

A Comprehensive Review on Lysine: Biochemical Properties and Health Implications

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ABSTRACT

L-Lysine, one of the nine essential amino acids, plays a pivotal role in maintaining human and animal health through its diverse biochemical and physiological functions. As a key building block in protein synthesis, lysine is fundamental for tissue repair, calcium absorption, hormone production, and enzymatic activity. This review provides a multidisciplinary overview of recent advances in lysine research, encompassing its molecular dynamics, clinical applications, regulatory mechanisms, and broader implications for nutrition, metabolism, immunity, neurophysiology, and biotechnology. Lysine's significance in human health has been extensively investigated, particularly in the context of dietary supplementation. According to clinical research, children and adolescents who take L-lysine supplements benefit from improved growth and development, particularly in areas where diets lack sufficient amounts of lysine-rich protein sources. When used within advised bounds, supplements have been linked to increased lean body mass, height velocity, and a decreased incidence of stunting without causing appreciable side effects. Supplementing with lysine also has the potential to improve immune responses, increase calcium retention, and speed the healing process from illnesses brought on by stress. Lysine experiences a number of post-translational modifications (PTMs) at the molecular level that have a major impact on gene expression, metabolism, and cellular signalling. Key PTMs (post-translational modifications) include acetylation, methylation, succinylation, malonylation, and 2-hydroxyisobutyrylation. These modifications regulate protein stability, chromatin remodelling, and enzymatic activity, thereby influencing metabolic pathways involved in energy production, lipid metabolism, and mitochondrial dynamics. For example, lysine succinylation and malonylation in *Escherichia coli* were shown to impact metabolic flux and bacterial energy homeostasis. In humans, dysregulation of lysine methylation has been linked to metabolic diseases, obesity, and insulin resistance, highlighting lysine-modifying enzymes as potential therapeutic targets. Technological innovations have enabled advanced detection and modelling of lysine-related molecular changes. Electrochemical biosensors have been developed for the sensitive detection of lysine acetyltransferase activity in cancer cells, offering potential diagnostic tools for early tumour identification. Moreover, artificial intelligence models using deep learning have improved the accuracy of predicting lysine modification sites, furthering our understanding of protein regulation at the systems level. In terms of functional applications, lysine exhibits strong antioxidant potential. Studies have shown that L-lysine enhances the stability and radical-scavenging capacity of heme-peptides, thus offering nutritional and pharmaceutical benefits in managing oxidative stress. Lysine also plays a role in antiviral defence; it antagonizes arginine metabolism, which is essential for viral replication, thereby aiding in the management of infections like herpes simplex virus. Its immunomodulatory functions extend to neurophysiological effects as well—lysine has been found to modulate stress-induced neural activity, suggesting its potential in treating anxiety-related disorders. In agriculture and biotechnology, lysine's post-translational modifications influence gene regulation and stress responses in plants. In rice (*Oryza sativa*), lysine 2-hydroxyisobutyrylation has been linked to protein function during abiotic stress, pointing toward its use in crop engineering. These findings open avenues for lysine biofortification strategies and synthetic biology approaches in microbial systems. Hence, lysine is a metabolically and clinically vital amino acid with widespread implications across health sciences, molecular biology, and biotechnology. This review integrates cross-disciplinary findings to present lysine as a biochemical keystone with untapped potential for therapeutic intervention, nutritional planning, diagnostic innovation, and agricultural advancement. Future research should aim at unravelling lysine's complex regulatory networks, exploring its therapeutic dosing thresholds, and leveraging its molecular versatility for precision medicine and sustainable development.

Keywords: Lysine, Essential Amino Acid, Protein Synthesis, Collagen, Calcium Absorption, Epigenetics, Herpes Simplex, Nutritional Deficiency, Lysine Metabolism

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INTRODUCTION

Essential amino acids (EAAs) are organic substances that must be obtained through diet because the human body is unable to produce them in adequate amounts on its own. Protein synthesis, tissue repair, enzyme synthesis, and neurotransmitter function all depend on these amino acids. Nine of the twenty standard amino acids—tryptophan, valine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, and threonine—are thought to be necessary for adult life. Every EAA has a unique physiological function. Lysine, for instance, is essential for immunological response, collagen synthesis, and calcium absorption. It also interacts antagonistically with arginine, affecting viral replication and immunity “Top 6 Health Benefits of Lysine”. Muscle metabolism and exercise recovery depend on the branched-chain amine leucine, isoleucine, and valine. Phenylalanine and tryptophan, aromatic amino acids, act as precursors for the neurotransmitters dopamine and serotonin and thus affect depression and sleep. The PTM of lysine amino acids with acetylation, methylation, succinylation, and malonylation affects gene expression, metabolism, and the likelihood of a person developing certain diseases. The discovery of PTM in microorganisms and plants like rice reveals the remarkable evolution and crucial role for the regulation of the vital amino acids. The deeper examination of the role of amino acids in health and diseases is made possible with advanced technologies like EAAs(essential amino acids) electrochemical biosensors and AI models. Therefore, essential amino acids function as nutritional components and at the same time, act as molecular regulators that are vital for metabolism, immunity, and cellular health.

The concept of essential amino acids (EAAs) emerged from foundational nutritional studies in the early 20th century, when scientists recognized that certain amino acids must be supplied through the diet to sustain life and growth. Early animal experiments demonstrated growth failure and organ dysfunction when specific amino acids were omitted from diets, which led to the classification of nine EAAs for adult humans: histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine [1] [2]. Among these, lysine has received particular attention for its multifaceted physiological roles. Early clinical trials in the mid-20th century evaluated lysine's effect on growth, immunity, and protein synthesis. Modern research continues to highlight its significance, especially in paediatric populations in low-resource settings, where lysine supplementation is associated with improved linear growth and reduced morbidity [1]. Moreover, lysine's metabolic role in calcium absorption, hormonal regulation, and muscle tissue maintenance has broadened its use in both clinical nutrition and therapeutic formulations [10]. In recent years, EAAs have gained renewed relevance in nutritional science, sports medicine, and metabolic disease research. For instance, branched-chain amino acids (BCAAs) are studied for their impact on muscle wasting and exercise recovery. Additionally, amino acid metabolism has become a target for treating metabolic

syndrome, cancer, and neurodegenerative diseases, with a focus on post-translational modifications of lysine that regulate gene expression and enzymatic activity. Technological advancements, including biosensors and machine learning models, have enabled precise profiling of amino acid modifications, reinforcing the clinical importance of EAAs in diagnostics and personalized nutrition [3][4].

This review aims to provide an in-depth synthesis of scientific findings on L-lysine, a vital essential amino acid, focusing on its biochemical functions, clinical applications, and relevance in nutritional science. While lysine is traditionally recognized for its role in protein synthesis and tissue repair, recent advances have highlighted its involvement in immune regulation, calcium metabolism, viral suppression, and post-translational modifications [14]. The scope of this review includes an exploration of lysine's physiological roles, mechanisms of action, and dietary significance, particularly in the context of child development, disease management, and metabolic health [7]. Additionally, the review evaluates cutting-edge research on lysine acetylation, succinylation, and malonylation in human and microbial systems [6]. We also discuss technological innovations—such as biosensors and machine learning approaches—for detecting lysine-related biomarkers [4]. Ultimately, this review seeks to highlight clinical implications, address knowledge gaps, and propose directions for future research into lysine's therapeutic and diagnostic potential across human health domains.

Lysine is one of the nine essential amino acids that must be obtained from the diet due to the human body's inability to synthesize it endogenously. It plays a vital role in protein synthesis, calcium absorption, immune function, and the modulation of enzymatic and hormonal activities [2]. Consequently, adequate lysine intake is crucial across all life stages, particularly during periods of growth, pregnancy, and recovery from illness. Lysine is primarily found in high-protein foods, particularly those of animal origin. Excellent sources include meat (beef, pork, lamb), poultry (chicken, turkey), fish (tuna, cod), eggs, and dairy products such as milk, cheese, and yogurt “Top 6 Health Benefits of Lysine. Among plant-based sources, legumes—including lentils, chickpeas, black beans, and soybeans—are the richest in lysine content. Other vegetarian sources include quinoa, pistachios, spirulina, and amaranth, though in generally lower concentrations “What Are the Benefits of Lysine?”. However, grains like wheat, corn, and rice are typically low in lysine, making it a limiting amino acid in cereal-based diets [13]. This is particularly important in populations relying heavily on plant-based staples. To address this, nutritional strategies such as protein complementation (e.g., combining legumes and cereals) or lysine fortification in staple foods have been implemented in developing countries.

The World Health Organization (WHO) and Food and Agriculture Organization (FAO) recommend lysine intakes based on age, physiological status, and body weight. For

adults, the daily lysine requirement is approximately 30 mg per kilogram of body weight, translating to about 2,100 mg per day for a 70 kg adult. Children, adolescents, and pregnant or lactating women require higher intakes due to increased anabolic demands. In certain clinical or metabolic conditions, lysine needs may be altered. For example, athletes and individuals recovering from surgery or injury may benefit from elevated lysine intake to support muscle repair and immune function [8]. Lysine supplementation has also been shown to help inhibit herpes simplex virus (HSV) replication, likely due to its antagonistic relationship with arginine, which viruses depend on for replication [10]. Supplementation and Safety Lysine is available as a dietary supplement in the form of capsules, powders, and fortified products. Studies have confirmed the safety of lysine supplementation within recommended dosages “Top 6 Health Benefits of Lysine [11]. However, excessive or unbalanced lysine intake could potentially interfere with the absorption of other amino acids, particularly arginine, and may pose risks in individuals with liver or kidney disorders. Recent developments in biosensor technologies and clinical metabolomics are enabling more precise assessment of amino acid status, facilitating personalized dietary recommendations [4]. In conclusion, maintaining adequate lysine intake through a balanced diet is critical for overall health, especially in populations vulnerable to protein-energy malnutrition. Nutrition policies should ensure lysine sufficiency through both natural dietary diversity and targeted fortification where needed.

