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Circular Biomanufacturing of Non-Grain Feeds: Synergizing Microbial Fermentation and Insect Bioreactors for Animal Health

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Abstract

The escalating global "food-feed competition" and the drive for agricultural carbon neutrality have intensified the search for sustainable animal feed alternatives. Non-grain feed resources (NGFRs)—encompassing crop residues, agro-industrial co-products, and food waste—represent a vast nutrient reservoir. However, their direct application in monogastric and analogous aquatic animal diets is severely hindered by inherent physicochemical barriers, such as high lignocellulosic content, anti-nutritional factors (ANFs), and biosafety risks (pathogens and mycotoxins). To unlock the nutritional value of NGFRs, biological transformation has emerged as a highly efficient paradigm. This review systematically evaluates current bioconversion strategies, transitioning from standalone microbial fermentation and enzymatic hydrolysis to advanced insect-based bioconversion using the Black Soldier Fly (*Hermetia illucens*, BSF). Specifically, we highlight the disruptive innovation of the "multi-stage bioconversion system" multi-stage bioconversion networks. This synergistic approach not only accelerates fiber depolymerization and ensures profound detoxification but also maximizes nitrogen recovery and biomass accumulation. Furthermore, by integrating recent multi-omics data—spanning 16S rRNA sequencing, transcriptomics, and metabolomics—this paper elucidates the underlying mechanisms by which these upcycled resources modulate the "feed-gut-muscle" axis. Bioconverted NGFRs actively remodel the host's intestinal microecology, leverage AMPs for pathogen competitive exclusion, and significantly enhance terminal meat quality through improved antioxidant capacity and optimized lipid deposition. Despite scale-up challenges, current techno-economic and life cycle assessments confirm the long-term profitability of these integrated systems. Ultimately, the multi-stage bioconversion of NGFRs stands as a vital engine for achieving sustainable bio-manufacturing, ensuring global protein security, and fostering a circular bioeconomy.

Keywords

Non-grain feed resources; Bioconversion; *Hermetia illucens*; Multi-omics; Solid-state fermentation; Circular bioeconomy; Comparative nutrition

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1. Introduction

The escalating global demand for animal-derived protein has profoundly intensified the competition for conventional feed ingredients, exacerbating the ecological footprint of the livestock industry. Consequently, the repurposing of organic waste and agro-industrial by-products as alternative animal feed has become a critical strategy to lower feed costs and improve environmental sustainability.

Non-grain feed resources (NGFRs), including crop residues, food waste, and agro-industrial co-products, represent a vast reservoir of nutrients[1]. However, their direct incorporation into monogastric and sensitive aquatic animal diets is significantly hindered by inherent physicochemical barriers. These include high lignocellulosic fiber content and diverse anti-nutritional factors (ANFs) such as phytic acid and tannins, which severely limit nutrient digestibility and negatively impact animal gut health[2,3].

To unlock the nutritional value of these alternative ingredients, bioconversion technologies have emerged as highly efficient paradigms. Traditional approaches, such as solid-state fermentation (SSF), employ beneficial microorganisms to effectively degrade ANFs and produce digestible feed ingredients[2]. Concurrently, insect-based bioconversion using the Black Soldier Fly (*Hermetia illucens*, BSF) has gained unprecedented global traction. BSF larvae function as robust "micro-bioreactors", capable of rapidly upcycling heterogeneous, low-value organic wastes into premium biomass rich in proteins and lipids[4,5].

The exceptional degradation capacity of BSF larvae is largely attributed to the synergistic action of their dynamic gut microbiota and a highly robust innate immune system[4,6]. During the bioconversion of microbial rich or recalcitrant substrates, BSF larvae trigger the expression of a broad spectrum of AMPs. These insect-derived AMPs not only shape the resident gut microbiota for optimal waste breakdown but also offer immense potential as natural alternatives to in-feed antibiotics, modulating host immunity and safeguarding animal health[6,7].

While the individual benefits of microbial fermentation and insect bioconversion are documented, a comprehensive synthesis integrating modern molecular tools remains limited. Recently, advanced multi-omics approaches—such as transcriptomics, metagenomics, and metabolomics—have been deployed to elucidate the underlying adaptive mechanisms of BSF during waste bioconversion[8]. Therefore, this review systematically evaluates current biological strategies for valorizing NGFRs, with a primary

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focus on monogastric livestock and analogous aquatic animal models. Notably, aquatic species exhibit physiological sensitivity to dietary anti-nutritional factors and share comparable enzymatic hydrolysis limitations — specifically the restricted secretion of endogenous chitinase and cellulase — with monogastric livestock. Consequently, bioconversion kinetic data and intestinal microecological responses derived from these aquatic models function as biological indicators. This cross-species comparative approach provides a mechanistic extrapolation for monogastric physiological adaptations. By integrating multi-omics data, we uncover the correlative mechanisms of nutrient enhancement and pathogen suppression, establishing a theoretical foundation for large-scale biomanufacturing applications.

While previous reviews have predominantly evaluated microbial fermentation or insect-based rearing in isolation — often confining their scope to apparent nutritional metrics — this paper pioneers a holistic paradigm. The core novelty of this comprehensive review lies in proposing the "multi-stage bioconversion system" as a synergistic bioconversion network. The "multi-stage bioconversion system" strictly denotes the external, physical processing engineering. In contrast, the "feed-gut-muscle axis" delineates the internal, physiological signal transduction network within the host animal following ingestion of the bioconverted products. Furthermore, by systematically integrating recent multi-omics data, we uniquely map the molecular trajectories of upcycled non-grain feed resources along the nutritional metabolic pathway. This multi-dimensional approach not only addresses current biosafety bottlenecks but also bridges the critical gap between waste valorization and terminal meat quality enhancement, providing a definitive roadmap for sustainable bio-manufacturing.

2. Physicochemical Matrix of Non-grain Feed Resources

Despite the vast availability and low cost of NGFRs, their direct utilization in animal nutrition is severely restricted by their complex physicochemical matrices.

