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REVIEW ARTICLE

Host Lipids as Modulators of Avian Pathogenic *Escherichia coli* Infection: Mechanisms of Virulence Suppression, Microbiota-Mediated Colonization Resistance, and Therapeutic Potential

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ABSTRACT

Colibacillosis caused by avian pathogenic *Escherichia coli* (APEC) is a significant threat to poultry, with substantial economic and public health implications, especially with the emergence of multidrug-resistant APEC strains. In this comprehensive review, we present recent evidence that host lipids, both exogenous and endogenous, are increasingly recognized as important contributors in the regulation of host responses to APEC, via the complex interplay of mechanisms. We outline four complementary mechanisms of lipid-mediated protection: (1) direct down-regulation of APEC virulence genes, particularly through interactions of polyunsaturated fatty acids (PUFAs) such as arachidonic acid with bacterial regulators such as FadR; (2) modification of the microbiota to potentially enhance colonization resistance by promoting beneficial bacteria like Lactobacillus and Bifidobacterium and suppressing pathogenic Enterobacteriaceae; (3) enhancement of gut barrier function via increased tight junction protein expression and mucin secretion; and (4) modulation of pro-inflammatory and pro-resolving immune factors may contribute to improved pathogen clearance and tissue repair processes. Recent research has demonstrated that ω-3 PUFA supplementation in the diet reduced pathogen burden and improved gut health in experimental poultry systems, although the magnitude and reproducibility of these effects remain variable across studies. But critical research gaps exist, such as avian-specific mechanistic investigations, time-dependent effects of lipid-microbiota-pathogen interactions, and formulations suitable for commercial use in terms of stability, affordability and delivery efficiency. This review, which bridges lipid biology, microbiome research and immunology, offers a scientific foundation for precision nutrition approaches that can simultaneously modulate pathogens, microbiota and host immunity. These lipid interventions have great potential for sustainable APEC control in poultry.

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INTRODUCTION

Avian Pathogenic *Escherichia coli* (APEC) is the main cause of colibacillosis. It results in billions of US dollars in annual poultry industry losses (Nawaz *et al*., 2024, Xue *et al*., 2024). Unlike other commensal *E. coli*, APEC harbors virulence factors such as adhesins (FimH, PapC), invasins (IbeA), siderophores (aerobactin, salmochelin), toxins (α-hemolysin, CNF), and serum resistance proteins (Iss, TraT) that allow it to overcome the gut barrier and spread to

extraintestinal sites (Kathayat *et al*., 2021; Abuseir *et al*., 2025; Abuseir *et al*., 2026). The disease is site-specific and presents with respiratory symptoms (airsacculitis, pneumonia), polyserositis, and reproductive tract infections (salpingitis, oophoritis), resulting in mortality, reduced egg production, and vertical transmission (Nawaz *et al*., 2025b). The rise of multidrug-resistant APEC carrying plasmid-borne β-lactam and fluoroquinolone resistance genes makes therapy challenging (Hafez and Attia, 2020; Shoaib *et al*., 2025b). APEC not only has adverse effects on mortality, but also on growth, veterinary expenses, and carcass condemnations, making it a major limiting factor for the poultry industry (Fancher *et al*., 2020).

Lipid metabolism is a complex network of pathways that goes beyond energy storage to play important roles in immune modulation and signaling, which are critical factors in host-pathogen interactions. This is especially notable in the gut, where dietary, synthesized, and microbially modified lipids interact to create a hostile or conducive environment for pathogen establishment (Brown *et al*., 2023). Gastrointestinal processing emulsifies and hydrolyzes lipids to bioactive components, free fatty acids (FFAs), monoglycerides, and lysophospholipids. Lipids are further categorized by chain length: long-chain fatty acids (such as palmitic and stearic) influence membrane integrity and protein function; medium-chain fatty acids have direct antimicrobial effects, and polyunsaturated fatty acids (PUFAs) stimulate the production of inflammatory and pro-resolving mediators. The gut microbiota also modulates this system by deconjugating bile acids and producing short-chain fatty acids (SCFAs) resulting from lipid metabolism, which in turn modulate the immune system and gut barrier functions. Importantly, dietary fats can affect microbial ecology, and the resulting response loop regulates disease susceptibility (Dyall *et al*., 2022) (Fig. 1A-E).

Resistance to colonization, commonly known as the "barrier effect," is an important host protective mechanism whereby the gut microbiota protects the host against pathogens via inhibition through competition for nutrients, production of toxic metabolites, and regulation of the immune system. Omega-3 fatty acids (ω-3s) stimulate the growth of Lactobacillus and Bifidobacterium, and suppress the growth of pathogens like Enterobacteriaceae (Taha *et al*., 2025). Host-derived lipids, including bile acids, also shape microbial community structure. Modest changes in lipid composition can shift the microbial balance, highlighting the promise of lipid-based interventions to enhance colonization resistance and prevent disease (Hung *et al*., 2021).

Several important gaps remain in understanding lipid-mediated immunity against APEC (Brown *et al*., 2023). Most studies rely on mammalian models despite major avian-specific differences in bile acid composition, cecal fermentation, and immune physiology (Sun *et al*., 2022). Temporal aspects of lipid signaling and microbiota interactions also remain poorly characterized (Gidden *et al*., 2009). In addition, mechanisms regulating APEC virulence through lipid-responsive pathways such as FadR remain incompletely understood, while lipid oxidation during feed processing limits commercial application (Chen *et al*., 2024). Long-term safety and environmental effects of lipid supplementation also require further investigation.

