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Microbiome–Host Signaling Produces Nutritional, Immune, and Developmental Effects Only Under Specific Biological and Environmental Conditions

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ABSTRACT

Insect microbiomes are often discussed as if microbial presence itself predicts host nutritional, immune, or developmental benefit. That interpretation is too coarse for the available evidence. This molecular perspective argues that host phenotype is better understood as the outcome of conditional signaling: microbes must occupy an appropriate niche, generate or transform a biologically relevant signal, encounter a responsive host pathway, and do so within a nutritional, developmental, genetic, and environmental state that permits the signal to matter. Evidence from *Drosophila*, mosquitoes, honey bees, and other insects shows that microbial metabolites, cell-envelope features, redox-active products, and nutrient transformations can alter growth, metabolism, immunity, behavior, fecundity, and survival. Yet equally important boundary evidence shows that stable resident communities are absent in some insects, that similar host phenotypes can arise under different microbial states, and that developmental requirements can depend on diet formulation, vitamin stability, host genotype, and experimental method. The central synthesis proposed here therefore separates microbial presence from microbial function and separates function from host consequence. It treats nutritional, immune, and developmental effects as context-dependent outputs of an interaction among microbial signal production, host sensing, physiological state, and environmental constraint. This formulation yields testable expectations for axenic, gnotobiotic, metabolite-rescue, host-genetic, and stage-specific experiments without assuming that any single microbiome configuration is universally necessary or beneficial.

Keywords: Insect microbiome, Microbial metabolites, Nutritional mutualism, Gut immunity, Developmental signaling, Host genotype

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Introduction

Microbiome research in insects has moved from cataloguing bacterial associates toward asking when microbes alter host physiology. In *Drosophila*, gut-associated microorganisms participate in processes linked to epithelial homeostasis, metabolism, and immune regulation, making the system a powerful model for mechanistic host–microbe analysis [1]. Yet even within insects that reproducibly associate with gut bacteria, microbiome effects cannot be inferred from taxonomic membership alone. Intraspecific variation in microbial communities can alter

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host phenotypes, and strain-level differences may be relevant to the evolutionary and physiological consequences attributed to a nominally similar microbiome [2].

A central interpretive problem follows from the diversity of insect–microbe relationships. Caterpillars provide an important boundary case because many species do not maintain a resident gut microbiome comparable to that described in *Drosophila* or social bees, despite continuous microbial exposure through food and the environment [3]. Consequently, the statement that "the insect microbiome" drives a phenotype can conceal fundamentally different biological situations: persistent colonization, transient passage, environmentally reacquired bacteria, strain-specific symbiosis, or indirect modification of the food substrate. Host-associated community composition itself is shaped by multiple ecological and biological filters rather than by host identity alone [4].

This article develops a molecular perspective around a narrower proposition: nutritional, immune, and developmental effects require more than microbial presence. A microorganism must produce, consume, transform, or expose a molecular cue that is available in the relevant anatomical compartment; the host must possess a sensing or metabolic pathway capable of responding; and the interaction must occur under a diet, developmental stage, genotype, and environmental condition in which that response changes phenotype. The analytical distinction is therefore between association, biochemical activity, host sensing, and organismal consequence.

This distinction also accommodates null and conflicting results without treating them automatically as experimental failure. A microbe can be present but functionally irrelevant, active but buffered by the host, beneficial under undernutrition but neutral under nutrient sufficiency, or developmentally important in one experimental formulation yet dispensable in another. The inferential task is therefore not to decide whether microbiomes are generally beneficial, but to identify the biological conditions under which a microbial function becomes a consequential host signal.

Microbial signals and metabolites

The first conditional step is spatial and biochemical access. In *Drosophila melanogaster*, a specialized physical niche can support stable association of a multispecies gut microbiota, demonstrating that persistence is not simply a consequence of repeated ingestion but can depend on host-associated microanatomy that permits microbial residence [5]. This matters mechanistically because a microbial product cannot act as a sustained host signal unless production, localization, and exposure overlap in time and space.