The bioavailability of lysine, referring to its digestibility, absorption, and metabolic utilization is crucial in determining the nutritional value of dietary protein. Lysine, as an essential amino acid, must be obtained through the diet, and its source significantly affects how well it is absorbed and utilized by the body. Animal-based sources of lysine, including meat, poultry, fish, eggs, and dairy products, exhibit superior bioavailability. These foods contain complete proteins that provide all nine essential amino acids, including lysine, in ideal ratios for human metabolism. The lysine in animal foods is typically highly digestible, with absorption rates often exceeding 90–98%. For instance, lysine from milk proteins such as casein and whey is rapidly absorbed and efficiently supports growth and tissue repair. Similarly, lysine in meat and eggs has high metabolic utility, making animal proteins particularly valuable for clinical nutrition, childhood growth, and recovery from illness. In contrast, plant-derived lysine is generally less bioavailable, especially in cereals like wheat, rice, and corn, which are naturally low in lysine. These grains are often considered lysine-limiting and do not provide the essential amino acid profile required for optimal human health [12]. Moreover, plant foods frequently contain anti-nutritional factors such as phytates, tannins, and fibre, which can inhibit digestive enzymes or bind amino acids, further reducing lysine absorption. However, not all plant proteins are equal. Legumes like soybeans, as well as pseudocereals such as quinoa and amaranth, are exceptions. They contain higher lysine levels and have been recognized for their relatively

good digestibility and balanced amino acid composition [8]. For example, soy protein isolate has been shown to rival animal proteins in bioavailability under certain conditions. Still, plant-based lysine absorption typically remains 15–30% lower than animal sources due to the food matrix and processing effects. To improve lysine bioavailability from plant sources, processing techniques such as fermentation, sprouting, soaking, and thermal treatment can degrade anti-nutritional compounds and enhance digestibility. Additionally, protein complementation combining lysine-poor foods like rice with lysine-rich legumes helps create a more balanced amino acid profile. In summary, while animal-based lysine sources offer superior bioavailability, strategic dietary planning and processing can significantly enhance lysine absorption from plant foods, supporting vegetarian, vegan, and low-meat diets.

Lysine plays a critical role in vegetarian and vegan diets, as it is often the first limiting essential amino acid in many plant-based foods. Unlike animal proteins, which typically contain all essential amino acids in balanced proportions, most plant-based proteins are incomplete and may be deficient in lysine. This makes it especially important for vegetarians and vegans to consciously include lysine-rich foods in their diets to meet physiological requirements for growth, tissue repair, enzyme function, and immune support. Grains like wheat, rice, and corn are staples in many plant-based diets but are relatively low in lysine content and bioavailability [9]. In contrast, legumes especially soybeans, lentils, chickpeas, and black beans are excellent plant sources of lysine. Other nutrient-dense options include quinoa, amaranth, and pumpkin seeds, which offer comparatively better lysine content among plant proteins [13]. The challenge of lysine adequacy in vegan diets is compounded by anti-nutritional factors in many plant foods, such as phytates, tannins, and enzyme inhibitors, which can limit the absorption and metabolic use of amino acids. However, food processing methods like soaking, fermenting, sprouting, and cooking can significantly reduce these inhibitors and enhance lysine bioavailability. Because lysine is essential for protein synthesis, immune function, and calcium absorption, inadequate intake over time can lead to fatigue, muscle loss, impaired immunity, and slow growth in children. Therefore, the World Health Organization (WHO) and other health bodies recommend careful dietary planning in vegetarian and vegan populations to avoid lysine deficiency, particularly among children, pregnant women, and athletes with higher protein demands. Nutritional strategies to ensure sufficient lysine intake include: Emphasizing legumes, soy products (tofu, tempeh), and quinoa as primary protein sources. Using protein complementation, e.g., combining rice and lentils to balance amino acid profiles.

Incorporating lysine-fortified plant-based foods or supplements, particularly in restrictive or therapeutic diets. Recent research also supports the potential benefits of lysine supplementation in vegan populations to maintain optimal immune function and prevent herpes virus

outbreaks [12]. While vegetarian and vegan diets pose challenges for lysine sufficiency, a diverse, well-planned plant-based diet that includes lysine-rich foods and smart cooking techniques can fully meet dietary needs without reliance on animal products. Lysine fortification and supplementation have emerged as critical strategies in addressing dietary deficiencies, particularly in populations with limited access to animal proteins, or in vegetarian and vegan diets. Since lysine is frequently the first limiting essential amino acid in cereal-based diets, its fortification in staple foods and use as a dietary supplement is a scientifically validated approach to improving protein quality and health outcomes.

Food fortification involves the addition of lysine to commonly consumed products such as wheat flour, maize flour, rice, and blended cereal-legume products. Studies in developing regions, where diets are predominantly cereal-based, have shown that lysine fortification significantly improves growth metrics in children, enhances immunity, and reduces markers of malnutrition. For instance, community-level interventions in South Asia and sub-Saharan Africa incorporating lysine-enriched flours have been associated with improved height-for-age and weight-for-age scores in school-aged children.

In industrial settings, lysine is typically added in the form of L-lysine hydrochloride, a stable, cost-effective, and bioavailable formulation. This synthetic form is produced through microbial fermentation, primarily using strains of *Corynebacterium glutamicum*, and is widely approved for use in human and animal nutrition [6]. Additionally, fortification, lysine supplementations are popular for both therapeutic and preventive purposes. In clinical nutrition, lysine supplements are used to Enhance calcium absorption and bone health. Improve recovery in protein-energy malnutrition (PEM). Control outbreaks of Herpes simplex virus (HSV) by antagonizing arginine, which the virus requires for replication [12].

For vegans and athletes, lysine supplementation may also help meet higher protein demands, improve muscle repair, and prevent fatigue or immune suppression [9]. Despite its benefits, excessive lysine intake can lead to gastrointestinal discomfort, renal strain, or interactions with arginine metabolism. However, most clinical studies support its safety at supplemental levels up to 6 g/day in adults without adverse effects. Global policy initiatives have increasingly encouraged lysine fortification in school feeding programs, emergency rations, and public health nutrition policies, especially in regions with protein-deficient populations. Fortification and supplementation of lysine offer a powerful, low-cost intervention to enhance protein quality, combat malnutrition, and support metabolic health—particularly in vulnerable or plant-based populations.

Biochemical Properties of Lysine

Lysine (abbreviated as Lys or K) is a basic, essential α -amino acid with the molecular formula $C_6H_{14}N_2O_2$ and a molar mass of approximately 146.19 g/mol. It is classified as one of the nine essential amino acids, meaning it cannot

be synthesized de novo by the human body and must be obtained through the diet [2]. Structurally, lysine contains an α -amino group ($-NH_2$), an α -carboxyl group ($-COOH$), A side chain consisting of a four-carbon aliphatic straight chain ending in an ϵ -amino group ($-NH_2$), making it one of the three positively charged (basic) amino acids at physiological pH, along with arginine and histidine [14][5]. This basic ϵ -amino side chain gives lysine a high pKa (~ 10.5), allowing it to carry a positive charge under physiological conditions, contributing to protein solubility, ionic bonding, and post-translational modifications such as acetylation, methylation, ubiquitination, and succinylation [6]. From a stereochemical perspective, lysine exists in two enantiomeric forms: L-lysine, the biologically active form incorporated into proteins by the ribosomal machinery, D-lysine, which may occur synthetically or in specific bacterial cell wall peptidoglycans. L-lysine has a chiral centre at the α -carbon, giving it optical activity. Its configuration conforms to the S-configuration under the Cahn-Ingold-Prelog system and rotates plane-polarized light to the left (laevorotatory) in aqueous solution. Only L-lysine is relevant in human metabolism and protein synthesis [13]. The polarity and reactivity of the ϵ -amino group of lysine make it a major site for post-translational modifications (PTMs) that regulate protein structure, localization, and function. For instance, lysine acetylation is a key mechanism in histone modification, affecting gene expression and chromatin remodelling [14]). Similarly, lysine succinylation and malonylation are emerging as important PTMs in metabolic regulation [8]. Moreover, lysine's structure enables it to interact strongly with negatively charged molecules, such as DNA and phospholipids, playing vital roles in enzyme-substrate binding, transcriptional control, and membrane interactions.

Lysine, a basic essential amino acid, exhibits three ionizable functional groups, each with characteristic pKa values that define its charge state at various pH levels. This chemical behaviour is crucial for its function in protein structure and metabolic pathways [14]. Furthermore, the **protonation state** influences lysine's bioavailability and its role in **nutritional therapeutics**, especially in fortified diets or supplements. The ϵ -amino group of lysine is one of the most chemically and biologically reactive side chains in proteins. Its high nucleophilicity, positive charge at physiological pH (~ 7.4), and location at the terminal end of a flexible four-carbon aliphatic chain enable it to participate in a wide range of chemical interactions and biological modifications [9]. This reactivity is fundamental not only to protein function and regulation but also to therapeutic design and metabolic control [14].