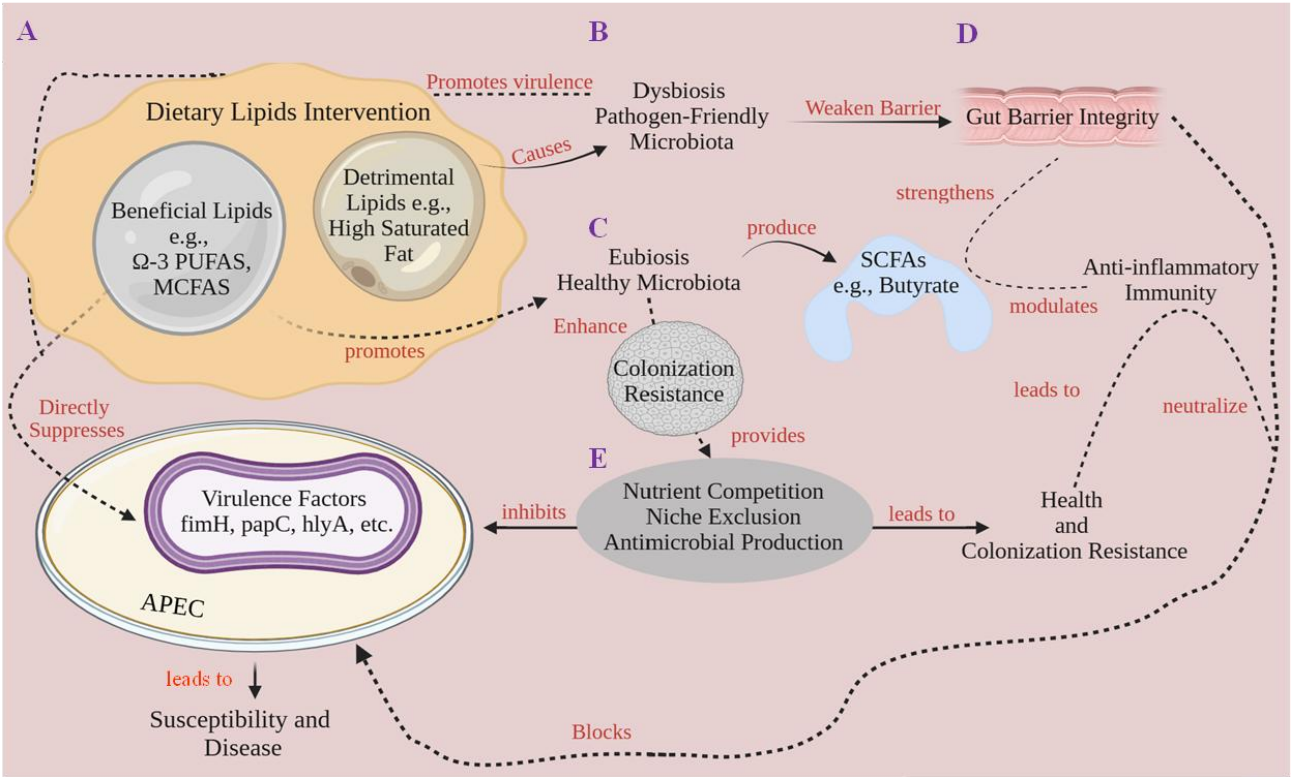

Fig. 1: Host lipids regulate APEC resistance in poultry. (A) ω-3 PUFAs (EPA/DHA) modulate poultry immunity against APEC. (B) Detrimental lipids cause dysbiosis (pathogen-friendly microbiota). (C) Beneficial ω-3 PUFAs promote eubiosis (healthy microbiota). (D) In contrast, detrimental saturated fats drive dysbiosis, weaken barrier function, and create pathogen-friendly conditions. ω-3 PUFAs also directly suppress APEC virulence factors, collectively determining host resistance or susceptibility to disease. (E) Eubiosis enhances colonization resistance and provides nutrient competition, niche exclusion, and antimicrobial production for better health and colonization resistance.

Lipids Modulate Immunity Against APEC: Lipids regulate avian immunity against APEC through conserved, but poultry-relevant mechanisms (Garcia *et al*., 2023). Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) as precursors for bioactive mediators regulate inflammation and resolution: eicosanoids (prostaglandins, leukotrienes) derived from arachidonic acid induce early anti-pathogen responses, while EPA and DHA-derived specialized pro-resolving mediators (SPMs) promote pathogen clearance and tissue repair (Soliman *et al*., 2025). Membrane lipid composition further shapes immune function: ω-3 PUFAs disrupt cholesterol-rich lipid rafts, blocking Toll-like receptor 4 (TLR4) signaling and reducing pro-inflammatory cytokines (Mazgaeen and Gurung, 2020), while saturated/unsaturated fatty acid ratios regulate phagocytosis and immune cell migration (Zhang *et al*., 2021). Lipids also regulate antimicrobial peptide (AMPs) production: butyrate (a microbiota-derived short-chain fatty acid) epigenetically enhances cathelicidins/β-defensins (Ney *et al*., 2023), and ω-3s PUFAs modulate AMP expression in a tissue-specific manner (Bodur *et al*., 2025). Collectively, these mechanisms link lipid metabolism with host immune regulation during APEC infection. However, immune regulation through lipids is context-dependent and protective in some experimental systems but not in others. While ω-3 PUFAs can have anti-inflammatory and beneficial effects on the microflora, their overuse or the change of the ω-6: ω-3 ratio, or the accumulation of oxidized lipid products, can negatively affect immune function, oxidative stress and gut homeostasis (Lamarre *et al*., 2021). Lipid effects are also species-, dose-, age-, stage-, host-, strain and environmental dependent. Furthermore, dietary lipids can have differential effects on the composition of the microbiota, production of SCFAs, and colonization resistance depending on the type of feed and housing. In mammalian systems, there are several mechanisms that prevent APEC, such as Treg polarization, disruption of lipid rafts, and specialized pro-resolving mediator signaling; these mechanisms have yet to be validated in poultry systems (Tan *et al*., 2022). These restrictions suggest further mechanistic investigations and dose optimization testing in poultry before general field use.

APEC Virulence and Regulation by Host Lipids

Virulence Arsenal of APEC: APEC employs a repertoire of virulence factors to colonize the host, evade the immune system, and disseminate systemically. These strategies, including adhesins, invasins, toxins, iron acquisition systems, and factors that confer serum resistance, enable APEC to survive in challenging extraintestinal environments characterized by immune surveillance, complement activity, and limited nutrients (Shoaib *et al*., 2024; Nawaz *et al*., 2025a). Key adhesins help in tissue attachment; type 1 fimbriae (FimH) interact with mannosylated receptors, P pili (PapG) promote tissue-specific invasion, and temperature-sensitive hemagglutinin (Tsh) exhibits both adhesive and proteolytic functions (Biran *et al*., 2021; Shoaib *et al*., 2025c) **(**Fig. 2**)**. Invasins such as IbeA assist in penetrating cellular barriers, including the blood-brain barrier, by engaging host receptors and activating internalization signaling pathways. The expression of many virulence genes is affected by environmental signals, allowing a flexible response during infection (Bui *et al*., 2024) (Table 1). APEC uses additional invasins, such as OmpA, to promote host cells' internalization, thereby forming protective intracellular niches that are conducive to replication. Its toxins, α-hemolysin (HlyA) and cytotoxic necrotizing factor 1 (CNF1), inflict direct damage on host tissues by lysing cell membranes and disrupting cytoskeletal signaling by modulating Rho GTPases, respectively. To counteract host nutritional immunity, APEC utilizes high-affinity siderophores, such as aerobactin and salmochelin, for iron acquisition, which are essential for virulence and are expressed at high levels *in vivo*. Serum resistance is facilitated by factors, including the Iss, TSH, and TraT proteins, which together prevent complement deposition and activation, thereby allowing for systemic dissemination (Shoaib *et al*., 2025a). These coordinated adaptations allow APEC to evade innate immune responses and establish a persistent infection.