Agricultural by-products, primarily comprising crop residues and milling by-products, represent the most abundant category of NGFRs. The principal barrier to their utilization is their highly recalcitrant lignocellulosic structure. For instance, untreated rice straw contains excessively high levels of neutral detergent fiber (NDF) and acid detergent fiber (ADF), which encapsulate intracellular nutrients and resist enzymatic degradation in the monogastric gut[9]. Furthermore, agro-industrial co-products are generated during the processing of crops and fruits, including brewer's spent grain (BSG), oilseed cakes, fruit pomace, and coffee silverskin. Unlike field residues, these materials present distinct molecular complexity; their fibrous carbohydrates are tightly bound to proteins[10] and compounded by ANFs such as tannins, which restrict their safe inclusion levels in animal diets. Conversely, municipal organic streams are characterized by extreme nutritional heterogeneity, high moisture content, and significant biosafety risks, including pathogenic microbial loads[11]. Consequently, disrupting these distinct physical and biological barriers forms the prerequisite for designing targeted bioconversion strategies[12].

3. Key Bioconversion Strategies for Nutritional Valorization

Despite the immense potential of NGFRs, conventional physical and chemical processing methods are often energy-intensive, environmentally burdensome, and insufficient to fully neutralize their complex anti-nutritional barriers. Consequently, biological transformation — utilizing microorganisms, exogenous enzymes, and insect-based systems — has emerged as the most sustainable and highly efficient paradigm for nutritional valorization and biosafety enhancement.

3.1 Microbial Fermentation: Kinetic Depolymerization of Fibrous Matrices

The bioconversion efficiency of NGFRs relies fundamentally on the initial depolymerization of fibrous matrices. Experimental observations demonstrate that the integration of Black Soldier Fly Larvae (BSFL) bioreactors significantly accelerates the structural breakdown of complex carbohydrates. For instance, the BSFL system achieves a lignocellulose biodegradation rate of 26.5% within 14 days, which is markedly higher than the 4.06% observed in natural composting[13]. Similarly, when processing highly recalcitrant agricultural residues such as corn straw, larval bioconversion facilitates a digestion rate of 37.4%[14].

The kinetic efficiency of this depolymerization is strictly substrate-dependent. For instance, the degradation rate of wheat bran is significantly higher than that of rice bran. This kinetic discrepancy is primarily attributed to the structural variations in their lignocellulosic matrices; rice bran and rice straw possess a highly silicified epidermis and a more complex, tightly cross-linked lignin-carbohydrate complex (LCC), which presents stronger steric hindrance against microbial enzymatic access compared to the relatively accessible hemicellulose matrix of wheat bran.

This kinetic enhancement is directly mediated by the recruitment of functional lignocellulose-degrading microbiota into the larval intestine and the subsequent upregulation of carbohydrate-active enzymes (CAZymes). This kinetic enhancement is directly mediated by the recruitment of functional lignocellulose-degrading microbiota into the larval intestine and the subsequent upregulation of carbohydrate-active enzymes (CAZymes). Metagenomic profiling reveals that the expression levels of genes encoding cellulase and hemicellulase in the larval gut are 3.36 and 2.79 fold higher, respectively, than those in the uningested substrate[13]. The dynamic degradation process correlates with a distinct succession in the microbial community, characterized by the enrichment of keystone lignocellulolytic taxa, including *Dysgonomonas*, *Bacteroides*, and specific cellulase-producing strains such as *Klebsiella pneumoniae* and *Bacillus subtilis*[14,15]. These recruited microbial consortia synchronize the secretion of extracellular hydrolases. Specifically, the system exhibits elevated activities of β-glucosidase alongside specific hemicellulolytic enzymes[14]. This synergistic enzymatic action effectively cleaves the structural carbohydrate networks into bioavailable monomeric sugars and volatile fatty acids (VFAs), providing the necessary metabolic precursors for larval biomass accumulation.

3.2 Enzymatic Synergy and Substrate Heterogeneity

Beyond the static lignocellulosic barrier, agro-industrial co-products like brewer's spent grain (BSG) present a "molecular lock" where structural carbohydrates are tightly bound to residual proteins, severely limiting amino acid digestibility and metabolizable energy[11]. While physical treatments such as extrusion can modify the surface and molecular structure — reducing fiber fractions and increasing the absorbance of amide groups — the true liberation of nutrients requires targeted enzymatic action to drive metabolic reprogramming[11].

The kinetic performance of biological agents is further complicated by the extreme heterogeneity of food waste. Untreated

food waste often harbors high counts of *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*, particularly in spoiled or unhomogenized samples[11]. To counter this, robust bioconversion systems must function as "biological filters." Integrated approaches utilizing BSF larvae act as high-throughput micro-bioreactors, but their kinetic efficiency is strictly governed by the substrate's chemical properties and initial microbial load. For instance, the bioconversion of heterogeneous food waste into insect biomass is not only a matter of mass balance but a complex interaction where the gut microbiota of the larvae must outcompete the indigenous spoilage bacteria of the substrate to maintain metabolic homeostasis[16]. Transitioning to a circular bioeconomy necessitates that these fermentation and enzymatic strategies provide a predictable, standardized output despite the inherent variability of the input NGFRs[12].

3.3 Insect-based Bioconversion: The Black Soldier Fly as a Micro-Bioreactor

The industrial-scale valorization of NGFRs is fundamentally impeded by the extreme nutritional heterogeneity and physicochemical instability of organic waste streams. Substrates such as municipal food waste, livestock manure, and agro-industrial residues often exhibit imbalanced carbon-to-nitrogen (C/N) ratios, high moisture content, and a high prevalence of recalcitrant fibers or ANFs[17-19]. Standalone biological treatments, such as traditional composting or anaerobic digestion, frequently suffer from prolonged processing times, significant gaseous nitrogen losses (notably ammonia emissions), and unstable nutrient recovery efficiencies when faced with these complex matrices[12,20,21].

To overcome these barriers, BSFL function as high-throughput biological upcyclers. The core of their efficacy lies in a highly elastic gut microbiota that undergoes directional succession to adapt to specific dietary challenges. Meta-analyses and metagenomic surveys have identified a stable "core microbiome" within BSFL — comprising members of the genera *Enterococcus*, *Klebsiella*, *Morganella*, *Providencia*, and *Scrofimicrobium* — which facilitates organic matter assimilation regardless of substrate variability[12,22]. However, the abundance of these functional taxa is dynamically modulated by the substrate. For instance, when reared on lignocellulose-rich materials like corn straw or brewery spent grain, BSFL gut communities selectively enrich cellulase-producing strains such as *Acinetobacter*, *Dysgonomonas*, and *Actinomyces* to accelerate fiber depolymerization[20,23].