1. Chemical Reactivity and Structural Role

At pH 7.4, the ϵ -amino group remains protonated (NH_3^+) due to its pKa (~ 10.5), allowing it to interact electrostatically with negatively charged biomolecules, including DNA, RNA, phospholipids, and acidic amino acids like glutamate and aspartate. It serves as a

nucleophilic site, readily forming amide, imine (Schiff base), and acyl derivatives, especially in chemical conjugation, cross-linking, and probe development. In proteins, ϵ -amino groups are commonly involved in intramolecular salt bridges that stabilize tertiary and quaternary structures. Lysine-rich motifs, such as those in histones, play central roles in nucleosome assembly and chromatin remodelling [14].

2. Post-Translational Modifications (PTMs)

The ϵ -amino group is the primary site of several post-translational modifications that modulate protein activity, localization, and interactions. Key PTMs include: Acetylation by lysine acetyltransferases (KATs), which neutralizes the positive charge and alters DNA-binding capacity, transcriptional regulation, and enzyme activity [14]. Methylation, especially in histone tails, modulates epigenetic gene regulation. Succinylation and malonylation disrupt lysine's basicity and introduce negative charge, affecting metabolic enzymes in mitochondria [6]. Ubiquitination, where the ϵ -amino group forms iso-peptide bonds with ubiquitin, marking proteins for degradation via the proteasome pathway [4]. These modifications serve as regulatory switches and are dynamically controlled by enzymes such as deacetylases and demethylases. Aberrant lysine modification patterns are implicated in cancer, neurodegenerative diseases, and metabolic dysfunctions [9].

3. Applications in Biotechnology and Medicine

Due to its accessibility and modifiability, the ϵ -amino group is extensively used in: Site-specific bioconjugation for drug delivery systems (e.g., antibody-drug conjugates), Design of biosensors and activity probes, including electrochemical sensors that detect enzyme activity via ϵ -amino group reactivity [3], Protein labelling and purification strategies in structural biology and proteomics [6]. The ϵ -amino group of lysine functions as a versatile molecular interface, integrating structural, regulatory, and catalytic dimensions of protein biology. Its diverse reactivity underlies key physiological functions and offers numerous therapeutic and diagnostic applications [14]. Lysine plays a critical role in both primary protein structure formation through peptide bonds and in the post-translational regulation of protein function. These dual roles highlight its structural and dynamic importance in molecular biology, epigenetics, cellular signalling, and disease mechanisms. As an α -amino acid, lysine is directly involved in the formation of peptide bonds during protein biosynthesis. Its α -amino group (attached to the central carbon) reacts with the carboxyl group of the preceding amino acid during ribosomal translation, forming a covalent bond essential for building polypeptide chains [5]. This foundational role contributes to lysine's presence in structural motifs like α -helices, coiled-coils, and binding domains. Its long aliphatic side chain, terminating in the ϵ -amino group, projects outward from polypeptide backbones, offering a chemically reactive and positively charged site for subsequent modification and interaction [5]. Beyond its incorporation into the polypeptide backbone, lysine's ϵ -amino group is one of the most

frequently targeted residues for post-translational modifications (PTMs). These modifications regulate protein stability, activity, localization, and interaction networks and are crucial in cell signalling, chromatin remodelling, and metabolic control [14].

Acetylation, mediated by lysine acetyltransferases (KATs), neutralizes the positive charge of the ϵ -amino group and alters protein-DNA interaction, particularly in histone tails, influencing gene expression and epigenetic regulation [14]. Methylation of lysine, in mono-, di-, or trimethyl forms, is prevalent in histone code modifications that direct chromatin accessibility and transcriptional outcomes [5]. Succinylation and malonylation, introduce bulky, negatively charged groups that disrupt lysine's electrostatic interactions and are strongly associated with mitochondrial enzymes and metabolic flux [6]. Ubiquitination, a process where ubiquitin is covalently attached to lysine via its ϵ -amino group, is pivotal for proteasomal degradation, signal transduction, and immune responses [4]. Other lysine PTMs include biotinylation, glycation, and simulation, each influencing protein function in a context-specific manner. Alterations in lysine PTMs are associated with a variety of pathological states, including cancer, neurodegenerative disorders, metabolic syndromes, and inflammation [9]. These PTMs are now therapeutic targets, with drugs like histone deacetylase inhibitors (HDACis) and lysine-specific demethylase inhibitors being actively explored for clinical use [14]. Lysine is a structural cornerstone of peptide formation and a regulatory hotspot through PTMs, underlining its indispensable role in protein biochemistry and human health [14]. Lysine is a strictly essential amino acid in humans, meaning it must be obtained from the diet as the body lacks the enzymatic machinery to synthesize it de novo. Its metabolism and catabolism are tightly regulated processes central to nitrogen balance, energy production, and modulation of key post-translational modifications. Once absorbed, lysine participates in protein synthesis or is directed toward various catabolic pathways, especially during states of excess intake, energy demand, or specific physiological signalling. Lysine metabolism predominantly occurs in the liver and kidneys, with contributions from intestinal and muscular tissues [5]. A unique feature of lysine is that it is exclusively ketogenic, unlike most other amino acids that are glucogenic or both. Upon catabolism, lysine does not yield glucose precursors but instead produces acetyl-CoA and acetoacetyl-CoA, which can enter the tricarboxylic acid (TCA) cycle or contribute to ketone body synthesis [6].

Two principal pathways govern lysine degradation in mammals:

Saccharopine Pathway: This is the dominant lysine catabolic route in mammals. Initially, lysine is converted to saccharopine via lysine-ketoglutarate reductase (LKR), followed by its transformation into α -amino adipate semialdehyde and finally into acetyl-CoA [9]. Mutations in enzymes of this pathway, such as amino adipate-

semialdehyde dehydrogenase, are associated with hyperlysinaemia and neurological defects. Pipecolic Acid Pathway: This is a minor but significant route, especially active in the brain and peroxisomes. It converts lysine to pipecolic acid, which serves as a biomarker in several metabolic disorders, including Zellweger syndrome and peroxisomal biogenesis disorders [9]. Both pathways underscore lysine's involvement not just in energy metabolism but also in neurological health, oxidative stress response, and amino group transfer for nitrogen disposal [14]. Lysine metabolism is also linked to epigenetic modifications, as catabolic intermediates like acetyl-CoA are substrates for lysine acetylation, a central mechanism of gene regulation [14]. Additionally, recent evidence indicates that succinylation and malonylation of lysine residues in mitochondrial proteins—using intermediates from lysine catabolism impact oxidative phosphorylation, ATP production, and metabolic flux [6]. Lysine metabolism serves as a crossroads between amino acid catabolism, epigenetic regulation, and mitochondrial function, making it a critical target for metabolic and therapeutic research [9]. Here is a detailed 450-word explanation on Lysine catabolism in mammals is governed predominantly by the saccharopine pathway, which involves several key enzymes that function sequentially to convert lysine into acetoacetyl-CoA for entry into energy metabolism.

LKR is the initial enzyme in the saccharopine pathway. It catalyses the condensation of lysine with α -ketoglutarate to form saccharopine, an NADPH-dependent reaction. LKR activity is highly regulated at both the transcriptional and post-translational level. For instance, glucocorticoids and high protein intake upregulate LKR expression, while feedback inhibition by saccharopine or lysine restriction downregulates it [6]. This enzyme plays a rate-limiting role, making it a key control point in lysine metabolism. **SDH** catalyses the next step, oxidizing saccharopine into α -aminoadipate semialdehyde, which is further oxidized to α -aminoadipate. SDH often exists as a bifunctional complex with LKR in mammals, forming the LKR/SDH enzyme complex, encoded by the AASS (Aminoadipate Semialdehyde Synthase) gene. This dual functionality enables efficient channelling of intermediates and tight regulation under metabolic demand [9]. The AASS gene encodes a single polypeptide that performs the dual function of LKR and SDH. Mutations in AASS have been implicated in hyperlysinaemia, a rare metabolic disorder characterized by elevated plasma lysine levels and mild developmental delays [14]. AASS expression is modulated by dietary lysine levels, glucagon, insulin, and energy state, making it a key integrator of anabolic-catabolic balance [14]. Lysine catabolism is not uniform across tissues. Liver and kidney are the principal sites, given their rich expression of AASS and active TCA cycle for energy production [6]. However, emerging evidence suggests tissue-specific regulation:

Brain: In the central nervous system, an alternative pipecolic acid pathway operates, important for neurodevelopment and peroxisomal function. Dysfunction

here is linked with Zellweger syndrome and epileptic phenotypes.

Muscle: Skeletal muscle utilizes lysine for protein synthesis rather than catabolism, and expresses lower levels of AASS. However, under catabolic stress (e.g., starvation or exercise), lysine-derived acetyl-CoA may contribute to mitochondrial energetics.

Adipose Tissue: Plays a minor role but can metabolize lysine during states of increased energy demand, contributing to ketogenesis. The regulation of lysine catabolism is tightly controlled through enzyme expression, feedback inhibition, and tissue-specific activity, reflecting its dual role in protein synthesis and energy production [14].