Some of the clearest evidence links defined bacterial features to host nutrient-sensing pathways. *Lactiplantibacillus plantarum* symbiotic cues encoded by r/tRNA operons can engage intestinal GCN2-dependent signaling that influences systemic growth in *Drosophila*, connecting bacterial molecular state with a host amino-acid-stress sensor rather than merely correlating bacterial abundance with body size [6]. Cell-envelope chemistry can also be functionally important: D-alanylation of *L. plantarum* teichoic acids contributes to the bacterium-mediated promotion of *Drosophila* growth during chronic undernutrition [7]. These findings argue against treating all strains of a nominally beneficial bacterial species as physiologically interchangeable.

Microbial metabolites can also impose costs. Microbiota-derived lactate can activate intestinal NADPH oxidase Nox, increase reactive oxygen species production, and shorten *Drosophila* lifespan, showing that a product of microbial metabolism can become detrimental through a particular host redox pathway [8]. The sign of a microbiome effect therefore depends on the host pathway engaged and the physiological context, not simply on whether the producer is classified as a commensal.

Other systems broaden the molecular repertoire. Coenzyme A precursors can flow from microbiome to host, demonstrating transfer of metabolically useful molecules across biological partners [9]. In honey bees, gut *Lactobacillus* has been linked to learning and memory through modulation of tryptophan metabolism, extending microbiome-associated molecular effects beyond gut physiology and growth to neurobehavioral phenotype [10].

Collectively, these examples support a general analytical rule without establishing a universal mechanism: microbial products become host-relevant signals only when production, availability, host uptake or recognition, and downstream responsiveness coincide. The proposed synthesis is therefore a signal-qualification criterion. A microbiome claim becomes mechanistically stronger when four components are resolved separately: the microbial feature that changes, the anatomical or biochemical location in which it is encountered, the host pathway that responds, and the phenotype that follows under the tested condition. Taxonomic association without this chain remains biologically informative but mechanistically underdetermined.

Nutritional effects

Nutrition is one of the most reproducible domains of insect microbiome research, yet it also illustrates why environmental context cannot be discarded. *Drosophila*-associated bacteria can differentially shape the host's nutritional requirements during juvenile growth, indicating that microbial effects depend on which nutrients are limiting and on the metabolic capacities of the bacterial partner [11]. A phenotype described simply as "microbiome-enhanced growth" may therefore result from altered nutrient requirements or availability rather than from a generic growth-promoting signal.

The relationship can also be reciprocal. *Drosophila* can promote the fitness of intestinal *L. plantarum* while receiving nutritional benefits from the association, showing that nutritional mutualism can involve bidirectional effects between the host and its bacterial partner [12]. Microbial function measured outside that reciprocal nutritional environment may consequently fail to predict function in the host-associated state.

Experimental work on *D. melanogaster* further demonstrates that gut microbiome interactions affect nutritional traits and that those effects must be interpreted relative to diet and microbial composition [13]. Even apparently technical features of food preparation can alter the phenotype. *Acetobacter pomorum* can buffer host metabolic effects associated with dietary preservative formulation and batch variation in dietary yeast [14]. Diet formulation is therefore not merely laboratory background; it can become part of the biological interaction being measured.

Ecological specialization provides a complementary boundary. In *Drosophila suzukii*, a gut bacterium can promote host fitness in a specialized ecological niche through effects on sugar metabolism [15]. The significance of this observation is not that sugar metabolism represents a universal function of insect gut bacteria, but that a bacterial contribution can become important when host ecology creates a specific metabolic problem.

The nutritional evidence therefore favors a conditional interpretation. Microbes can supply compounds, modify substrates, change host nutritional requirements, or buffer variation in food quality, but the resulting phenotype depends on the nutritional limitation being addressed. A bacterium that rescues growth under one imbalance need not improve performance under another. Nutritional benefit is consequently better represented as a microbe × diet × host-state interaction than as a fixed property of a microbial species.