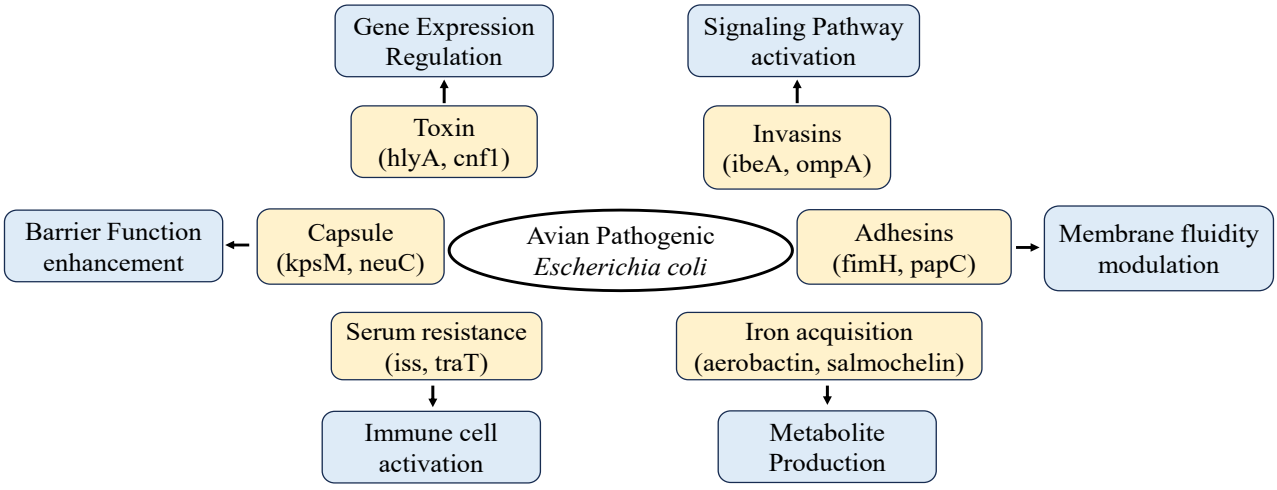

Fig. 2: APEC virulence factors and host lipid-mediated modulation. APEC uses adhesins (*fimH*, *papC*), invasins (*ibeA*, *ompA*), toxins (*hlyA*, *cnf1*), iron acquisition systems, serum resistance factors (*iss*, *traT*), and capsule components to colonize and infect hosts. Host lipids counteract these via membrane fluidity modulation, signaling pathway regulation, virulence gene control, metabolite production, immune cell activation, and barrier function enhancement.

Table 1: Major APEC virulence factors and their functions

Virulence Factor	Gene(s)	Protein Function	Role in Pathogenesis	Lipid-Mediated Regulation	References
Type 1 Fimbriae	*fimH*, *fimA*	Mannose-binding adhesin; epithelial attachment	Initial colonization of intestinal epithelium, respiratory tract, and oviduct	Downregulated by ω-3 PUFAs (EPA, DHA); upregulated by saturated fatty acids; suppressed by arachidonic acid via FadR	Kathayat *et al*., 2021; Nawaz *et al*., 2024; Watts and Wigley, 2024
P Pili	*papA*, *papC*, *papG*	Gal-α-1,4-Gal-specific adhesin	Extraintestinal colonization; kidney and respiratory tropism	Strongly inhibited by PUFAs; reduced by MCFAs	Bui *et al*., 2024
Invasion protein	*ibeA*	Host cell invasion; blood–brain barrier crossing	Systemic dissemination; meningitis; intracellular survival	Transcriptionally suppressed by PUFAs; reduced by ω-3 supplementation	Kathayat *et al*., 2021; Paris *et al*., 2024
α-Hemolysin	*hlyA*, *hlyC*, *hlyB*, *hlyD*	Pore-forming toxin; cytolysis	Tissue damage; inflammation; cell death; immune suppression	Enhanced by saturated fats; strongly reduced by EPA/DHA	Wang *et al*., 2020; Watts and Wigley, 2024
Cytotoxic Necrotizing Factor 1	*cnf1*	Rho GTPase activator; cytoskeleton disruption	Tight junction damage; persistent infection; inflammation	Inhibited by ω-3 PUFAs; downregulated by lipid rafts modulation	Mazgaeen and Gurung, 2020; Chaoprasid and Dersch, 2021
Aerobactin siderophore	*iucA*, *iucB*, *iucC*, *iucD*	High-affinity iron chelation	Overcomes nutritional immunity; critical for virulence	Downregulated by arachidonic acid; suppressed by ω-3 PUFAs	Li *et al*., 2021
Salmochelin siderophore	*iroA*, *iroB*, *iroC*, *iroD*, *iroE*	Glucosylated enterobactin; iron uptake	Evades lipocalin-2; enhances systemic infection	Reduced by ω-3 PUFAs supplementation	Kathayat *et al*., 2021
Increased Serum Survival protein	*iss*	Complement resistance; anti-phagocytosis	Survives blood dissemination; extraintestinal infection	Reduced expression with fish oil (ω-3) supplementation	Biran *et al*., 2021; Nawaz *et al*., 2024
Temperature-sensitive hemagglutinin	*tsh*	Serine protease and adhesin; Mucinase activity	Mucosal adhesion; tissue invasion; extracellular degradation	Inhibited by MCFAs; downregulated by ω-3 fatty acids	Nawaz *et al*., 2025a
Outer membrane protein A	*ompA*	Structural integrity; invasin; serum resistance	Cell entry; immune evasion; intracellular niche formation	Modulated by host membrane fatty acid composition	Guan *et al*., 2021; Nawaz *et al*., 2025b
Capsule polysaccharide	*kpsM*, *kpsT*, *neuC*	Anti-phagocytic barrier; serum resistance	Systemic infection; environmental persistence	Regulated by host lipid membrane fluidity	Hafez and Attia, 2020
TraT	*traT*	Serum resistance; surface exclusion	Inhibits complement deposition; immune evasion	Repressed by PUFAs	Watts and Wigley, 2024; Abuseir *et al*., 2025; Batool *et al*., 2026
Biofilm-associated protein	*fimC*, *pdeN*	Adhesion; aggregation; biofilm maturation	Persistence; environmental tolerance; antibiotic tolerance	Inhibited by ω-3 PUFAs; reduced by MCFAs	Wang *et al*., 2024; Nawaz *et al*., 2025a
Quorum-sensing regulator	*lsrR*	Virulence network control; gene expression	Coordinates adhesion, invasion, toxin secretion	Modulated by host lipids; inhibited by PUFA-dependent signaling	Nawaz *et al*., 2025b
Two-component system	*phoP*/*phoQ*	Stress response; membrane remodeling	Antimicrobial resistance; immune evasion	Targeted by fatty acids; downregulated by ω-3 PUFAs	Marotta *et al*., 2023; Kamel *et al*., 2024