Lysine metabolism is closely interconnected with mitochondrial function, contributing significantly to cellular energy production, redox balance, and metabolic regulation. The mitochondrial degradation of lysine occurs primarily through the saccharopine pathway, where lysine is initially condensed with α -ketoglutarate by lysine-ketoglutarate reductase (LKR) to form saccharopine, which is subsequently oxidized by saccharopine dehydrogenase (SDH) to generate α -aminoadipate semialdehyde [5]. This sequence, catalysed by bifunctional AASS (aminoadipic semialdehyde synthase), is localized in the mitochondrial matrix, directly linking lysine catabolism to acetyl-CoA and acetoacetate production, and ultimately feeding into the TCA cycle [6]. Furthermore, lysine residues on mitochondrial proteins are subject to numerous post-translational modifications (PTMs) such as acetylation, succinylation, malonylation, and methylation [9]. These modifications are highly dynamic and reversible, primarily regulated by mitochondrial enzymes like SIRT3, which mediate lysine deacetylation. PTMs significantly alter enzyme activity and substrate specificity. For instance, lysine succinylation can dramatically modulate mitochondrial enzymes involved in fatty acid oxidation and oxidative phosphorylation [9]. Lysine catabolism also plays a crucial role in maintaining mitochondrial redox balance. The oxidative degradation of lysine influences the NAD⁺/NADH ratio, a vital determinant of mitochondrial respiration [9]. Additionally, antioxidant enzymes such as SOD2 (superoxide dismutase 2) are modulated through lysine acetylation, which affects cellular reactive oxygen species (ROS) levels and oxidative stress responses [9]. In broader metabolic terms, lysine catabolism intersects with pathways involving glutamate, tryptophan, and one-carbon metabolism, all of which converge on mitochondrial networks that regulate nucleotide synthesis, epigenetic modification, and cellular repair processes [9]. Its catabolites are also precursors for ketone body production and urea cycle intermediates, further integrating lysine into mitochondrial and hepatic metabolic homeostasis [6]. Genetic mutations affecting AASS or its associated enzymes result in hyperlysinaemia, a rare metabolic disorder characterized by elevated lysine levels in plasma and cerebrospinal fluid, which can impair neurodevelopment and cognitive function [10]. Thus, mitochondrial lysine metabolism is not only central to

energy and redox balance but also has clear implications in neurological and metabolic diseases. Current research also highlights the therapeutic relevance of lysine metabolism. Modulating lysine-related PTMs offers potential strategies for mitochondrial-targeted therapies in conditions such as metabolic syndrome, diabetes, and neurodegeneration [9]. Understanding this metabolic axis may therefore unlock novel clinical interventions and biomarkers of mitochondrial health.

Disorders Related to Lysine Metabolism

Lysine metabolism is a tightly regulated process, and disruptions in its enzymatic pathways can lead to a spectrum of rare but clinically significant metabolic disorders. These conditions typically stem from mutations in genes encoding key lysine-catabolizing enzymes, particularly those involved in the saccharopine pathway, such as amino adipic semialdehyde synthase (AASS), Lysine-ketoglutarate reductase (LKR), and saccharopine dehydrogenase (SDH) [6].

Hyperlysinaemia

One of the most studied disorders is familial hyperlysinaemia, a rare autosomal recessive condition caused by mutations in the AASS gene. The disorder is characterized by elevated concentrations of lysine in blood and urine. Although many individuals with hyperlysinaemia are asymptomatic, some may experience developmental delays, hypotonia, seizures, and intellectual disability in more severe phenotypes [10]. The lack of consistent clinical presentation suggests variable expressivity and possibly the involvement of modifier genes or nutritional factors [10].

Pyridoxine-Dependent Epilepsy (PDE)

Another major lysine-related disorder is pyridoxine-dependent epilepsy (PDE), which arises from mutations in the ALDH7A1 gene, encoding α -amino adipic semialdehyde dehydrogenase an enzyme responsible for metabolizing α -AASA, a lysine catabolite [10]. Accumulation of α -AASA and pipercolic acid leads to inactivation of pyridoxal phosphate (PLP), a cofactor critical for neurotransmitter metabolism. PDE typically presents in neonates with intractable seizures and requires lifelong pyridoxine (vitamin B6) supplementation. Early diagnosis through urinary metabolite screening or genetic testing significantly improves outcomes [10].

Glutaric Acidaemia Type I (GA-I)

Although not a primary defect of lysine degradation, glutaric acidaemia type I is closely related, as it involves the metabolism of lysine, hydroxylysine, and tryptophan. It results from a deficiency in glutaryl-CoA dehydrogenase (GCDH). GA-I is marked by accumulation of glutaric acid and 3-hydroxyglutaric acid, leading to encephalopathy, macrocephaly, and movement disorders [10]. Dietary restriction of lysine and tryptophan is a mainstay of therapy, along with carnitine supplementation and emergency protocols during illness [10].

Other Emerging Disorders

Recent studies also suggest that defective lysine post-translational modifications (PTMs) may underlie or exacerbate neurodegenerative and metabolic diseases. Abnormal lysine acetylation, methylation, and succinylation of mitochondrial proteins have been implicated in Parkinson's disease, Alzheimer's disease, and metabolic syndrome [9]. Such dysregulations interfere with mitochondrial respiration, oxidative stress handling, and apoptosis pathways [9]. Moreover, some lysine metabolic intermediates such as N-hydroxy-pipercolic acid have been found to influence plant defence and may have analogy in humans involved in immune signalling, though their pathophysiological roles are still under investigation [13]. Diagnosis of lysine metabolism disorders typically relies on metabolite profiling, enzyme activity assays, and genetic sequencing. Emerging mass spectrometry techniques and metabolomics platforms are improving the sensitivity of early detection. Therapeutic interventions range from dietary management and vitamin supplementation to gene therapy, which is under experimental development for PDE and hyperlysinaemia. Understanding the molecular underpinnings of lysine-related disorders is crucial not only for rare disease management but also for unravelling broader metabolic and neurodevelopmental mechanisms.

Physiological and Cellular Functions

Lysine, an essential amino acid, plays a central role in protein synthesis and organismal growth, particularly during developmental and anabolic phases. As one of the nine essential amino acids, lysine must be obtained from dietary sources, given that humans lack the enzymatic machinery for its endogenous synthesis. It is involved in peptide bond formation during ribosomal translation, where its positively charged side chain at physiological pH promotes interactions with negatively charged nucleic acids and other acidic residues, thus contributing to protein structure and stability [7]. Lysine is particularly vital for growing children, adolescents, pregnant women, and individuals undergoing tissue repair. Several studies confirm its involvement in growth hormone regulation and insulin signalling, both of which are crucial in cell proliferation and musculoskeletal development [9]. A study by Hussain et al. (2024) demonstrated that lysine supplementation in children with protein-deficient diets enhanced height-for-age and weight-for-age scores, underscoring its relevance in clinical nutrition and child development [1]. Furthermore, lysine acts as a precursor for the biosynthesis of carnitine, a compound required for the transport of long-chain fatty acids into mitochondria for β -oxidation. This metabolic integration supports muscle energy homeostasis, which is essential for physical development and endurance, particularly in paediatric and athletic populations [9]. In the realm of molecular growth signals, lysine residues in histones are targets for acetylation and methylation, influencing chromatin dynamics and transcription of growth-related genes [9]. These epigenetic modifications determine gene accessibility and expression, thereby linking lysine availability to growth regulation at the transcriptional level. Dietary deficiency of lysine has been

associated with impaired growth, immune dysfunction, and poor wound healing, particularly in populations relying heavily on lysine-poor cereals such as maize and rice [7]. This concern has driven biofortification efforts, such as genetic enhancement of wheat and corn with higher lysine content, to address nutritional imbalances in vulnerable populations [12]. In animal models, lysine deficiency leads to reduced muscle protein synthesis, altered hormonal profiles, and stunted skeletal development [10]. Conversely, adequate lysine intake has shown to enhance protein retention and lean body mass, particularly when combined with exercise and sufficient caloric intake [9].

Lysine plays a pivotal role in collagen biosynthesis and tissue repair, processes central to wound healing and connective tissue integrity. Collagen, the most abundant structural protein in the extracellular matrix (ECM), requires lysine not only as a structural component but also as a precursor for post-translational modifications that stabilize the collagen triple helix [9]. During collagen synthesis, lysine residues in procollagen undergo hydroxylation by lysylhydroxylase, forming hydroxylysine. This modification is critical for intermolecular crosslinking, which imparts tensile strength to the collagen fibres [5]. The hydroxylation process also depends on adequate vitamin C, iron, and molecular oxygen, but without lysine, collagen cannot form stable fibrils, resulting in fragile tissues and impaired wound healing [9]. Lysine also facilitates collagen crosslinking through the enzyme lysyl oxidase, which catalyses oxidative deamination of specific lysine and hydroxylysine residues. These crosslinks are essential for forming insoluble, mature collagen fibrils that contribute to wound tensile strength and tissue remodelling [6]. In the context of wound healing, lysine serves multiple functions. It is a substrate for protein synthesis, aiding the formation of new tissues, skin cells, and blood vessels during the proliferative phase of healing [9]. Furthermore, it exhibits chemoattractant properties, enhancing the migration of fibroblasts and macrophages to the wound site, which are key players in tissue regeneration and immune defence [10].

Experimental evidence supports the importance of lysine in tissue repair. In vitro studies have shown that lysine supplementation enhances fibroblast proliferation, collagen deposition, and angiogenesis, thereby accelerating wound closure [6]. In animal models, lysine-deficient diets result in delayed epithelialization, reduced granulation tissue formation, and weaker scar strength [9]. Lysine's indirect effects also support healing. It assists in calcium absorption and enzyme activity required for skin matrix remodelling, and through carnitine synthesis, it contributes to cellular energy availability at the wound site [9]. Clinically, lysine is used as a topical agent or oral supplement in individuals with delayed wound healing, especially in diabetic ulcers or postoperative recovery scenarios. Its use has also shown promise in managing pressure ulcers and skin graft

healing, especially when combined with other essential nutrients like zinc, arginine, and vitamin C [12].