Quantitative assessments highlight the superior nutrient recovery potential of BSFL systems compared to conventional methods. In pilot-scale food waste treatments, BSFL can effectively convert 34.4% of substrate nitrogen and 32.7% of phosphorus into high-value larval biomass, achieving peak yields of 309.2 g/kg dry matter[20]. This efficiency is further enhanced through synergistic "co-treatment" strategies. Mixing chicken manure with vegetable waste and discarded fish organs has been shown to increase larval biomass yield by up to 101.07% and protein content by 14.52% compared to pure manure substrates, while simultaneously reducing greenhouse gas emissions by over 56%[17].

Furthermore, the introduction of functional microbial consortia — such as a combination of *Gordonia* sp., *Lysinibacillus macroides*, and *Lactobacillus plantarum* — during bioconversion has been proven to mitigate environmental hazards. Such bioaugmentation strategies can reduce environmental NH_3 emissions by 37% and boost larval bioconversion efficiency by 12%[21]. The resilience of the BSFL bioconversion system is also reflected in its capacity for “entomoremediation”, where larvae can recycle nutrients from hazardous sewage sludge or butchery waste into safe protein sources (37% – 48.3% crude protein), provided that heavy metal accumulation is strictly monitored[18,24,25]. Ultimately, the directional succession of the BSFL microbiota not only homogenizes nutrient-imbalanced wastes but also establishes a zero-waste loop, where the residual frass serves as a mature, nutrient-dense bio-fertilizer that promotes crop productivity and soil health[23,26-28].

3.4 Detoxification and Pathogen Suppression

The utilization of NGFRs is pervasively constrained by biological hazards, specifically the presence of zoonotic pathogens such as *Salmonella* spp. and potent mycotoxins like Aflatoxin B1 (AFB1), which exhibit extreme carcinogenicity and immunotoxicity[29]. While conventional decontamination remains economically prohibitive, BSFL function as living microbial reactors, leveraging a sophisticated host-microorganism co-degradation system that integrates robust signaling pathways with a potent humoral arsenal[29,30].

The bioconversion of mycotoxin-contaminated substrates by *Hermetia illucens* larvae is governed by dose-dependent kinetic thresholds. In vivo validations demonstrate that larvae do not bioaccumulate AFB1 when exposed to naturally contaminated substrates up to 99.4 μg/kg dry mass[31], or artificially spiked diets up to 200 μg/kg[32,33]. The degradation mechanism is mediated by a synergistic host-microbiome interaction. The larval gut microbiota, specifically strains such as Stenotrophomonas acidaminiphila, directly facilitates AFB1 cleavage[30], while host-derived Cytochrome P450 and Glutathione S-transferase enzymes convert residual AFB1 into metabolites including aflatoxicol and aflatoxin P1, achieving a complete mass balance[34]. A comprehensive comparison of the apparent nutritional profile alterations and bioconversion parameters of various non-grain feed resources mediated by *Hermetia illucens* larvae is summarized in **Table 1**.

Table 1. Apparent nutritional profile alterations and bioconversion parameters of non–grain feed resources mediated by *Hermetia illucens* larvae

Substrate Category	Specific NGFR	Bioconversion Strategy	Key Bio–agents / Insects	Nutritional Profile Alteration	Animal Model & Inclusion Level	Ref.
Industrial By–products	Palm kernel meal	Solid–state fermentation	*Lactobacillus*, *Bacillus*, Yeast	CP ↑ 20.79%; CF ↓ 36.45%	Red Tilapia (50% replacement of SBM)	[35]
	Brewer's spent grain	SSF & Insect conversion	*Pleurotus ostreatus* / BSFL	Protein enrichment ↑ 49.49%	Fish, poultry and pigs	[36,37]
	Copra meal	Probiotic fermentation	Mixed microbial consortia	Enhanced amino acid bioavailability	Black tiger shrimp (40% FM replacement)	[38]
	Corn fermented protein	Ethanol co–processing	*Saccharomyces cerevisiae*	High protein (50%); Reduced fiber content	Pacific white shrimp (20% inclusion)	[39]

Table 1. Apparent nutritional profile alterations and bioconversion parameters of non–grain feed resources mediated by *Hermetia illucens* larvae(continued)

Substrate Category	Specific NGFR	Bioconversion Strategy	Key Bio–agents / Insects	Nutritional Profile Alteration	Animal Model & Inclusion Level	Ref.
Industrial By–products	Soybean meal	Probiotic fermentation	*Bacillus subtilis*	Reduced anti–nutritional factors	Broilers (1%–3% replacement)	[40,41]
Agro–Residues	Rice straw	Two–stage: Acid + Fungal	*T. harzianum* / *A. terreus*	Lignin ↓ 80.90%; Reducing sugars 56.60 g/100g	Biofuel focus (182 L ethanol/tonne)	[42,43]
	Rice straw	Insect–microbe synergy	BSFL / *Actinomyces*	Cellulose decomposition ↑ 70.90%	Aquafeed potential (11.40% conversion)	[44]
	Corn stover	Enzymatic–Insect	*O. furnacalis enzymes*	Strengthen the degradation effect	Fodder for livestock or poultry	[45,46]
	Wheat straw	Fungal SSF	*Phlebia floridensis*	In vitro digestibility ↑ 50%; Lignin ↓ 27.60%	Ruminant feed enhancement	[47]
	Sugarcane bagasse	Steam + Enzymatic	*Trichoderma reesei*	Liberated monomeric sugars; 16% dry conversion	BSFL rearing feedstock	[48,49]
Animal/Waste Streams	Chicken manure	Co–treatment (Fish / Veg)	BSFL	Biomass yield ↑ 101%; Larval protein ↑ 14.50%	Aquafeed (Superior growth in PL)	[17]
	Chicken manure	Bioaugmentation	BSFL / *Gordonia* sp.	NH_3 emission ↓ 37%; Bioconversion ↑ 12%	Sustainable protein production	[21,29,30,32]
	Animal manure	Life–stage optimized	3nd instar BSFL	Enhanced decomposition	Frass	[30,32]
	Sewage sludge	Entomoremediation	BSFL / Housefly larvae	N recovery 34.40%; Pathogen exclusion	Fish feed (Catfish juveniles)	[20,50]
	Silkworm pupae	Defatting & Bioprocess	*Bombyx mori* pupae	Balanced Methionine/Lysine	ROSS 308(40 g/kg)	[51]
	Fish protein hydrolysate	Enzymatic hydrolysis	Marine–derived enzymes	Umami enrichment; Better texture / flavor	Broilers (7.50% inclusion)	[52]
	Tuna industry waste	Silage hydrolysis	Lactic acid bacteria	CP 35%; Enhanced SGR and WGR	Nile tilapia fingerlings	[53]
	Iberian pig viscera	Rendering	Thermal processing	High protein digestibility (PMM 66.20%)	Pacific white shrimp (35% FM replacement)	[54,55]