Direct Downregulation of Virulence Gene Expression by Fatty Acids: Fatty acids can directly repress virulence gene transcription via host-derived fatty acids. Transcriptional regulators like FadR that coordinate fatty acid metabolism and virulence gene expression in Gram-negative bacteria play a role in the repression of virulence gene transcription by host-derived fatty acids. Long-chain fatty acids (LCFAs) such as arachidonic acid (ARA) inhibit virulence-associated genes like *fimH*, *hlyA*, and iron acquisition systems and diminish bacterial adhesion, invasion, and colonization by altering FadR DNA-binding activity. Also, ω-3 PUFAs could affect membrane fluidity and the envelope's stress responses, potentially impacting virulence regulation. While a lot of insights have been gained from ExPEC, UPEC, and *in vitro* studies, now there are more and more similar pathways being identified in APEC and need to be further validated in poultry (Kathayat *et al*., 2021). Host lipids disrupt bacterial communication and stress-response systems. Alterations in the membrane induced by fatty acids can alter the signaling through PhoP/PhoQ, which can impact stress tolerance, immune evasion, and remodeling of the outer membrane (Marotta *et al*., 2023) **(**Fig. 3A-E**).**

Likewise, envelope stress response pathways CpxA/CpxR and BaeS/BaeR could play a role in virulence attenuation via lipid changes, which affect membrane permeability and metabolic adaptation (Allen and Martinez, 2020). Another interface between host lipid metabolism and virulence regulation of bacteria is quorum sensing. The pathways involved in biofilm formation, adhesion, motility, and virulence gene expression are regulated by AI-2 and LuxR-associated pathways in APEC (Nawaz *et al*., 2026). Host-derived fatty acids might alter membrane-associated signal transport or lsr operon-associated regulators, which may suppress the coordinated activation of virulence and biofilm maturation, thereby interrupting quorum-sensing signaling. Most mechanistic evidence is from related ExPEC or *in vitro* models, however, and there are restrictions on poultry-specific validation (He *et al*., 2026).

Host–Pathogen Metabolic Interactions: Host lipid metabolism and APEC pathogenicity are dynamic metabolic interactions and not a straightforward immune response. The adaptation, energy utilization, virulence regulation, iron scavenging, and stress tolerance of bacteria are affected by host-derived and microbiota-derived metabolites, including fatty acids and bile acids. In turn, lipid-mediated microbiota modulation impacts SCFA production, bile acid metabolism, and colonization resistance and indirectly affects pathogen survival. The interactions imply that lipid-based interventions could simultaneously affect the fitness of the bacteria, the microbial ecology, and the host immunity (Huiqing *et al*., 2013). In poultry systems, however, the metabolic signaling pathways between host lipids and APEC virulence are not fully understood.

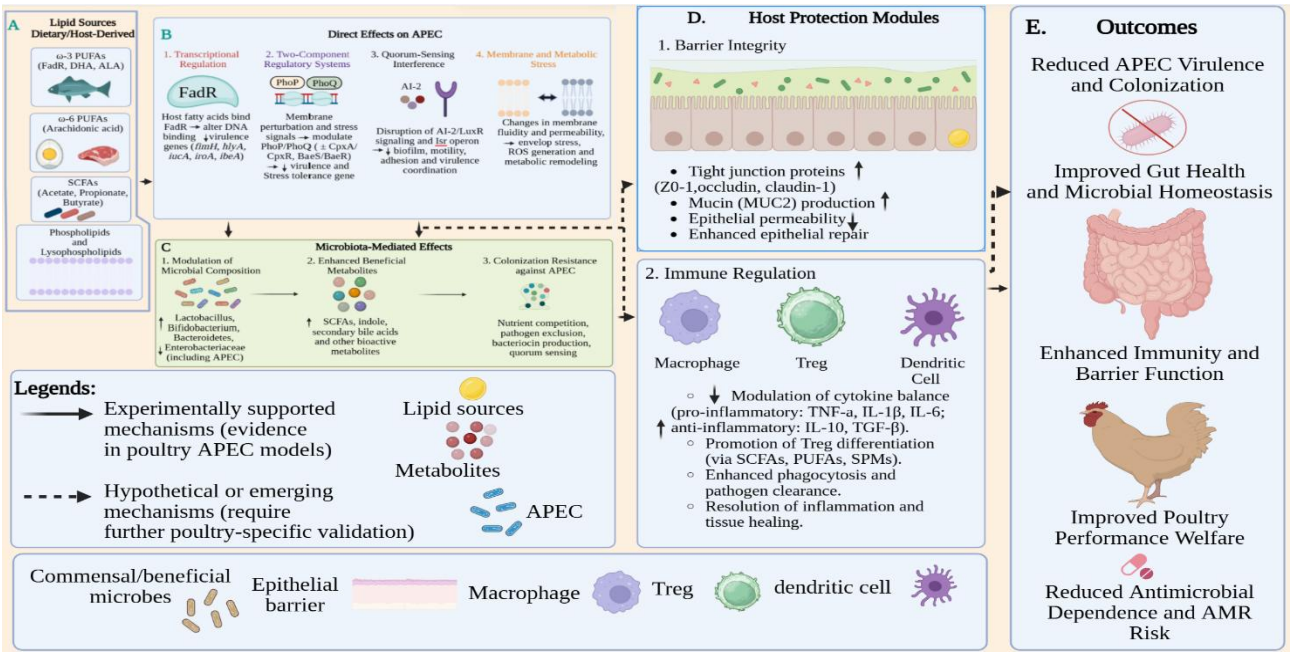

Fig. 3: Model of lipid-mediated regulation of APEC pathogenesis and host responses at the systems level. Lipids of diet and host origin (such as ω-3 and ω-6 PUFAs, short-chain fatty acids (SCFAs), phospholipids, and bile acids) are important modulators. (B) Lipids have a direct effect on APEC by altering membrane fluidity, modulating two-component systems (PhoP/PhoQ and envelope stress regulators), affecting quorum sensing and inducing membrane/metabolic stress, which all result in down-regulation of virulence genes. (C) Lipids alter the gut microbiota, increase the production of beneficial metabolites, and increase resistance to APEC. (D) These activities create and regulate immune response and maintain the integrity of the epithelial barrier. (E) This combination of effects leads to decreased APEC virulence and colonization, better gut health, immunity and poultry performance, and reduced use of antimicrobials. Solid arrows are pathways supported by experiments; dashed arrows are pathways that are not yet well established but are plausible (www.BioRender.com).