Lysine, as an essential amino acid, contributes significantly to the regulation and enhancement of immune responses, particularly through antibody production, modulation of immune cell function, and viral suppression mechanisms. These roles have been recognized in both nutritional immunology and clinical virology research. In the adaptive immune system, lysine is crucial for immunoglobulin (antibody) biosynthesis, which requires high rates of protein turnover and amino acid availability. B lymphocytes, responsible for antibody production, depend on adequate lysine to sustain ribosomal activity and immunoglobulin gene expression during clonal expansion and plasma cell differentiation [9]. Several studies have demonstrated that lysine supplementation improves humoral immune responses in animals and humans, especially under conditions of stress, infection, or malnutrition [2]. Lysine's influence on innate immunity is also notable. It facilitates macrophage and neutrophil recruitment, enhances phagocytosis, and boosts the secretion of pro-inflammatory cytokines during early pathogen detection. This immunomodulatory effect is especially critical in maintaining mucosal immunity and protecting barrier surfaces from microbial invasion. Beyond its general immunological roles, lysine has shown specific efficacy in viral suppression, especially against herpes simplex virus (HSV). Lysine and arginine share common transport mechanisms and metabolic pathways. Because arginine is required for viral replication, lysine competes with arginine uptake and incorporation, thereby inhibiting HSV replication [11]. Multiple clinical trials and meta-analyses have shown that lysine supplementation reduces the frequency, severity, and healing time of herpes labialis and genitalis episodes, making it a widely used adjunct therapy for recurrent HSV infections [12]. Furthermore, lysine modulates viral pathogenesis by altering host cell methylation and acetylation patterns, interfering with viral transcription factors. In vitro studies confirm that increased extracellular lysine reduces viral titers, promotes apoptosis of infected cells, and may enhance the efficacy of antiviral medications [11]. These findings have prompted exploration of lysine-based therapeutic strategies not only for herpes but also for other enveloped viruses, including influenza and corona viruses [11]. Recent research also indicates that lysine supplementation may help maintain gut-associated lymphoid tissue (GALT) function, supporting mucosal immunity through the regulation of gut microbiota and epithelial integrity, particularly under protein-deficient or inflammatory conditions [9]. Lysine, an essential amino acid, has emerged as a key player in neuroendocrine regulation due to its ability to modulate stress and mood-related hormones, particularly cortisol and serotonin.

1. Lysine and Cortisol Regulation

Cortisol, the primary stress hormone, is released by the adrenal cortex in response to hypothalamic-pituitary-adrenal (HPA) axis activation. Elevated cortisol levels are

commonly associated with chronic stress, anxiety, immune suppression, and metabolic dysfunction. Lysine has been shown to attenuate the stress response by downregulating cortisol secretion. Clinical studies have demonstrated that oral lysine supplementation (especially when combined with arginine) significantly lowers cortisol levels in both animal models and humans under psychological stress [2]. Lysine is believed to act by inhibiting serotonin receptor 4 (5-HT₄) and partially modulating the activity of GABAergic neurotransmission, which helps to reduce excitatory responses in the central nervous system. This results in dampened HPA axis activity and lower systemic cortisol output.

2. Lysine and Serotonin Modulation

Serotonin (5-hydroxytryptamine or 5-HT) is a neurotransmitter involved in regulating mood, sleep, appetite, and cognition. Lysine has shown the ability to modulate serotonin receptor activity, especially 5-HT₄, as mentioned earlier. This modulation helps enhance serotonergic tone, promoting anxiolytic and antidepressant effects without disrupting normal neurotransmission [7]. In stress-related disorders like anxiety and depression, where serotonin signalling is impaired, lysine helps by stabilizing emotional responses and improving emotional regulation. This function aligns lysine's role not only as a structural amino acid but also as a functional modulator of neurotransmitter systems.

Lysine plays a vital role in maintaining calcium homeostasis and enhancing bone health, primarily through its synergistic interaction with vitamin D and its influence on calcium absorption, retention, and bone matrix formation. Lysine enhances intestinal absorption of calcium by improving the efficiency of calcium-binding proteins and facilitating its uptake across the gut epithelium [2]. This function complements the action of vitamin D, which increases the expression of calcium transporters such as TRPV6 and calbindin-D9k. Together, lysine and vitamin D ensure optimal calcium bioavailability for skeletal development and remodelling [4]. Furthermore, lysine is believed to decrease calcium excretion through the kidneys, thereby preserving systemic calcium levels. This conservation mechanism is especially critical in populations at risk for osteoporosis or calcium-deficiency disorders [5]. Lysine also promotes the production of collagen, a major component of the bone extracellular matrix, and supports cross-linking of collagen fibres necessary for bone strength and integrity [7]. In bone cells, lysine indirectly supports osteoblast proliferation and mineralization processes. Its interaction with growth factors such as insulin-like growth factor 1 (IGF-1) further promotes bone anabolism [8]. Clinical and experimental studies show that lysine supplementation, particularly in combination with vitamin D and calcium, leads to increased bone mineral density and improved bone turnover profiles in both elderly and postmenopausal individuals [10]. Overall, lysine acts as a modulator of calcium kinetics and a critical cofactor in the anabolic pathways of bone metabolism. It complements the physiological functions of vitamin D, making it essential

in therapeutic strategies targeting osteoporosis, bone repair, and growth.

Lysine, an essential amino acid, plays a notable role in **modulating neurological function**, particularly through its **anxiolytic (anxiety-reducing) properties**. Emerging evidence from both clinical and experimental studies indicates that lysine can influence brain chemistry by modulating neurotransmitters and stress hormones [7]. One of the primary mechanisms by which lysine exhibits anxiolytic effects is through its interaction with the **serotonin and GABA systems**, which are centrally involved in the regulation of mood and anxiety. Lysine competes with **arginine** at the cellular level, affecting nitric oxide pathways, which have been linked to stress responses and cortical excitability [10]. This balance appears to reduce the neurochemical signals associated with heightened stress and anxiety. A pivotal study by Vorobyov et al. (2019) demonstrated that L-lysine administration influenced **selective brain activity**, especially in the **hippocampus and amygdala**, regions known for their roles in emotion processing [7]. Their findings highlighted lysine's ability to attenuate **pain-induced behavioural changes** and anxiety-like responses in rats, suggesting its modulation of neurotransmission in stress circuits. Furthermore, clinical trials in human populations have shown that dietary lysine, particularly when combined with arginine or consumed in lysine-rich diets (e.g., cereals fortified with lysine), leads to **reduced cortisol levels and improved psychological stress resilience** [11]. These effects are especially pronounced in populations with low baseline lysine intake, such as those in developing countries with cereal-based diets. Interestingly, lysine also has a role in stabilizing **hormonal fluctuations** that accompany stress, including the suppression of **adrenocorticotrophic hormone (ACTH)** and subsequent **cortisol release**, offering a biochemical basis for its anxiolytic action [9]. Lysine's anxiolytic potential is supported by its role in neurotransmitter modulation, hormonal regulation, and region-specific brain effects. These findings underscore the therapeutic promise of lysine-enriched nutrition in managing stress and anxiety disorders, particularly in vulnerable or nutritionally at-risk populations.

Lysine in Epigenetic and Regulatory Mechanisms

Lysine residues on histone proteins are central to epigenetic regulation through post-translational modifications (PTMs), particularly methylation and acetylation. These modifications modulate chromatin architecture, thereby influencing gene transcription, DNA replication, and repair processes. The ϵ -amino group of lysine is uniquely reactive, serving as a primary site for these regulatory modifications [9]. Histone acetylation involves the enzymatic transfer of an acetyl group from acetyl-CoA to the ϵ -amino group of lysine residues, primarily mediated by histone acetyltransferases (HATs). This neutralizes the positive charge on lysine, weakening its interaction with the negatively charged DNA backbone. Consequently, chromatin adopts a relaxed, transcriptionally active configuration (euchromatin).

Notably, acetylation at histone H3 lysine 9 (H3K9ac) and H3K14ac has been extensively associated with active gene promoters [5]. This modification is dynamically regulated by histone deacetylases (HDACs), which remove acetyl groups, leading to chromatin condensation and transcriptional repression. Disruption in the balance of HAT and HDAC activity has been linked to oncogenesis, inflammatory diseases, and neurodevelopmental disorders [9]. Histone lysine methylation is catalysed by lysine methyltransferases (KMTs), using S-adenosylmethionine (SAM) as a methyl group donor. Unlike acetylation, methylation does not affect the charge state of lysine but instead alters the chromatin landscape by serving as a docking site for chromatin remodels and reader proteins. Depending on the degree (mono-, di-, or tri-) and site of methylation, the functional outcome varies significantly. For instance, tri-methylation of H3K4 (H3K4me3) is a hallmark of transcriptional activation, whereas tri-methylation at H3K9 (H3K9me3) or H3K27 (H3K27me3) is generally associated with heterochromatin formation and gene repression [13]. These marks are essential for lineage specification, cellular differentiation, and maintenance of genome integrity. Emerging research suggests that histone lysine modifications are intricately linked to the cell's metabolic state. Availability of substrates such as SAM and acetyl-CoA ties lysine modification dynamics to glucose, lipid, and amino acid metabolism [9]. Therefore, lysine not only serves as a structural and functional component in histone regulation but also as a mediator connecting metabolic flux to epigenomic outcomes. Aberrant regulation of lysine PTMs has been implicated in various pathologies, including cancer, metabolic syndromes, and neurodegenerative disorders. Understanding these modifications expands the potential for developing epigenetic therapies targeting lysine-modifying enzymes. In particular, HDAC inhibitors and KMT antagonists are being actively explored as therapeutic agents in clinical trials.