Note: Abbreviations in the table are defined as follows: BSFL, Black Soldier Fly Larvae; CF, Crude Fiber; CP, Crude Protein; FM, Fish Meal; NGFRs, Non-grain feed resources; PMM, Post-mortem muscle quality; PL, Post-larvae; SBM, Soybean Meal; SGR, Specific Growth Rate; SSF, Solid-state Fermentation; WGR, Weight Gain Rate.

3.5 Physiological Bottlenecks and Biosafety Risks

Despite the unprecedented potential of biological transformation via insect-microbiome synergies, the transition from controlled laboratory environments to the industrial-scale valorization of heterogeneous NGFRs reveals critical physiological bottlenecks and biosafety risks. An objective evaluation of these limitations — specifically regarding heavy metal bioaccumulation, microplastic-induced ecotoxicity, and the anti-nutritional properties of chitin — is imperative for establishing safe and viable circular bioeconomies.

3.5.1 The Biosafety Risk of Heavy Metal Bioaccumulation

A primary biosafety concern in upcycling municipal or agro-industrial NGFRs is the presence of persistent inorganic pollutants, particularly heavy metals. While insects like *Hermetia illucens* possess robust detoxification mechanisms for certain organic toxins, they function as bioconcentrators for specific heavy metals, posing a severe risk of trophic transfer into the livestock food chain[56,57]. Empirical studies demonstrate that the bioaccumulation factor (BAF) — defined as the metal concentration in the insect body divided by its concentration in the substrate — varies significantly among elements. For instance, Cadmium is highly prone to accumulation, with BSF prepupae exhibiting a BAF ranging from 2.32 to 2.94 when reared on contaminated substrates[58]. Conversely, Lead (Pb) tends to remain below initial feed concentrations, and Zinc displays a dose-dependent decrease in BAF[58]. This differential accumulation indicates that while BSF larvae can effectively process organic fractions, they cannot act as a universal "biological filter" for heavy metals. Consequently, utilizing highly contaminated NGFRs without pre-treatment risks exceeding the stringent heavy metal thresholds established by global feed regulatory frameworks.

3.5.2 Microplastic-Induced Oxidative Stress and Gut Dysbiosis

Substrate contamination with synthetic polymers presents a dose-dependent physiological barrier in insect-based bioconversion. Experimental models demonstrate that the biological effects of microplastics on BSFL vary significantly by polymer composition and concentration. While larvae exhibit morphological tolerance to polyvinyl chloride with associated particle fragmentation[59], biodegradable alternatives present distinct toxicity profiles. Specifically, exposure to 5% polylactic acid microplastics induces excessive oxidative stress and disrupts energy metabolism, resulting in a 15.30% reduction in larval body weight and a 10.86% decrease in survival[60]. Furthermore, prolonged exposure to mixed plasticizers and

microplastics significantly retards larval development, triggering an adaptive shift in the gut microbiota to enrich xenobiotic-degrading taxa.

From a feed safety perspective, current kinetic models indicate negligible systemic bioaccumulation of microplastics in the larval gut. Implementation of a three-day pre-harvest starvation protocol effectively eliminates over 90% of ingested polyethylene particles[61]. Despite these intrinsic physiological clearance mechanisms, a critical operational vulnerability exists at the administrative level. Current agricultural regulatory frameworks, including European Union animal feed directives, lack standardized, mandatory testing protocols for microplastic contamination in incoming organic waste streams. This regulatory vacuum limits the standardized risk assessment required for the scaled commercialization of insect-derived feed ingredients.

3.5.3 Nutritional Antagonism: The Chitin Digestibility Barrier

From a nutritional perspective, the intrinsic composition of insect biomass presents a significant physiological bottleneck for monogastric animals. While BSF meal boasts an excellent amino acid profile, the presence of chitin — a structural polysaccharide in the insect exoskeleton — acts as a potent anti-nutritional factor when included at high dietary levels[62]. In vitro and in vivo models confirm a strong negative correlation between the chitin content of insect meal and the apparent digestibility of crude protein (CP) and organic matter[63]. Regression analyses indicate that chitin content can explain up to 98.3% of the variability in CP digestibility of *H. illucens* meal[64]. Although low-level dietary inclusion of insect meal modulates the gastrointestinal microbiome and significantly enriches endogenous chitinolytic bacteria strains[65], this microecological adaptation is kinetically insufficient to compensate for high concentrations of exogenous chitin. The secretion capacity of host endogenous chitinase in monogastric animals and the catalytic throughput V_{max} of the enriched intestinal microbiota possess strict upper limits[66]. When dietary replacement exceeds this physiological threshold, the unhydrolyzed chitin matrix establishes spatial hindrance, effectively encapsulating proteins and lipids[62,66]. This steric barrier prevents host proteases and lipases from accessing their specific substrates, significantly decreasing the apparent total tract digestibility of crude protein and ether extract. Consequently, decoupling this nutritional antagonism requires either maintaining the insect meal inclusion at optimal lower ratios or utilizing exogenous microbial chitinase supplementation to directly degrade the structural barrier and restore amino acid standardized ileal digestibility[65,66].

Ultimately, these interconnected physiological and toxicological bottlenecks underscore that insect-based bioconversion is not an absolute panacea. Industrial scale-up mandates the implementation of rigorous substrate screening for heavy metals and plastics, alongside advanced post-harvest processing of insect biomass to neutralize anti-nutritional factors, thereby ensuring both the safety and efficacy of the final feed products.

4. Synergistic Application: Multi-stage Bioconversion Systems

Single-tier bioconversion strategies exhibit kinetic limitations when processing NGFRs characterized by complex physicochemical matrices. A multi-stage bioconversion system circumvents these barriers through the spatial and temporal integration of microbial and insect metabolisms.