Contradictory Findings and Knowledge Gaps: The lipid-mediated suppression of APEC virulence is a promising approach, but there are some discrepancies that still need to be answered. Some studies have shown that polyunsaturated fatty acids have been shown to decrease the expression of adhesion- and toxin-associated genes, but this effect is limited under stress and nutrient-rich conditions. Likewise, different breeds of poultry, age, type of feed, housing, and experimental design affect lipid-induced microbiota changes. Furthermore, the majority of evidence for FadR signaling, quorum-sensing interference, and membrane fluidity-associated virulence regulation has come from mammalian ExPEC or *in vitro* systems, but not from poultry infection systems (Kathayat *et al*., 2021). Thus, more mechanistic and controlled *in vivo* studies are needed for poultry.

Lipid-Microbial Interface for Colonization Resistance

Dietary Lipids Act on the Gut Microbiota: Dietary lipids influence gut microbiota through direct antimicrobial effects, nutrient provision, and host factors (Feng *et al*., 2022). Medium-chain saturated fatty acids (C8-C14) generally affect bacterial membranes; long-chain saturated fatty acids (C16-C18) modulate membrane rigidity and permeability; and ω-3 PUFAs stimulate the growth of Lactobacillus and Bifidobacterium over Enterobacteriaceae (Arellano *et al*., 2023, Borreby *et al*., 2023; Taha *et al*., 2025). Lipid fermentation by bacteria produces SCFAs, which also impact communities through pH metabolism. Effects occur over short (hours to days) and long (weeks to months) timeframes; interactions between lipid interventions and time-dependent microbial responses may influence pathogen survival and colonization dynamics (Fig. 4). Beneficial bacteria enhanced by dietary lipids improve colonization resistance through acidification, bacteriocin production, immune modulation, and maintenance of epithelial barriers (Darbandi *et al*., 2022). APEC infection disrupts gut microbial balance by promoting Enterobacteriaceae expansion and reducing SCFA-producing bacteria, thereby weakening colonization resistance and immune function (Hrala *et al*., 2021; Watts and Wigley, 2024).

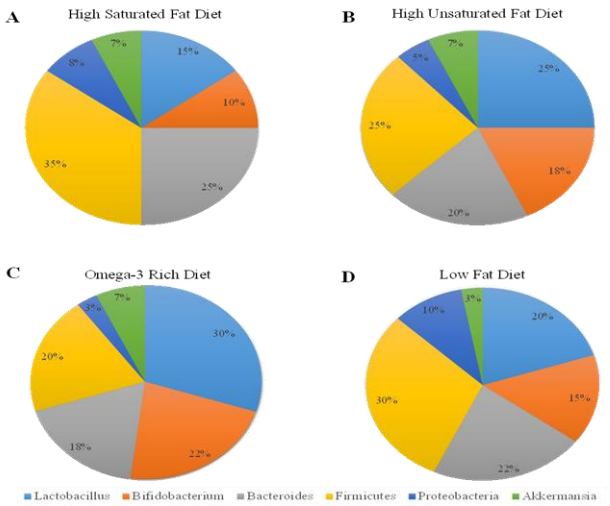

Fig. 4: Gut microbiota composition and APEC resistance are affected by dietary lipids. Dietary shifts in microbiota: (A) Saturated fat-rich: Firmicutes/Bacteroides increase, beneficial genera decrease. (B) High-unsaturated fat: Beneficial genera increase, pathogens decrease. (C) ω-3 PUFA: Best enrichment of Lactobacillus/Bifidobacterium, low pathogens. (D) Low-fat: Firmicutes increase, Proteobacteria increase, and resistance decreases. Fat composition affects microbiota and APEC resistance.

Microbiota Metabolites as Host Defense Effectors: Microbiota metabolites mediate host defense, including bactericidal activity, immune regulation, and intestinal barrier function, and their synthesis is modified by dietary lipids that modify microbiota composition (Liu *et al*., 2022; Li *et al*., 2025). Key SCFAs (butyrate, acetate, propionate) fuel colonocytes, strengthen barriers, induce antimicrobials, and regulate inflammation via GPR receptors (Caballero-Flores *et al*., 2023). Additional protective metabolites include organic acids, hydrogen peroxide, and pathogen-targeting bacteriocins. Lipid-rich diets potentially enhance colonization resistance by promoting microbiota that generate these defensive metabolites, disrupting pathogenic cycles (Liu *et al*., 2023; Zhong *et al*., 2026).

Mechanisms of Colonization Resistance Against APEC

Nutrient Competition: Beneficial microbiota outcompete pathogens for iron, amino acids, and carbohydrates (Horrocks *et al*., 2023). Commensals sequester iron, induce lipocalin-2, and deplete essential nutrients required for APEC virulence. Fermentation produces SCFAs that reinforce the gut barrier and immunity (Deleu *et al*., 2021). High microbial abundance and metabolic activity maximize nutrient exclusion and colonization resistance (Horrocks *et al*., 2023).

Physical Niche Exclusion: Beneficial gut microbiota physically blocks pathogens by occupying key ecological niches. They form extracellular polymeric substance (EPS) embedded biofilms on the intestinal epithelium (physical and chemical barrier) (Al-Madboly *et al*., 2024) and use high-affinity adhesins to outcompete pathogens for host receptors. This triggers enhancement of intestinal barrier, mucin production, and antimicrobial peptide expression and establishes epithelium-proximal commensal niches, critical for colonization resistance (Ahmed *et al*., 2024).

Antimicrobial Metabolites: "Good" bacteria produce a range of antimicrobials. Organic acids (such as lactic, acetic, and propionic) acidify and disrupt membranes; bacteriocins (nisin and lactocin) specifically target pathogens; hydrogen peroxide activates immunity and oxidative stress. This multi-faceted approach maintains gut health and APEC resistance (Liu *et al*., 2022).