Lysine residues in histone proteins are key modulators of epigenetic regulation, primarily through post-translational modifications (PTMs) such as methylation, acetylation, ubiquitination, and simulation. These chemical changes to lysine residues affect chromatin structure and gene transcription by altering the interaction between DNA and histone proteins or by recruiting regulatory complexes [14]. Histone lysine acetylation, catalysed by histone acetyltransferases (HATs), neutralizes the positive charge on lysine side chains, leading to chromatin decondensation and increased transcriptional accessibility. Acetylated histones are typically associated with transcriptionally active regions of the genome. Histone deacetylases (HDACs) reverse this modification, leading to transcriptional repression [10]. Lysine can be mono-, di-, or tri-methylated by lysine methyltransferases (KMTs), such as SUV39H1 and SETD1, and removed by lysine demethylases (KDMs) like LSD1 and JMJD family enzymes. Unlike acetylation, methylation does not affect charge but instead serves as a platform for the binding of transcriptional regulators. The effect of methylation is site-specific: for instance, H3K4me3 is linked to gene

activation, whereas H3K9me3 and H3K27me3 are markers of gene repression [14]. Lysine modifications serve as metabolic sensors. For example, acetyl-CoA is the donor for acetylation, and S-adenosylmethionine (SAM) provides the methyl group for methylation. Thus, nutrient availability and cellular energy status can directly influence gene expression via lysine PTMs [5][9]. Aberrant regulation of lysine methylation and acetylation is implicated in cancer, inflammation, neurodegeneration, and metabolic disorders. Therapeutic targeting of these processes such as through HDAC inhibitors (e.g., vorinostat) and KMT inhibitors is a growing area of epigenetic drug development [14]. Lysine-mediated epigenetic regulation exemplifies the link between gene expression, cellular metabolism, and disease. Understanding the diverse roles of lysine PTMs provides a foundation for novel therapies aimed at restoring epigenetic balance.

Lysine plays a multifaceted role in oncogenesis and cell cycle regulation through its involvement in protein architecture and post-translational modifications (PTMs), notably histone acetylation, methylation, ubiquitination, and SUMOylation. As a critical substrate for histone-modifying enzymes, lysine residues on histone tails—such as H3K4, H3K9, and H3K27—undergo site-specific methylation and acetylation that influence chromatin accessibility and transcriptional outcomes. Aberrations in these modifications are implicated in epigenetic reprogramming events associated with malignant transformation and tumour progression [12]. Histone acetylation, mediated by histone acetyltransferases (HATs), typically correlates with transcriptional activation by reducing nucleosome compaction. Conversely, histone deacetylases (HDACs) remove acetyl groups from lysine residues, thereby restoring chromatin condensation and repressing gene expression. Dysregulation of HDACs, commonly observed in haematological malignancies and solid tumours, contributes to oncogene overexpression and resistance to apoptosis. Several HDAC inhibitors, including Vorinostat and Romidepsin, have received FDA approval for clinical use in cutaneous T-cell lymphoma and other cancers [13].

Additionally, non-histone proteins, such as the tumour suppressor p53 and the retinoblastoma (Rb) protein, are also regulated by lysine-specific modifications. Acetylation of lysine residues on p53 (e.g., K373 and K382) enhances its DNA-binding capacity and transcriptional activity, whereas ubiquitination at the same sites promotes proteasomal degradation. The dynamic interplay of these PTMs determines cell cycle arrest, DNA repair fidelity, and apoptotic outcomes under genotoxic stress [10]. Moreover, lysine-derived metabolites, such as α -amino adipate from its catabolic degradation via the saccharopine pathway, may intersect with metabolic signalling nodes that affect redox homeostasis and epigenomic stability—two hallmarks of cancer cell survival and adaptability [9]. Emerging data also suggest that intracellular lysine levels modulate the mechanistic target of rapamycin complex1 (mTORC1) pathway,

thereby linking amino acid sensing to cell growth, biosynthetic capacity, and proliferation [6]. Lysine acts as a biochemical nexus connecting epigenetic regulation, protein stability, and metabolic signalling within cancerous cells. Targeting lysine-modifying enzymes or manipulating lysine availability represents a promising therapeutic avenue, supported by growing preclinical and clinical evidence [13]. Lysine plays a crucial regulatory role in metabolic reprogramming by modulating pathways central to energy homeostasis, particularly glucose and lipid metabolism. This modulation occurs both directly—via post-translational modifications (PTMs) of metabolic enzymes—and indirectly—through its metabolites and interaction with nutrient-sensing pathways.

1. Regulation of Glucose Metabolism

Lysine influences glucose metabolism via the acetylation of key glycolytic and gluconeogenic enzymes. Acetylation of lysine residues on enzymes such as hexokinase 2 (HK2), pyruvate kinase M2 (PKM2), and phosphoenolpyruvate carboxykinase (PEPCK) can alter their enzymatic activity, localization, and interaction with other proteins [1]. This post-translational control is vital in cancer and immune cells, where metabolic reprogramming (i.e., the Warburg effect) prioritizes aerobic glycolysis to fuel rapid proliferation [2]. Moreover, lysine-derived α -amino adipic acid has been identified as a biomarker associated with insulin resistance and type 2 diabetes, suggesting that disturbances in lysine metabolism impact glucose tolerance and insulin sensitivity [3].

2. Lipid Metabolism and Mitochondrial β -Oxidation

Lysine acetylation and crotonylation extend into the realm of lipid metabolism. Mitochondrial enzymes involved in fatty acid β -oxidation (e.g., long-chain acyl-CoA dehydrogenase, LCAD) are regulated by reversible lysine acetylation. SIRT3, a mitochondrial NAD⁺-dependent deacetylase, targets these enzymes to maintain lipid catabolism and prevent lipid accumulation under metabolic stress [4]. Additionally, lysine methylation of transcription factors like PPAR γ and SREBP-1c alters the transcriptional landscape of lipogenic genes, impacting adipogenesis and hepatic lipid storage [5].

3. Integration with Nutrient Sensing Pathways

Lysine acylation intersects with key signalling pathways such as AMPK and mTOR, which orchestrate anabolic and catabolic processes based on nutrient availability. Acetylation of TSC2 or LKB1 can influence mTORC1 signalling, linking lysine acetylation with broader cellular energy status regulation [6].

4. Disease Implications

Disruption in lysine-mediated regulation of glucose and lipid metabolism is implicated in metabolic syndromes, including obesity, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD) [7]. Furthermore, cancer cells exploit lysine-driven epigenetic and metabolic pathways to meet their biosynthetic and energetic demands, making lysine-modifying enzymes attractive therapeutic targets [8].

4. Safety and Drug Interactions

Lysine is generally safe and well-tolerated. However, its interaction with calcium absorption should be considered, particularly in hypercalcaemic patients. It may enhance the effect of antiviral drugs like acyclovir, though co-administration should be evaluated case by case. Osteoporosis, a metabolic bone disease characterized by low bone mass and deteriorated bone microarchitecture, is a growing global concern, particularly among postmenopausal women and the elderly. Nutritional interventions have been increasingly recognized as complementary strategies in its management. Among amino acids, **lysine plays a pivotal role in calcium metabolism and bone tissue remodelling**, often in synergy with vitamin D and other cofactors.

2. Clinical Evidence Supporting Lysine Supplementation

3. Synergy with Vitamin D and Calcium

Lysine potentiates vitamin D₃'s role in promoting calcium absorption by:

This synergy is especially beneficial in populations with compromised bone health, such as postmenopausal women, individuals with chronic inflammatory conditions, or elderly patients with impaired nutrient absorption [10].

4. Therapeutic Applications and Recommendations

These combinations have shown favourable effects on bone turnover markers (e.g., ALP, CTX) and radiologically assessed BMD [13]. Lysine is emerging as a key player in bone health through multifaceted mechanisms involving mineral retention, collagen stabilization, and osteoblast stimulation. Its inclusion in osteoprotective regimens may help bridge nutritional gaps in aging populations and support skeletal health when combined with conventional osteoporosis therapies. Lysine, beyond its classical nutritional roles, has garnered attention for its **neuroregulatory functions**, especially in the modulation of anxiety and stress responses. These effects are mediated primarily through **interactions with neurotransmitter systems**, particularly **serotonin** and **gamma-aminobutyric acid (GABA)**, as well as via its influence on **hypothalamic–pituitary–adrenal (HPA) axis activity**.

3. Dietary Relevance and Public Health Implications

In populations with **low protein or plant-based diets**, lysine deficiency may exacerbate susceptibility to stress-related disorders. Thus, **lysine fortification or supplementation** may offer preventive benefits.

5. Nutritional Strategy

Lysine's role in **collagen maturation, immune defence, and vascular remodelling** underscores its importance in wound healing and post-surgical recovery. Its supplementation presents a safe, cost-effective adjunct to standard medical care, particularly in populations at high risk for delayed tissue repair. Lysine is an essential amino acid vital for human health and is increasingly recognized for its critical role in parenteral nutrition (PN), particularly in patients unable to meet nutritional requirements via the

enteral route. In clinical settings, lysine supplementation in PN formulations has demonstrated positive impacts on nitrogen balance, protein synthesis, immune modulation, and tissue repair, which are indispensable during critical illness, postoperative recovery, and prolonged hospitalization [10]. Lysine plays a central role in maintaining nitrogen equilibrium and enhancing lean body mass preservation in hypercatabolic states, such as sepsis and trauma [2]. It is a precursor to carnitine biosynthesis, which is essential for mitochondrial fatty acid oxidation and cellular energy homeostasis [6]. Its anabolic potential contributes to improved wound healing outcomes, collagen formation, and enhanced recovery post-surgery, particularly when co-administered with arginine and other essential amino acids [5]. Moreover, lysine facilitates calcium absorption and bone mineral retention, supporting skeletal health in immobilized or elderly patients receiving long-term PN [10]. Its role in immunological functions—especially in immunoglobulin biosynthesis and modulation of antiviral responses—adds further value to lysine-enriched formulations, particularly in immunocompromised individuals [8]. Pharmacokinetic studies have guided lysine dosing in PN, with recommendations ranging from 80 to 100 mg/kg/day for adults and up to 160 mg/kg/day in neonates, depending on metabolic demands and disease severity [1]. Importantly, lysine must be balanced with other branched-chain and essential amino acids to avoid metabolic imbalances and ensure optimal utilization. Lysine, an essential amino acid, cannot be synthesized endogenously and must be obtained through diet, making several populations susceptible to its deficiency. These include malnourished children, individuals on plant-based diets, and the elderly, where intake or bioavailability may be insufficient [17].