While direct head-to-head empirical comparisons within a single experimental framework remain limited, a cross-study synthesis of the available literature reveals the quantitative superiority of the integrated multi-stage system over standalone bioconversion methods. Traditional standalone microbial fermentation typically yields limited continuous biomass conversion, and direct BSFL rearing on recalcitrant NGFRs often results in prolonged developmental cycles and suboptimal nutrient recovery due to structural hindrances. Conversely, the synergistic multi-stage bioconversion system exhibits a profound advantage. Evidence indicates that microbial pre-treatment significantly accelerates lignocellulose depolymerization, potentially elevating larval biomass yield and crude protein enrichment compared to unfermented controls. Furthermore, this multi-stage approach demonstrates environmental benefits, as the initial microbial stabilization of the carbon-to-nitrogen flux substantially mitigates subsequent greenhouse gas and ammonia emissions during the BSFL rearing phase. Therefore, this integrated system represents a fundamental shift from simple waste reduction to an optimized, environmentally controlled bio-refinery process.

4.1 Substrate Co-conversion and Kinetic Enhancement

The physical integration of complementary organic streams modifies the initial substrate matrix, thereby upregulating bioconversion kinetics. Quantitative assessments indicate that co-treating chicken manure with specific proportions of discarded fish organs and vegetable waste increases larval biomass yield by 101.07% and elevates crude protein content by 14.52% compared to single-substrate processing[17]. Furthermore, pilot-scale evaluations confirm that optimized BSFL systems achieve a stable mass transfer efficiency, converting 34.40% of initial nitrogen and 32.70% of phosphorus from food waste into larval biomass[20].

4.2 Microbial Augmentation and Gas Mitigation

Targeted microbial inoculation provides a defined biological mechanism for both conversion enhancement and emission control. The continuous introduction of a specific functional microbial consortium into the BSFL[15] rearing matrix upregulates nitrogen assimilation pathways. This microbial augmentation results in a 12% increase in bioconversion efficiency and a 37% reduction in ammonia (NH_3) emissions[21]. Concurrently, specific co-conversion matrices dynamically alter carbon and nitrogen distribution, leading to a measured greenhouse gas emission reduction of 56.38%[17].

4.3 Frass Valorization and System Closure

The terminal phase of the multi-stage system processes the residual larval frass. Sequential biological routes, such as thermophilic anaerobic digestion (TAD) and aerobic co-composting, extract residual energy and stabilize the organic fractions. Processing frass via TAD ensures the destruction of resilient pathogens while functioning as an optimized substrate for biomethane yield[67]. Alternatively, co-composting BSFL frass with specific carbon/nitrogen amendments extends the thermophilic phase and facilitates humification. This process minimizes nitrogen loss by suppressing denitrification genes and achieves a stable germination index, thereby establishing a closed-loop bio-manufacturing network.[27,68]

A conceptual visualization of this integrated, multi-stage bioconversion cascade, emphasizing the flow of materials from raw non-grain resources to premium products and the closing of the nutrient loop via frass recycling, is depicted in **Figure. 1**.

The synergistic material flow utilizes microbial-enzymatic pre-treatment (Stage 1) to depolymerize complex agricultural fibers and neutralize ANFs. The biotransformed substrate is subsequently

processed by *Hermetia illucens* larvae (Stage 2) acting as micro-bioreactors. This cascaded system yields high-value biomass (premium larva meal, functional lipids rich in lauric acid, and antimicrobial peptides) that structurally improves animal health through the targeted enhancement of gut microbiota balance, systemic immune responses, and growth performance metrics.

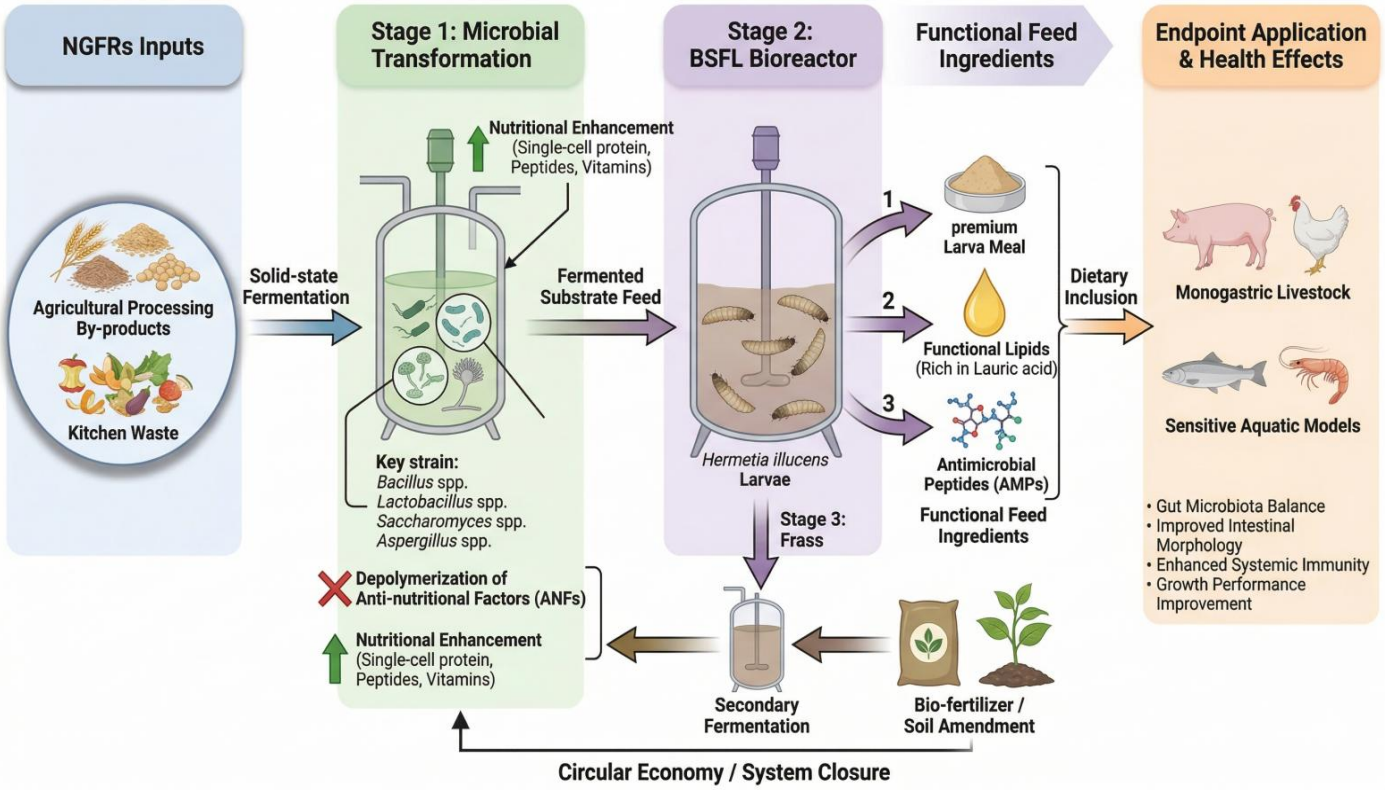

Figure. 1 Conceptual framework of the multi-stage bioconversion network for NGFRs. NGFRs: Non-grain feed resources; BSFL: Black Soldier Fly Larvae. Created with BioRender.com.