Immune signaling

The immune system is not only a defense against microbes; it also helps determine which host-associated microorganisms persist. In *Drosophila*, resistance to host antimicrobial peptides contributes to the resilience of gut commensals during infection and aging, showing that microbial persistence can depend on the capacity to withstand changing immune pressure [16]. The observed microbiome is therefore partly an output of host immunity rather than merely an upstream regulator of it.

Host recognition pathways can likewise support rather than eliminate commensals. Bacterial recognition through PGRP-SA and downstream Toll/DIF signaling sustains commensal gut bacteria in *Drosophila* [17]. This finding complicates a pathogen-centered interpretation of immune activation because recognition can contribute to maintenance of particular host-associated bacteria.

Antimicrobial effectors also participate in community filtering. *Drosophila* antimicrobial peptides and lysozymes regulate gut microbiota composition and abundance [18]. At the epithelial interface, a Mesh–Duox pathway regulates insect gut homeostasis, linking intestinal organization and signaling to controlled reactive-oxygen activity [19]. Together, such mechanisms create reciprocal regulation in which microbial exposure influences host immune activity while immune pathways reshape the microbial environment to which the host remains exposed.

These relationships can acquire additional consequences in disease vectors. Vector microbiota and immune responses can interact in ways that modulate arthropod susceptibility to vertebrate pathogens [20]. Such observations nevertheless require system-specific interpretation because effects can depend on vector species, pathogen, microbial community, tissue, and environmental context.

The resulting synthesis is a reciprocal immune gate rather than a one-directional microbiome-to-immunity pathway. Microbial molecules can alter host immune signaling, but immune signaling simultaneously controls microbial survival, abundance, and composition. A host phenotype attributed to microbiome-mediated immunity may therefore arise from direct sensing, immune-mediated restructuring of the microbiota, or both. Distinguishing these alternatives is necessary before assigning a specific phenotype to a specific microbial signal.

Developmental signaling

Development provides an especially strong test of whether microbiome effects should be interpreted as obligatory or conditional. In mosquitoes, riboflavin instability is a key factor underlying an apparent requirement for gut

microbiota during development, indicating that microorganisms can compensate for a chemically unstable dietary vitamin rather than necessarily provide an intrinsically indispensable developmental signal [21]. "Microbiome dependence" can therefore emerge from properties of the host–diet–microbe system rather than from the microbial state alone.

Stage-specific manipulation sharpens this distinction. Transient colonization can be used to produce germ-free mosquitoes and thereby investigate host–microbiota interactions at defined developmental stages [22]. This experimental separation is important because microbial exposure during larval development need not have the same biological meaning as microbial presence in the adult.

In *Drosophila*, a bacteria-regulated gut peptide can determine host dependence on specific bacteria for juvenile development and survival, demonstrating that developmental responsiveness can be controlled by a host signaling component rather than by bacterial presence alone [23]. Host genetic pathways can also interact with microbial state: Arc1 and the microbiota together modulate growth and metabolic traits, illustrating that microbiome-associated developmental phenotypes may be contingent on host molecular state [24].

Mosquito studies further indicate that microbiota status can affect adult phenotypes including fecundity, longevity, and vector competence, so microbiome-associated consequences can extend beyond completion of larval development [25]. However, a critical boundary comes from axenic *Aedes aegypti*: live bacteria were shown not to be required for mosquito development under the tested conditions [26]. This finding does not require microbiome-dependent developmental observations to be dismissed. Instead, it demonstrates why dietary formulation, microbial products, and experimental design must be separated when defining what is biologically "required."