Modulation of Host Immunity: Beneficial gut bacteria potentially enhance colonization resistance by modulating; they activate pattern recognition receptors (PRRs) (TLR2/TLR4/TLR5) to induce antimicrobials/sIgA, use SCFAs (butyrate) to promote regulatory T-cell differentiation and immune balance, and support the integrity of gut-associated lymphoid tissue (GALT). SCFAs signal via GPR receptors to regulate immunity, underscoring therapeutic potential for infections (Zheng *et al*., 2020; Duan *et al*., 2022).

Improvement of Intestinal Barrier Function: Beneficial gut bacteria strengthen the intestinal epithelial barrier via direct interactions and metabolites. Butyrate (a key SCFA) fuels colonocytes, upregulates tight junction proteins, reducing translocation (Deleu *et al*., 2021). Commensals stimulate mucin secretion and modulate epithelial gene expression for repair and antimicrobial production (Gieryńska *et al*., 2022) **(**Fig. 5**)**. To provide an integrated overview of current evidence, the major lipid classes implicated in APEC regulation, microbiota modulation, and host immune responses are summarized in Table 2. It highlights their proposed mechanisms of action, biological effects, and current evidence supporting their application in poultry health management. Together, these findings show that lipid-mediated protection against APEC includes interconnected effects on bacterial virulence regulation, microbiota ecology, epithelial barrier integrity, and host immune homeostasis rather than a single isolated mechanism.

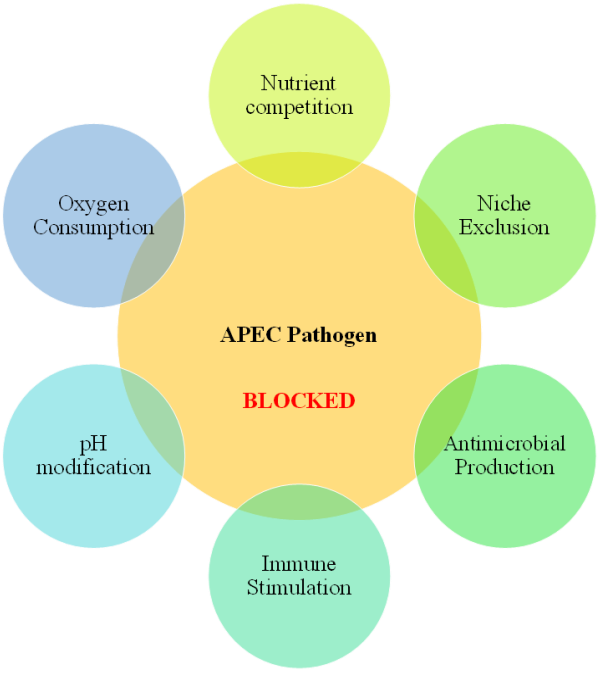

Fig. 5: Probiotics mechanisms to block APEC colonization via six mechanisms: outgrowth and competition for nutrients; exclusion; direct antimicrobials; host immune modulation; pH lowering; and an anaerobic environment that is hostile to facultative anaerobes such as APEC (www.BioRender.com).

Therapeutic Implications and Intervention Strategies

Dietary Lipid Supplementation: Targeted lipid supplementation reduces APEC infections via microbiota and immune modulation, requiring optimized type, dosage, and timing (Waliaula *et al*., 2024). ω-3 PUFAs (2–3% fish oil) reduce APEC colonization, attenuate virulence-associated traits, and improve intestinal microbial balance and host immune responses in poultry systems (Saini *et al*., 2021; Tina *et al*., 2025). MCTs improve gut barrier and reduce mortality (Torres-Vanegas *et al*., 2025). Early administration primes immunity, with continuous supplementation needed in high-pathogen environments (Watanabe and Tsujino, 2022) (Fig. 6).

Precision Nutrition Approaches: Precision nutrition to prevent APEC combines biomarker-based risk profiling and supplementation with technological monitoring. Biomarkers include genetic, metagenomic, and physiological markers of dysbiosis and immune function.

Flocks at high risk of APEC receive high-dose lipid supplements, while those at low risk receive low-dose supplements; IoT sensors allow real-time adjustments (increased ω-3s during heat stress). Emerging precision nutrition and digital monitoring technologies may eventually facilitate individualized dietary modulation strategies for poultry disease prevention, although their application to lipid-mediated APEC control remains largely conceptual at present (Ma *et al*., 2025).

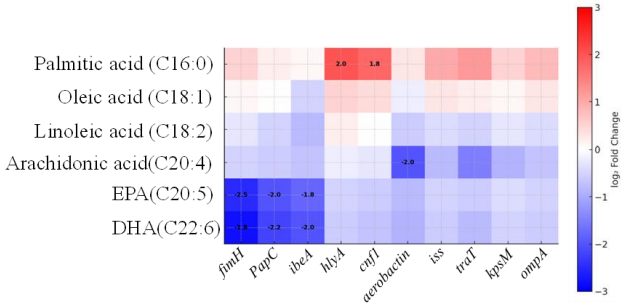

Fig. 6: Heatmap of log_2 fold-changes in virulence gene expression with six different lipid treatments. ω-3 PUFAs (EPA/DHA) downregulate genes for adhesion/invasion; saturated palmitic acid upregulates toxin genes (*hlyA*, *cnf1*); and arachidonic acid downregulates iron acquisition (aerobactin). Red= upregulation, blue= downregulation ($|log_2 FC| > 1.5$, $P<0.05$).

Combinations with Probiotics, Prebiotics and Other Interventions: Lipid-based anti-APEC strategies work best in concert with other methods: probiotics (lipid-metabolizing, improved survival) (Wu *et al*., 2022). Prebiotics (promotion of SCFA-producers), vaccination (lipid adjuvants, timing), and phytogenics (antimicrobial synergy) (Wang *et al*., 2024). This maximizes resistance.

Formulation and Delivery Systems: Lipid-based approaches to preventing APEC should protect against oxidation during processing and storage (Musakhanian *et al*., 2022). Microencapsulation (spray drying, coacervation) protects lipids for controlled release while synergistic antioxidants (tocopherols, BHT/BHA) preserve stability (Gulcin, 2025). ω-3 PUFAs are susceptible to oxidative deterioration during feed manufacturing and extended storage in commercial chicken farms. To preserve lipid bioactivity and efficacy, stabilization strategies such as antioxidant inclusion, oxygen-limiting packing, and ideal storage conditions are crucial (Idowu *et al*., 2022). Particle size, shape, and coating impact stability and absorption, and uniform feed distribution is essential for efficacy (Ng *et al*., 2022). Increased lipid peroxidation, oxidative tissue damage, dysregulated inflammatory signaling, altered microbial diversity, and compromised metabolic homeostasis are some of the unanticipated negative effects that can result from excessive or unbalanced lipid supplementation. Under heavy commercial production conditions linked to heat stress, environmental stresses, or concomitant infections, these risks may be very significant (Alagawany *et al*., 2026).