1. Malnourished Children

Protein-energy malnutrition (PEM), especially in low-resource settings, often results in lysine deficiency among children, leading to impaired growth, weakened immunity, and cognitive deficits [25]. Lysine is critical for the synthesis of growth hormone, collagen, and immune defence mechanisms—its absence exacerbates the manifestations of kwashiorkor and marasmus [25]. Supplementation has shown promise in improving linear growth and immune markers in paediatric populations.

2. Vegans and Vegetarians

Lysine is one of the most limiting amino acids in plant-based diets, especially those relying on cereals such as wheat, rice, or maize [21]. Although legumes provide moderate lysine levels, their bioavailability can be hindered by anti-nutritional factors such as phytates and tannins [24]. Unbalanced vegan or vegetarian diets may predispose individuals to chronic lysine insufficiency, with effects ranging from fatigue and poor immune function to delayed wound healing [16]. Targeted lysine fortification or supplementation may be warranted in these populations [21].

3. Elderly Individuals

With age, protein intake often declines, and absorption efficiency drops due to gastrointestinal and metabolic

changes [26]. The elderly, particularly postmenopausal women, are at higher risk of osteoporosis, where lysine plays a role in calcium absorption and bone matrix stability [27]. Moreover, sarcopenia—a hallmark of aging—is worsened by lysine deficiency due to its essential role in muscle protein synthesis [23]. Supplementation in elderly men has been shown to stimulate muscle anabolism effectively [23].

Implications for Public Health and Policy

Nutritional interventions must prioritize at-risk groups. In children, lysine-enriched school feeding programs can combat stunting. For vegans and vegetarians, promoting lysine-rich grains (e.g., quinoa) and plant-based fortified products is essential. Geriatric care should include routine evaluation of amino acid intake and consider lysine supplementation to prevent muscle loss and bone demineralization [27].

Lysine exhibits **biochemical antagonism** with L-arginine, particularly due to shared absorption and transport mechanisms across cellular membranes, including cationic amino acid transporters (CATs) [16]. This antagonistic relationship has important clinical implications, especially in **viral infections**, where lysine supplementation has been shown to suppress herpes simplex virus (HSV) replication by counteracting arginine-dependent viral proliferation [12]. The **lysine-to-arginine ratio** modulates immune function and nitric oxide (NO) synthesis. Arginine is the primary substrate for NO production via nitric oxide synthase (NOS), whereas excess lysine can **reduce arginine bioavailability**, potentially affecting vascular tone and inflammatory responses [16]. In protein metabolism, lysine also interacts with threonine and tryptophan in terms of limiting amino acid patterns in cereals and legumes [21]. These interactions are crucial in developing **balanced protein formulations**, particularly for plant-based diets and therapeutic nutrition, as imbalances may hinder protein synthesis or induce amino acid imbalances [24].

Currently, **no official Tolerable Upper Intake Level (UL)** for lysine has been established by bodies such as the WHO or EFSA due to its generally low toxicity profile and efficient renal excretion [15]. However, **excessive supplementation** (e.g., >6 g/day in adults) has occasionally been associated with **gastrointestinal distress, nausea, and abdominal cramps**, though these effects are transient and rare [10]. In clinical studies, doses ranging from **1–6 g/day** have been deemed **safe for therapeutic use** in adults, particularly in the context of HSV treatment and muscle metabolism, with no significant hepatotoxicity or renal adverse effects reported [23]. Nonetheless, caution is warranted in individuals with **renal impairment**, where amino acid excretion may be compromised [22]. Given the wide safety margin observed in both animal and human studies, lysine is considered **non-toxic at dietary and modest supplemental levels**, though further research is necessary to evaluate long-term effects of high-dose supplementation in vulnerable populations [19].

Lysine supplementation, while generally regarded as safe within therapeutic ranges, may elicit **adverse effects** under certain physiological or pathological conditions. **Gastrointestinal (GI) disturbances** are the most frequently reported side effects, especially at high doses (typically >6 g/day in adults). Documented symptoms include **nausea, diarrhoea, abdominal cramping, and flatulence**, often resolving upon dose reduction or discontinuation [2], [10]. Mechanistically, GI effects may result from **osmotic load** due to unabsorbed lysine in the intestinal lumen or from transient imbalances in amino acid absorption kinetics. This is especially relevant when lysine is co-administered with other cationic amino acids (e.g., arginine), which may compete for intestinal transporters [21]. In contrast, **nephrotoxicity** related to lysine intake is rare but has been **observed in preclinical models** where chronic high-dose lysine led to **renal tubular vacuolization** and altered glomerular filtration rates. These findings were primarily seen in rodent studies under pharmacologic dosing and are **not typically observed in healthy human subjects** consuming lysine within the recommended upper limit [19]. However, **individuals with pre-existing renal impairment**—such as those with chronic kidney disease (CKD), nephrotic syndrome, or diabetic nephropathy—may be **vulnerable to aminoacidic overload**, and **lysine supplementation in such populations should be approached cautiously** [22]. Renal clearance is a critical determinant of plasma lysine homeostasis, and excessive accumulation may exacerbate uraemia or aminoaciduria. Despite isolated reports of renal stress in vulnerable populations, **no consistent evidence exists in human clinical trials to support routine nephrotoxicity** from lysine at therapeutic or dietary doses [23]. Nevertheless, long-term safety data remain limited, highlighting the need for **renal function monitoring** in patients on high-dose or chronic lysine therapy.

Recent Advances and Future Directions

Lysine, owing to its bifunctional chemical structure (an α -amino group and an ϵ -amino side chain), serves as a versatile scaffold for the synthesis of **biodegradable polymers and functional nanomaterials**. Its natural biocompatibility, water solubility, and capacity for **post-synthetic functionalization** make it ideal for use in **drug delivery, tissue engineering, and nanomedicine** [6]. Lysine-based nanocarriers—such as **lysine-functionalized dendrimers, liposomes, and polymeric micelles** are increasingly explored as **targeted delivery systems** for anticancer and antiviral agents. For instance, lysine residues enhance **surface binding affinity to negatively charged cellular membranes**, improving intracellular uptake [6]. Furthermore, **lysine-modified gold or silica nanoparticles** have been engineered for **pH-responsive drug release**, benefiting from the protonation behaviour of the ϵ -amino group. Lysine can also be polymerized or grafted onto poly(lactic acid), polyethylene glycol (PEG), or chitosan backbones, conferring **cell-adhesive properties, improved biodegradability, and enhanced mechanical strength** for

tissue scaffolding [6], [20]. Through enzymatic or chemical condensation, lysine is used to create **poly-L-lysine (PLL)** and **ϵ -polylysine (ϵ -PL)**. PLL has found wide applications as a **non-viral gene delivery vehicle** due to its **cationic charge density** and low immunogenicity [6], [7]. Meanwhile, ϵ -PL is an FDA-approved **food-grade antimicrobial biopolymer**, known for its **broad-spectrum antibacterial activity** and resistance to proteolytic degradation [20]. These biopolymers can also be modified with **functional peptides, growth factors, or targeting ligands**, enabling **customized biomedical applications** such as neural regeneration, wound healing, and mucosal drug delivery [3]. From an environmental perspective, lysine-derived bioplastics offer a **green alternative** to petroleum-based materials. Biodegradable lysine-polymer composites are being tested for use in **agricultural films, bioresorbable implants, and smart packaging materials** [20], [24]. The integration of lysine moieties into smart nanomaterials also holds promise for **biosensing platforms and theragnostic**, particularly in oncology and metabolic diagnostics [24]. Lysine is an essential amino acid that is **limiting in most cereal-based diets**, particularly in developing regions where **maize, wheat, and rice** constitute dietary staples [25]. Unlike animal proteins, plant-derived proteins often fail to meet human lysine requirements, especially in **malnourished children, the elderly, and vegetarians** [20]. Genetic biofortification through **genetically modified (GM) crops** offers a sustainable, large-scale approach to address this lysine deficiency. Conventional breeding methods have shown limited success in enhancing lysine content due to **metabolic feedback inhibition** of lysine biosynthesis in plants. Genetic engineering overcomes these constraints by introducing **feedback-insensitive variants of key enzymes**, particularly **dihydrodipicolinate synthase (DHPS)** from *Corynebacterium glutamicum* into cereals [15]. This leads to **enhanced flux through the lysine biosynthetic pathway**, thereby increasing free lysine accumulation in seeds. In maize, the development of **Quality Protein Maize (QPM)** achieved via both conventional and transgenic approaches—has resulted in up to **two-fold increases in lysine and tryptophan levels** in the kernel, significantly improving its nutritional profile [15, 25]. Similarly, **rice and wheat varieties expressing bacterial or modified plant DHPS** show increased lysine content without compromising agronomic performance [21]. The **World Health Organization (WHO)** and **UNICEF** emphasize lysine deficiency as a key contributor to childhood stunting, immune dysfunction, and impaired cognitive development [25]. GM lysine-rich crops, when deployed in **school feeding programs and humanitarian food supplies**, can directly enhance **dietary amino acid adequacy** in vulnerable populations. Additionally, lysine-biofortified crops align with the **United Nations Sustainable Development Goals (SDGs)** by addressing **hidden hunger**, reducing reliance on costly supplements, and promoting agricultural sustainability [25]. Safety assessments of GM lysine-enriched crops have shown **no adverse effects** on growth,

metabolism, or allergenicity in animal models and clinical settings [24]. However, **consumer acceptance, biosafety regulations, and trade policies** remain major challenges for widespread adoption, especially in regions with strict GMO legislation [24]. L-lysine plays a critical role in muscle protein synthesis, immune function, tissue repair, and calcium absorption, making it an essential component of sports and clinical nutrition formulations. As an indispensable amino acid, lysine must be obtained exogenously, and its adequacy is especially crucial in populations with elevated physiological demands, such as athletes, postoperative patients, and the elderly [23].

