-specific expression and signaling: the same D-AA triggers antimicrobial responses in neutrophils, synaptic potentiation in neurons, or metabolic regulation in pancreatic cells depending on cellular context (Figure 6). The persistence of cross-reactivity exemplified by BMAA neurotoxicity is not a design flaw but an evolutionary consequence of maintaining versatile, ancient sensory machinery, revealing that eukaryotic cells never fully “left” the microbial vocabulary.

9. Conclusions

A further challenge in evaluating D-AAAs as nutraceuticals arises from their context-dependent and continuum-like biological actions, which resist simple classifications such as “beneficial versus harmful” or “drug versus toxin”. Similarly to ubiquitous signaling and redox-active molecules such as H_2O_2 , NO, H_2S [163], and ascorbate [268], D-AAAs can exert divergent effects depending on dose, metabolic state, and environmental conditions. Accordingly, their physiological significance should be interpreted within integrated biological contexts rather than in isolation.

From a practical perspective, traditional dietary patterns that incorporate diverse natural and fermented foods may offer an effective framework for balancing potential benefits with safety. Such diets implicitly integrate moderation, compositional diversity, and population-specific adaptation, features that are difficult to replicate through isolated, high-dose supplementation. In healthy adults, D-AAs derived from natural food sources are generally considered safe, likely reflecting their presence as evolutionarily optimized mixtures rather than as excessive amounts of single compounds. Moreover, many natural foods contain abundant antioxidants [217,268] and sulfur-containing metabolites [126], which may attenuate oxidative stress associated with D-AA metabolism. In contrast, special caution is warranted for supplements and certain fermented products containing unusually high concentrations of specific D-AAs, particularly in older individuals and in patients with renal dysfunction or metabolic disorders (Figure 7).

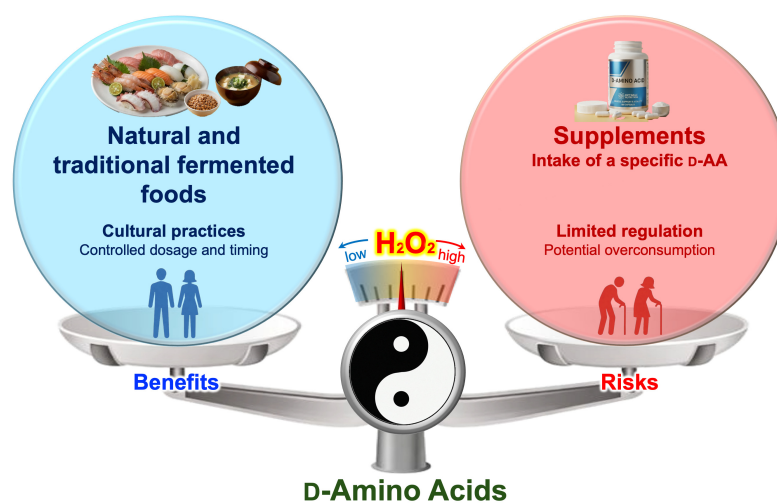


Figure 7. Balance between benefits and risks in dietary intake of D-AAs. Conceptual model illustrating the balance between benefits and risks associated with dietary intake of D-AAs. Natural and traditional fermented foods provide diverse D-AAs within culturally optimized patterns of dosage, timing, and restriction, supporting redox homeostasis and potential health benefits. In contrast, supplementation with isolated D-AAs may lead to excessive intake in the absence of strict regulation, increasing H_2O_2 generation and oxidative stress, particularly in susceptible populations. This framework conceptualizes D-AA intake as a context-dependent continuum, symbolized by the Yin-Yang, rather than a binary benefit–risk paradigm [163]. Photographic-style inset images were generated using Google Gemini (Google), whereas illustrative images were generated using ChatGPT 5.2 (OpenAI) and ImageFX (Google), for illustrative purposes and were reviewed and edited by the authors.

Many D-AAs exhibit sweet or umami taste, which differ from those of their L-enantiomers [269,270]. A growing body of evidence indicates that traditional Japanese cuisine is rich in D-AAs, particularly in fermented products such as miso and soy sauce [63], natto [271], as well as in seafood [109,110,232] and sake [47]. Notably, *washoku* (和食) was recognized by UNESCO in 2013 as an Intangible Cultural Heritage of Humanity [272], reflecting its cultural and nutritional significance. Umami, a term derived from Japanese (旨味), often referred to as the “fifth basic taste”, is a defining characteristic of traditional Japanese foods and was first scientifically conceptualized and named by Japanese chemist Kikunae Ikeda in 1909 [273], reflecting the absence of an equivalent term in Western languages at the time of its scientific identification.

In addition to its richness in polyphenols, the habitual consumption of diverse vegetables, fermented foods, and seafood characterizes Japanese dietary patterns and has been associated with reduced prevalence of chronic diseases and lower mortality in large cohort studies [274–276]. These epidemiological observations suggest potential synergistic effects

of fermentation-derived metabolites, including D-AAs, together with plant- and marine-derived bioactive compounds (such as antioxidant polyphenols [277]) in supporting redox balance and metabolic health.

In conclusion, D-AAs can be regarded as a context-sensitive class of biomolecules that bridge nutraceutical science, redox biology, microbial ecology, evolutionary biology, and physiology and medicine. Accumulating evidence indicates that their biological actions are best understood not in binary terms of benefit versus harm, but as continuum-like, context-dependent responses shaped by dietary exposure, microbial metabolism, host clearance capacity, and redox status. Future progress will depend on systematic identification of molecular targets, standardization of analytical workflows, and integration of dietary, microbial, and host factors. Such multidisciplinary approaches will be essential for establishing evidence-based strategies that harness the benefits of D-AAs while minimizing potential risks, as well as for positioning D-AAs as a new class of regulatory molecules in human stress and redox biology.

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Abbreviations

BMAA	β -N-methylamino-L-alanine
CAT	catalase
CBS	cystathionine β -synthase
CHD	coronary heart disease
CKD	chronic kidney disease
CVD	cardiovascular disease
CSE	cystathionine γ -lyase
D-Ala	D-alanine
D-AAs	D-amino acids
DAAO	D-amino acid oxidase
DDO	D-aspartate oxidase
D-Arg	D-arginine
D-Asn	D-asparagine
D-Asp	D-aspartate
D-Cys	D-cysteine
D-Glu	D-glutamate
D-Lys	D-lysine
D-Met	D-methionine
D-Phe	D-phenylalanine
D-Pro	D-proline
D-Ser	D-serine
D-Thr	D-threonine
D-Trp	D-tryptophan
D-Tyr	D-tyrosine

GLR	glutamate receptor-like Ca ²⁺ channel
GPx	glutathione peroxidase
LAB	lactic acid bacteria
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
PLP	pyridoxal phosphate
PTSD	post-traumatic stress disorder
PRDX	peroxiredoxin
SR	serine racemase

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