Economic Considerations: Lipid-based anti-APEC strategies need to balance the cost of supplementation with health and growth benefits. Efficacious fish oils are expensive, driving innovation for cost-effective EPA/DHA (Bagchi *et al*., 2025). Significant benefits include reduced mortality, better feed efficiency, and higher prices due to reduced antibiotic use (Schell *et al*., 2023). Potential long-term risks (oxidation, regulation) need to be addressed through risk-sharing measures (Fig. 7**)**.

Table 2: Major lipid classes and their reported effects against APEC

Lipid Type	Major Source	Proposed Mechanism of Action	Effect on APEC Virulence	Effect on Gut Microbiota	Effect on Host Immunity	Key References
Omega-3 PUFAs (EPA, DHA)	Fish oil, algae oil, flaxseed	Modulation of membrane fluidity, suppression of FadR signaling, anti-inflammatory mediator production	Downregulation of fimH, hlyA, ibeA, iron acquisition genes; reduced adhesion and invasion	Promotes Lactobacillus and Bifidobacterium; suppresses Enterobacteriaceae	Enhances immune resolution, modulates cytokines, reduces excessive inflammation	Kathayat *et al*., 2021; Garcia *et al*., 2023; Watts and Wigley, 2024
Arachidonic acid (ω-6 PUFA)	Animal fats, poultry tissues	Interaction with bacterial regulatory systems and eicosanoid signaling	Suppresses selected virulence genes under certain conditions	Variable effects depending on dose and inflammatory state	Promotes early inflammatory responses	Kathayat *et al*., 2021; Wu *et al*., 2023
Medium-chain fatty acids (MCFAs)	Coconut oil, palm kernel oil	Membrane disruption, stress-response activation	Reduced biofilm formation and virulence expression	Inhibits pathogenic Enterobacteriaceae	Improves gut barrier integrity	Watanabe and Tsujino, 2022; Arellano *et al*., 2023
Short-chain fatty acids (SCFAs)	Microbial fermentation products	GPR-mediated signaling, epigenetic regulation, epithelial energy support	Indirect suppression through enhanced colonization resistance	Supports SCFA-producing commensals	Enhances Treg responses, antimicrobial peptide expression, barrier function	Caballero-Flores *et al*., 2023; Ney *et al*., 2023
Saturated long-chain fatty acids	Animal fats, high-fat diets	Altered membrane rigidity and inflammatory signaling	May enhance toxin-associated gene expression	Can promote dysbiosis and pathogen expansion	May increase pro-inflammatory responses	Borreby *et al*., 2023; Brown *et al*., 2023
Phospholipids and lysophospholipids	Cell membranes, soybean lecithin	Membrane remodeling and signaling regulation	Potential interference with bacterial membrane adaptation	Modulates microbial membrane interactions	Supports epithelial repair and signaling	Dyall *et al*., 2022
Specialized pro-resolving mediators (SPMs)	EPA/DHA-derived metabolites	Resolution-phase immune signaling	Indirect reduction of pathogen persistence	Limited direct evidence	Promotes inflammation resolution and tissue repair	Soliman *et al*., 2025
Bile acids and lipid metabolites	Host liver metabolism and microbiota-modified bile acids	Antimicrobial activity and niche selection	Limits pathogen colonization	Shapes microbial ecological balance	Modulates mucosal immunity	Khan *et al*., 2021; Brown *et al*., 2023