In athletic populations, lysine supports collagen formation, which is vital for tendons, ligaments, and cartilage, reducing injury risk and accelerating recovery [8]. It is also required for optimal muscle protein turnover, working synergistically with other branched-chain amino acids (BCAAs) and arginine to promote lean body mass [23]. Kriengsinyos et al. demonstrated that lysine supplementation significantly increased muscle protein synthesis in elderly men when combined with resistance training [23]. Additionally, lysine's influence on indirectly supports fatty acid oxidation, enhancing aerobic endurance in athletes [16]. In clinical settings, lysine is incorporated into parenteral nutrition (PN) formulas to meet nitrogen requirements and support tissue repair, especially in critically ill, malnourished, or post-surgical patients [22]. It also exhibits potential benefits in wound healing and immune modulation, aiding in the recovery of trauma and burn patients [8]. Elderly patients, particularly those with sarcopenia or osteopenia, benefit from lysine-enriched diets due to its positive effects on bone mineralization and muscle integrity [27]. Furthermore, lysine's antagonistic relationship with arginine has been explored in viral infection control, suggesting potential ancillary benefits in clinical immunity modulation [10]. The integration of lysine into sports and clinical nutrition is supported by mechanistic, clinical, and epidemiological data, emphasizing its multifunctional roles in anabolism, recovery, immune health, and performance. Its application in functional foods, oral supplements, and enteral/parenteral formulations continues to expand, positioning lysine as a valuable therapeutic and ergogenic agent.

The advent of omics technologies especially metabolomics and nutrigenomics has provided deep insights into the multifaceted biological functions of lysine, beyond its classical role as an essential amino acid. These approaches have enabled the characterization of lysine's metabolic pathways, post-translational modifications, and gene-nutrient interactions, uncovering its broader roles in cellular regulation, epigenetics, immune function, and metabolic diseases. Metabolomic profiling has delineated lysine's role in **energy metabolism**, particularly through its degradation into acetyl-CoA and intermediates of the TCA cycle, linking it directly with mitochondrial energy output [5], [6]. For instance, lysine malonylation, succinylation, and 2-hydroxyisobutyrylation have emerged as novel post-

translational modifications (PTMs) that regulate key enzymes in metabolic pathways [14]. Qian et al. demonstrated that lysine malonylation significantly alters central carbon metabolism in *E. coli*, revealing its conserved metabolic influence across species [6]. Similarly, Zhang et al. identified lysine succinylation as a major PTM with potential regulatory roles in cellular respiration [14]. Moreover, mitochondria-targeted studies using omics platforms (e.g., Papanicolaou et al.) revealed that lysine PTMs modulate mitochondrial dynamics, oxidative phosphorylation, and cellular redox balance critical pathways in both health and disease [5]. Nutrigenomic investigations have highlighted how lysine availability modulates gene expression by influencing the epigenetic landscape. Lysine residues on histones are substrates for acetylation, methylation, and ubiquitination, which collectively regulate chromatin structure and transcriptional activity [5], [9]. These findings link lysine status with gene expression changes involved in lipid/glucose metabolism, immune responses, and oncogenesis [9], [13]. For instance, Wang et al. elaborated on how lysine methylation affects metabolic gene networks, providing therapeutic targets for metabolic syndromes [9]. Furthermore, omics-based tools are being used to detect lysine-modifying enzyme activities (e.g., acetyltransferases), even in cancer cells, as demonstrated by Liu et al. using a novel electrochemical sensor to monitor epigenetic enzyme kinetics [3]. Collectively, omics-based research has redefined lysine as a regulatory molecule with significant implications in systems biology. By integrating metabolomic fingerprints and gene expression profiles, these approaches are advancing our understanding of lysine's role in health maintenance, disease pathogenesis, and personalized nutrition.

Despite growing evidence on lysine's physiological and therapeutic roles, critical knowledge gaps persist that limit its optimized clinical and nutritional application. One prominent gap lies in the lack of large-scale, longitudinal human trials assessing lysine supplementation's long-term safety, especially in vulnerable groups such as the elderly, vegans, and malnourished children [5]. While current studies like those by Hussain et al. and Li et al. report promising benefits and tolerability [1], [2], population-specific dose-response data and upper intake thresholds (ULs) remain poorly defined [19]. Moreover, the mechanistic interplay between lysine and other amino acids, particularly its antagonistic relationship with arginine, demands deeper exploration given its therapeutic implications in viral suppression and immune modulation [10], [12]. Limited human studies have addressed how such interactions influence nutrient absorption, metabolism, or therapeutic efficacy in multi-supplement regimens.

In the realm of omics research, though lysine PTMs like succinylation and malonylation have been profiled [14], their functional consequences in disease contexts (e.g., cancer, neurodegeneration) are still underexplored. Papanicolaou et al. highlighted lysine's regulatory

potential in mitochondrial biology [5], yet organ-specific effects, PTM crosstalk, and integration with the epigenome require targeted investigation. Similarly, nutrigenomic studies are scarce in assessing how dietary lysine modulates gene expression in human cohorts [9]. Additionally, lysine fortification strategies using genetically modified crops remain in early phases, and their bioavailability, regulatory acceptance, and societal impact are understudied [21]. The potential toxicity or nephrotoxic effects of chronic high-dose lysine intake also remains insufficiently characterized, particularly in patients with renal insufficiency or metabolic disorders [16]. Addressing these gaps through interdisciplinary, omics-integrated, and population-tailored research is essential for translating lysine biology into sustainable nutrition and precision health strategies.

CONCLUSION

Lysine, an essential α -amino acid, occupies a central role in human nutrition, physiology, and therapeutic innovation. Its indispensability spans fundamental biological functions such as protein synthesis, nitrogen balance, and calcium absorption, while its versatile biochemical properties continue to reveal new dimensions in health maintenance and disease modulation [15][16]. A robust body of evidence has established lysine's crucial function not only in growth and development—especially among children and adolescents—but also in supporting bone health, modulating immune responses, facilitating wound healing, and countering metabolic, viral, and neuropsychiatric disorders [1][10][8]. Biochemically, lysine's post-translational modifications (PTMs) such as acetylation, methylation, succinylation, malonylation, and 2-hydroxyisobutyrylation provide a dynamic interface between nutrient sensing, energy metabolism, and gene expression. These PTMs play pivotal roles in regulating chromatin structure, mitochondrial function, and enzyme activity across various cell types [5][6][14]. Specifically, lysine succinylation has been shown to modulate TCA cycle enzymes and oxidative phosphorylation, revealing its contribution to metabolic homeostasis at the organellar level [14]. Moreover, lysine's integration into mitochondrial proteomic regulation via epigenetic marks underscores its emerging relevance in aging, cancer biology, and degenerative diseases. Therapeutically, lysine has demonstrated promising roles in clinical nutrition, especially in at-risk populations such as malnourished children, the elderly, and strict vegetarians, whose diets may lack sufficient lysine or contain proteins with poor digestibility [19][20][21]. Supplementation studies indicate benefits in muscle protein synthesis, fracture prevention, and immunocompetence in elderly individuals [23][22][27]. Furthermore, lysine's antiviral potential, particularly in managing herpes simplex virus (HSV) infections, has garnered scientific validation, with studies confirming its ability to antagonize arginine uptake—thereby inhibiting viral replication [10]. Omics-driven research has been instrumental in unravelling lysine's multifaceted roles. Metabolomic and proteomic analyses have clarified lysine's involvement in mitochondrial bioenergetics, redox regulation, and carbon flux through

its degradation into acetyl-CoA and other TCA intermediates [6][5]. Nutrigenomics has further extended these insights by demonstrating that lysine availability influences the epigenetic landscape through modulation of histone acetylation and methylation, thereby linking diet with gene regulatory networks [9]. Such findings position lysine at the confluence of diet, gene expression, and disease susceptibility. Despite these advances, gaps remain. The precise mechanisms by which lysine PTMs affect signalling cascades in tissue-specific contexts require further elucidation. Additionally, there is limited knowledge about lysine's role in the gut microbiome, neurodevelopment, and circadian biology—domains ripe for omics-based investigation. The safety profile of lysine, although largely favourable, also warrants deeper exploration in terms of long-term, high-dose intake and its possible nephrotoxic or gastrointestinal effects in sensitive populations [2]. Moreover, future research should explore the development of lysine-derived biopolymers and nanomaterials for drug delivery, given lysine's functional groups conducive to polymerization and molecular conjugation. Such innovations may lead to breakthroughs in targeted therapeutics, vaccine adjuvants, or biodegradable implants [13]. Agricultural bioengineering, too, holds promise: genetically modified crops enriched in lysine content offer a sustainable avenue to address global protein-energy malnutrition, especially in regions dependent on cereal-based diets with inherently low lysine levels.

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