5. Mechanisms of Action on Animal Health and Product Quality

The direct incorporation of untreated NGFRs frequently compromises intestinal integrity, induces oxidative stress, and deteriorates end-product quality due to the persistence of anti-nutritional factors and fibrous matrices. Conversely, biologically transformed NGFRs transcend their role as mere nutrient suppliers, functioning as potent modulators of host physiology. By bridging the "feed-gut-muscle" axis, these upcycled resources profoundly remodel animal health and terminal meat quality.

5.1 Modulation of Gut Microbiota

The gastrointestinal tract is the primary interface for nutrient absorption and immune defense. Unprocessed agro-industrial wastes often trigger dysbiosis by providing substrates for pathogenic proliferation. However, bioconverted feedstuffs introduce a synergistic matrix of prebiotics and beneficial microbial metabolites that competitively exclude pathogens.

Dietary inclusion of BSF larval meal has been proven to significantly reshape the intestinal microbial architecture. For example, replacing conventional protein sources with full-fat BSF meal markedly decreased the relative abundance of pathogenic *Proteobacteria* while enriching *Firmicutes*, specifically stimulating chitinolytic and lactic acid bacteria[69]. Similarly, feeding monogastric livestock and aquatic models with solid-state fermented plant residues elevates the abundance of beneficial taxa such as Ruminococcaceae and Romboutsia, while simultaneously suppressing the proliferation of *Ruminococcaceae_UCG-014, Ruminococcaceae_ UCG-010 and Romboutsia*[70]. This microecological remodeling strengthens the tight junction barrier and stimulates the secretion of immunoglobulins (IgM and IgG), fortifying systemic immunity.

5.2 Multi-omics Perspectives: Correlative Networks in the Feed-Gut-Muscle Axis

The integration of multi-omics technologies — encompassing 16S rRNA sequencing, metabolomics, and transcriptomics — provides an objective framework to evaluate the systemic effects of bioconverted diets, transitioning from observational phenotypes to correlative molecular networks.

5.2.1 Microbiome and Metabolome Associations

Dietary inclusion of BSFL derivatives (meal or fat) and microbial fermented feeds significantly modulates the gastrointestinal microecology. 16S rRNA amplicon sequencing reveals that such interventions alter cecal beta-diversity, consistently suppressing the relative abundance of opportunistic pathogens while enriching specific beneficial taxa, including Lactobacillus spp. and short-chain fatty acid (SCFA)-producing bacteria such as Alistipes[71,72]. Furthermore, lipidomic profiling of host muscle tissues demonstrates that bioconverted diets alter lipid partitioning, significantly reducing triacylglycerol concentrations and modifying specific lipid molecular markers closely linked to terminal meat quality [73,74].

5.2.2 Transcriptomic Signatures and Metabolic Reprogramming

Instead of asserting absolute causality in isolated signaling

pathways, transcriptomic and quantitative PCR (qPCR) data reveal broad correlative shifts in host energy and lipid metabolism[74,75]. Specifically, multi-omics integration suggests that these dietary interventions correlate with the reprogramming of skeletal muscle characteristics. Supplementation with co-fermented feeds corresponds with the upregulation of PGC-1α and an increased expression of slow-twitch Type I muscle fiber genes (MyHC I, MyHC IIa)[74]. Additionally, transcriptomic profiles of the muscle demonstrate an upregulation of antioxidant-related genes (GPX1, SOD1, CAT), providing a molecular basis for the observed improvements in antioxidant status[74,75].

Furthermore, recent integrated multi-omics models provide quantitative evidence for host-microbiome metabolic crosstalk. Specific substrate-driven bioconversion significantly enriches beneficial microbial taxa, such as Lactobacillus, in the gastrointestinal tract, which directly mediates enhanced nutrient assimilation[76]. Concurrently, dual-omics integration reveals that this microecological shift is highly correlated with systemic metabolic reprogramming. Notably, this includes the significant accumulation of indole derivatives and the activation of sphingolipid signaling pathways[77]. These biogenic metabolites function as critical signaling molecules or "bridge metabolites" that modulate intestinal barrier homeostasis and facilitate adaptive cellular differentiation. This data-driven multi-omics framework establishes a direct mechanistic link between diet-induced microbiome alterations and host physiological regulation, moving beyond isolated transcriptomic profiling.

5.3 Mechanistic Insights into Meat Quality Enhancement: The Gut-Muscle Redox Axis

While macroscopic improvements in carcass traits are frequently observed following the inclusion of insect-upcycled NGFRs, the underlying molecular mechanisms have only recently been elucidated through multi-omics integration. The pronounced elevation of specific medium-chain fatty acids (MCFAs)—most notably the 83.33% surge in capric acid derived from BSF bioconversion—acts far beyond a simple caloric provision. These metabolites function as potent signaling molecules that orchestrate a complex "gut-muscle axis," fundamentally remodeling the physiological and biochemical trajectories of skeletal muscle.

5.3.1 Intestinal Barrier Fortification and Systemic Homeostasis

The initial regulatory site of bioconverted feed occurs within the gastrointestinal tract. Bioactive components from insect meal, including MCFAs and antimicrobial peptides, actively modulate the structural integrity of the intestinal epithelium. Transcriptomic analyses reveal that these bioactive compounds significantly upregulate the expression of critical tight junction proteins, specifically Zonula Occludens-1 (ZO-1), Claudin-1, and Occludin[78]. By physically fortifying the paracellular spaces, the strengthened mucosal barrier successfully restricts the translocation of lipopolysaccharides and opportunistic enteric pathogens into the portal circulation. This containment averts endotoxemia and actively suppresses the TLR4/MyD88/NF-κB inflammatory signaling cascade, thereby downregulating pro-inflammatory cytokines (such as TNF-α and IL-6) and protecting the organism from systemic oxidative stress[79].