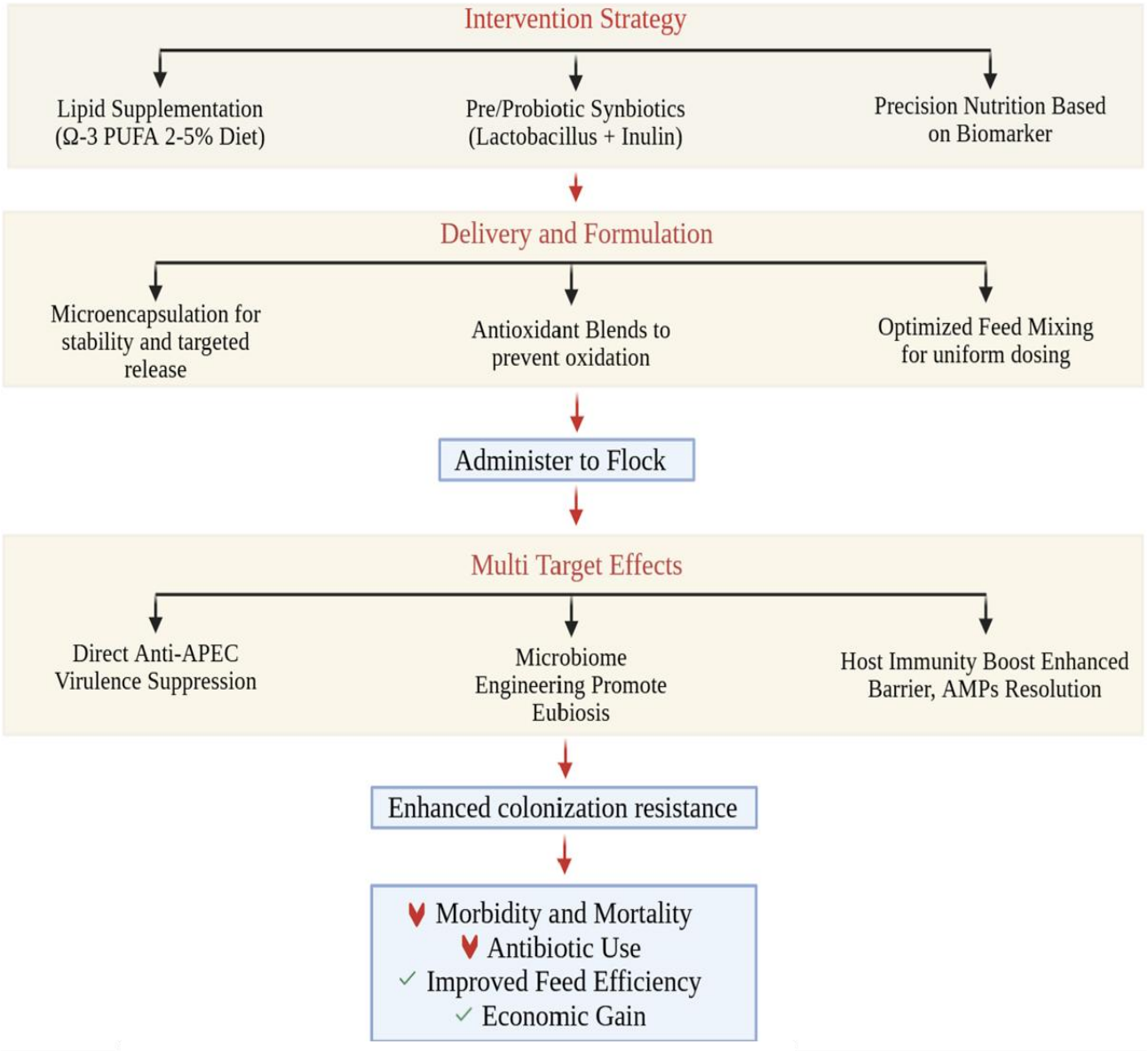

Fig. 7: APEC infection control intervention strategies. Supplements (lipids, synbiotics and precision nutrition) are manufactured for stability and consistency. Supplementation leads to direct virulence reduction, microbiome eubiosis and improved immunity, which increase colonization resistance and decrease mortality/antibiotic treatment, leading to better feed efficiency and economics (www.BioRender.com).

Future Research Directions: Mechanistic validation of lipid-mediated virulence regulation in poultry should be emphasized based on transcriptomics, metabolomics, and functional genetics in future studies (Fig. 8). Future microbiota research can help explain the effect of dietary lipids on microbiota, dissemination of antimicrobial resistance, and maintenance of colonization resistance in commercial poultry production (Table 3). Additionally, advances in precision nutrition technologies, combining sensory data with AI and multi-omics analysis, could enhance the effectiveness of lipid-based poultry interventions in the future, but their potential in APEC control is yet in its infancy and needs to be validated in poultry systems (Li *et al*., 2022). Environmental concerns of fish oil production can be mitigated through the use of sustainable sources of lipids such as those derived from algae containing ω-3 fatty acids. Yet, variability of lipid stability, dosage optimization, economic feasibility, and validation for poultry are still significant hurdles to commercialization (Qin *et al*., 2023; Mubashar *et al*., 2025).

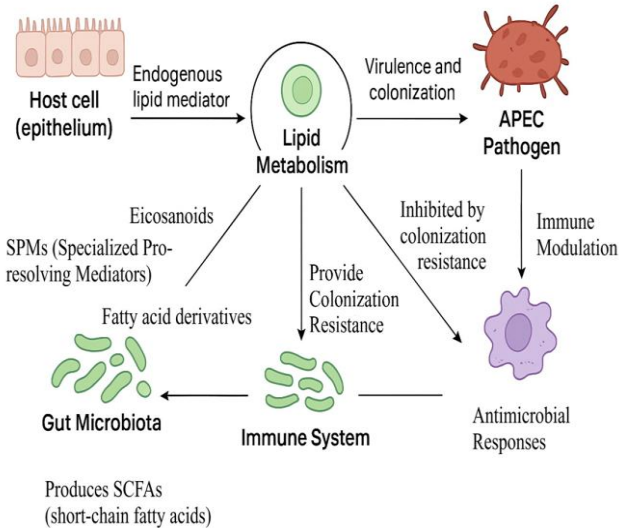

Fig. 8: Integrated model of lipid-mediated regulation of microbiota, immunity, and APEC virulence in poultry (www.BioRender.com).

Table 3: Major Knowledge Gaps and Future Research Priorities in Lipid-Mediated Control of APEC.

Research Area	Current Knowledge	Major Gap	Recommended Approach	Expected Impact
Lipid-mediated regulation of APEC virulence	ω-3 PUFAs and fatty acids can suppress selected virulence genes *in vitro*	Poultry-specific molecular mechanisms remain poorly characterized	Conduct avian *in vivo* transcriptomics, proteomics, and CRISPR-based validation studies	Identification of novel anti-virulence therapeutic targets
Host lipid–microbiota interactions	Lipids alter gut microbial composition and SCFA production	Temporal and causal relationships remain unclear in poultry systems	Longitudinal microbiome-metabolome studies in chickens	Improved precision nutrition strategies
Avian-specific immune modulation	Lipids regulate inflammation and immune signaling pathways	Most mechanistic evidence is extrapolated from mammals	Poultry-specific immunological and cytokine profiling studies	Development of targeted immune-modulating interventions
Lipid dosage optimization	Protective effects of ω-3 supplementation have been reported	Optimal dose, timing, and duration remain inconsistent	Controlled dose-response and feeding trials	Standardized commercial supplementation protocols
Oxidative stability of lipid formulations	PUFAs are highly susceptible to oxidation during feed processing	Limited data on long-term storage stability under field conditions	Development of microencapsulation and antioxidant stabilization systems	Improved efficacy and commercial feasibility
Lipid effects on antimicrobial resistance	Lipid supplementation may reduce pathogen abundance	Direct evidence regarding antimicrobial resistance gene dynamics is limited	Metagenomic analysis of resistance gene transfer and persistence	Reduction in antimicrobial resistance dissemination
Microbiota engineering approaches	Synthetic microbial communities show promise experimentally	Lack of validated poultry-specific microbial consortia	Multi-omics-guided microbiota engineering studies	Enhanced colonization resistance against APEC
Field-scale validation	Most studies are laboratory-based or short-term	Limited commercial poultry farm validation	Large-scale longitudinal field trials	Improved translational applicability
Precision nutrition technologies	AI and sensor-based nutrition systems are emerging	Integration with lipid interventions remains underdeveloped	Development of digital precision feeding platforms	Real-time optimization of poultry health management
Environmental sustainability	Fish oil supplementation raises sustainability concerns	Limited evaluation of ecological and economic sustainability	Life-cycle assessment and alternative lipid-source studies	Sustainable large-scale implementation

Conclusions: This review highlights the wide-ranging multifactorial influence of host lipids on modulation of APEC virulence, gut microbiota, epithelial barrier integrity, and immune responses. The current evidence indicates that lipid-based interventions can decrease the virulence of bacteria, enhance colonization resistance, and assist with reduction strategies of antimicrobials in poultry production. However, numerous insights into the mechanisms are derived from mammalian or *in vitro* systems, and there is still limited validation for poultry-specific systems. There are significant issues to address, such as dosage optimization, lipid stability, microbiota variability, and large-scale field reproducibility. Incorporation of poultry immunology, microbiome science, lipidomics and precision nutrition technologies into the future could help develop lipid-based anti-APEC strategies to be used in commercial poultry production in a sustainable fashion.

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