5.3.2 Skeletal Muscle Metabolic Reprogramming via AMPK/mTOR

Upon absorption, the enriched lipid profile and functional amino acids derived from the fermented-insect biomass exert profound regulatory effects on skeletal muscle energy homeostasis. At the cellular level, these nutrients act as metabolic modulators that activate the AMP-activated protein kinase (AMPK) pathway. As the master cellular energy sensor, AMPK activation stimulates peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α), which subsequently drives mitochondrial biogenesis and promotes the phenotypic transformation of muscle fibers from fast-twitch glycolytic (Type IIb) to slow-twitch oxidative (Type I) fibers[3,4]. Concurrently, the modulation of the mechanistic target of rapamycin (mTOR) signaling network optimizes the balance between protein synthesis and autophagy. This metabolic reprogramming effectively delays rapid postmortem glycolysis, thereby preventing a precipitous drop in muscle pH that typically leads to pale, soft, and exudative (PSE) meat[5].

5.3.3 Mitochondrial ROS Quenching and Myoglobin Stabilization

The terminal and most crucial phase of meat quality enhancement occurs within the mitochondria. Mitochondria are the primary loci of oxygen consumption and the main generators of reactive oxygen species (ROS) in postmortem muscle[6].The bioactive metabolites from the bioconverted feed are positively correlated with the upregulation of the Keap1/Nrf2/ARE antioxidant defense system in muscle tissue[2]. This activation translates into a significant upregulation of endogenous enzymatic antioxidants, notably superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px). By augmenting this redox shield, the structural integrity of the mitochondrial electron transport chain (ETC) is preserved, subsequently reducing the leakage of superoxide anions ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2). Furthermore, the attenuation of ROS prevents the irreversible opening of the mitochondrial permeability transition pore (MPTP), thereby inhibiting cytochrome c release and stalling caspase-3-mediated apoptosis, which otherwise degrades myofibrillar architecture[6].

5.3.4 Biochemical Manifestation: The Preservation of the a Value

The terminal phenotypic manifestation of mitochondrial redox homeostasis correlates with the stabilization of meat color, quantified by the redness index (a value). Postmortem oxidative stress accelerates the oxidation of the central iron atom within the porphyrin ring of myoglobin. Specifically, reactive oxygen species (ROS) mediate the conversion of ferrous oxymyoglobin (Fe^{2+}) into ferric metmyoglobin (Fe^{3+}), resulting in tissue discoloration[73,75]. The systemic antioxidant capacity, upregulated through biologically transformed diets, facilitates ROS scavenging via the activation of the Nrf2 signaling pathway and the subsequent expression of downstream antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT). This pathway effectively inhibits metmyoglobin formation. Furthermore, the enriched antioxidant components derived from the bioconversion process structurally stabilize the myoglobin microenvironment, establishing a protective barrier that mitigates overoxidation and maintains the iron atom in its ferrous (Fe^{2+}) state[74]. This coordinated biochemical preservation sustains the a value and oxidative stability of the muscle tissue during postmortem storage.

The comprehensive immune and metabolic regulatory pathways linking these converted non-grain feeds to improved animal health and meat quality, as elucidated by a cross-anatomical multi-omics analysis, are visually summarized in **Figure. 2**.

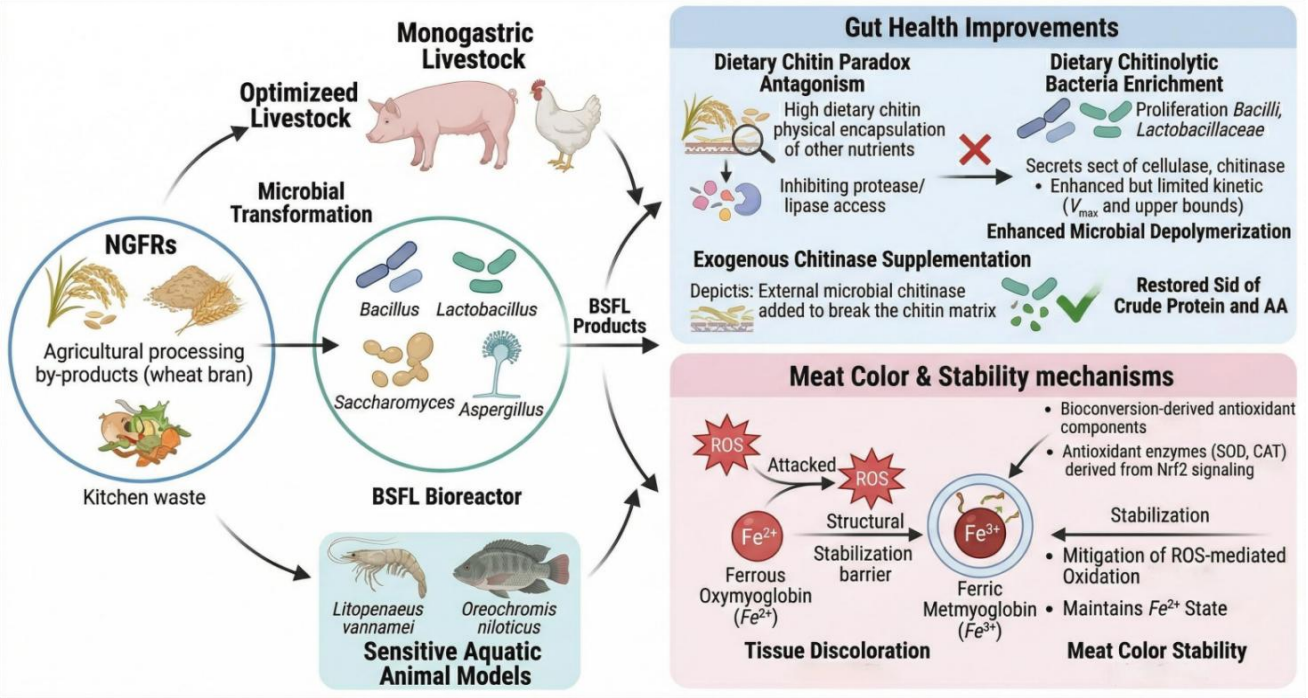

Figure. 2 Multi-omics mechanistic pathways illustrating the immunomodulatory and metabolic regulation of bioconverted non-grain feeds along the "feed-gut-muscle" axis. NGFRs：Non-grain feed resources; BSFL:Black Soldier Fly Larvae. Created with BioRender.com.

The diagram integrates monogastric livestock and sensitive aquatic animal models to demonstrate the systemic impacts of BSFL derivatives. In the gut lumen, the dietary chitin paradox highlights the kinetic limits of endogenous bacterial depolymerization (V_{max}), necessitating exogenous chitinase supplementation to break the physical encapsulation matrix and restore the standardized ileal digestibility (SID) of crude protein. At the terminal muscle tissue, upregulated antioxidant components (derived from bioconversion and Nrf2 signaling pathways) mitigate ROS-mediated oxidation. This antioxidant shield establishes a structural stabilization barrier, preventing the oxidation of ferrous oxymyoglobin (Fe^{2+}) to ferric metmyoglobin (Fe^{3+}) and ensuring long-term meat color stability.

6. Industrialization Challenges and Future Perspectives

The transition of insect-based bioconversion from controlled laboratory models to scaled biomanufacturing encounters substantial technical, regulatory, and socio-cultural barriers. While biological and engineering optimizations are continuously advancing, the commercial deployment of transgenic insect bioreactors remains a long-term research trajectory.

6.1 Genetic Engineering: Technical Realities and Long-term Trajectories

The application of CRISPR/Cas9 and homologous genome-editing technologies presents a targeted methodology for modulating insect metabolic efficiency and environmental stress adaptation. Currently, these molecular tools are predominantly utilized in functional genomics to elucidate specific xenobiotic detoxification mechanisms or pathogen resistance networks[80,81]. Although CRISPR-based breeding holds theoretical potential for optimizing larval bioconversion rates and nutrient profiles, its direct translation into industrial-scale production systems is constrained by significant technical hurdles, including target off-effects and genetic stability across multiple generations.

6.2 Regulatory Frameworks and Biosafety Governance

The industrial scaling of genetically modified (GM) insects is strictly governed by a fragmented international regulatory landscape. The commercialization of Genetically Modified Organisms necessitates rigorous safety governance models that balance technological adoption with ecological preservation[82]. Current legislative frameworks demand stringent biological containment protocols to prevent the unintended dissemination of transgenic insects into natural ecosystems. Furthermore, the mass rearing of insects on NGFRs requires harmonized international standards to mitigate endogenous risks, such as microbial contamination, heavy metal accumulation, and allergenicity, which currently complicate the legal categorization of insect-derived products in various jurisdictions[83].

To bridge these regulatory and operational vacuums, the industry is transitioning towards early-stage predictive modeling that merges economic viability with environmental sustainability. Recent industrial paradigms propose the "window of sustainable bioprocess operation" (SBO window), a concept designed to back-translate environmental constraints into actionable bioprocess optimizations, ensuring that large-scale insect rearing and fermentation comply with stringent eco-efficiency standards[84]. Furthermore, recognizing the inherent complexity and compositional variability of organic waste streams, advanced bioprocessing now leverages machine learning frameworks. For example, Artificial Neural Network models coupled with multi-objective genetic algorithms have proven superior to traditional response surface methodologies in predicting and optimizing dynamic biological transformations[85]. The integration of these digitally-enabled, uncertainty-aware modeling approaches, alongside comprehensive Life Cycle Assessments[86], provides the quantifiable traceability and process robustness required to satisfy

modern EU feed safety directives and achieve scalable, net-zero biomanufacturing[87].

6.3 Consumer Perception and Market Viability

Beyond technological and legislative impediments, public perception significantly dictates the market viability of insect-derived feed ingredients. Cultural resistance, coupled with consumer apprehensions regarding the safety of transgenic organisms and waste-upcycled products, constitutes a critical barrier to large-scale adoption[88]. To navigate the complex intersection of biotechnology and societal acceptance, future industrialization strategies must integrate transparent biosafety validation data with objective consumer education, ensuring that upcycled biomass meets both regulatory thresholds and market expectations.

7. Conclusion

The escalating "food-feed competition" necessitates a paradigm shift in animal nutrition. This review establishes that the biological transformation of NGFRs — driven by the synergistic application of microbial fermentation, targeted enzymatic hydrolysis, and insect-based micro-bioreactors — is the most effective strategy for nutritional valorization. By actively degrading anti-nutritional factors, remodeling the host's intestinal microecology, and enhancing terminal meat quality, these multi-stage bioconversion networks offer a sustainable alternative to conventional feedstuffs. As multi-omics technologies continue to decode the complex host-microbe-diet interactions, and as regulatory frameworks adapt to these innovations, the industrialized bioconversion of non-grain resources will serve as the core engine for achieving agricultural carbon neutrality and securing the global protein supply chain.

Author Contributions

Conceptualization: Ruxi Yuan and Shuibao Shen; Methodology: Xiaoyang Ma and Xiaochen Ma; Formal analysis: Ruxi Yuan and Xiaoyi Jia; Investigation: Xiaoyang Ma and Xiaochen Ma; Resources: Shuibao Shen and Xiaoyi Jia; Data curation: Ruxi Yuan and Xiaoyang Ma; Writing — original draft preparation: Ruxi Yuan; Writing — review and editing: Shuibao Shen; Visualization: Ruxi Yuan and Xiaochen Ma; Supervision: Shuibao Shen; Project administration: Shuibao Shen; Funding acquisition: Shuibao Shen. All authors have read and agreed to the published version of the manuscript.

Artificial Intelligence (AI) Statements

During the preparation of this work, the authors used large language models (LLMs) exclusively for language polishing, grammar correction, and improving the readability of the English text. The AI tools were not used to generate research ideas, analyze data, or draw scientific conclusions. After using these tools, the authors thoroughly reviewed and edited the content as needed and take full responsibility for the integrity, accuracy, and originality of the final publication.

Ethics Approval

This article is a review of previously published peer-reviewed studies, and does not involve any animal experiments, human trials, microbial isolation operations, or other research activities that require ethical approval. Therefore, no additional ethical approval is required for this study.

Conflict of Interest

The authors declare that they have no conflict of interest.

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