The developmental evidence therefore resolves into several mechanistically distinct states. Microorganisms may compensate for a limiting or unstable nutrient; microbial molecules may activate a host pathway that changes growth or survival; host genotype may change responsiveness to the same microbial condition; or development may proceed without live bacteria when the relevant biochemical requirement is supplied independently. These states should not be collapsed into a binary conventional-versus-germ-free comparison.

Table 1. Distinguishing developmental microbiome dependence from nutrient rescue, host-pathway responsiveness, and live-bacteria dispensability

Developmental signaling state	Evidence	Interpretive consequence	Limits and uncertainty · Biological setting	Research or test · Evidential standing
Vitamin-stability compensation	Developmental dependence changes when an unstable micronutrient is effectively supplied or supported	Apparent microbial requirement can reflect correction of a dietary biochemical deficit	Depends on diet chemistry, formulation, storage, and host vitamin handling Mosquito larval development	Compare axenic and colonized larvae under controlled vitamin availability Evidence-derived synthesis
Stage-restricted microbial exposure	Transient colonization permits microbial exposure to be restricted to defined stages	Timing of exposure can be separated from persistent colonization	Residual microbial products can outlast living cells Mosquito larval-to-adult transition	Manipulate exposure windows and distinguish immediate from deferred effects Evidence-derived synthesis
Host-peptide-gated dependence	A bacteria-regulated gut peptide changes dependence on particular bacteria	Host signaling state can determine whether a bacterial cue becomes developmentally consequential	May depend on host genotype, bacterial identity, diet, and pathway state Drosophila juvenile development	Combine host perturbation, defined bacteria, and rescue designs Evidence-derived synthesis
Gene × microbiota modulation	Arc1 and microbial state jointly influence host traits	Developmental phenotype reflects interaction between host molecular state and microbiota	Effect magnitude may vary with genetic background and nutrition	Factor genotype, microbial state, and diet within the same experiment

			Drosophila growth and metabolism	Evidence-derived synthesis
Cross-stage consequence	Microbiota status affects fecundity, longevity, and vector competence	Microbiome-associated effects can persist or emerge beyond juvenile development	Adult outcomes need not share the mechanism responsible for larval effects Aedes aegypti adult physiology	Separate developmental rescue from adult physiological phenotyping Evidence-derived synthesis
Live-bacteria dispensability	Development can occur without living bacteria under permissive conditions	Live microbial cells are not universally necessary when relevant biochemical requirements are otherwise met	Highly dependent on rearing conditions, diet, sterility verification, and endpoint Axenic Aedes aegypti	Distinguish requirements for cells from requirements for microbial products or transformations Evidence-derived synthesis
Conditional developmental gate	Similar developmental endpoints can arise through different nutrient, signal, genotype, and exposure routes	Proposed — microbiome-dependent development reflects alignment of microbial function, host responsiveness, and environmental need	The integrated gate has not itself been empirically validated as a single model Cross-system interpretation	Independently manipulate microbial function, host pathway, developmental stage, and diet Proposed synthesis

Host genotype and life stage

Host genotype changes both the microbiota that can assemble and the consequences of microbial activity. In honey bees, host genetics shape strain-level gut microbiota structure during social transmission, indicating that microbial acquisition occurs through a host-genetic filter rather than through exposure alone [27]. The relevant biological unit is therefore not necessarily bacterial species presence, because host lineages may differentially retain strains with distinct functional capacities.

Strain identity can itself dominate higher taxonomic categories. In an insect microbiome system, genetic identity and genotype × genotype interactions between symbionts outweighed species-level effects, showing that host-associated outcomes can depend on combinations of interacting genotypes rather than nominal symbiont species [28]. Honey bee gut communities also contain substantial genomic diversity within characteristic bacterial lineages, providing a molecular substrate through which strains occupying similar taxonomic positions can differ functionally [29].

Life stage adds a second filter. Larval nutrition, gut architecture, metamorphosis, adult diet, immune state, and opportunities for reacquisition can change which microbial functions are available or consequential. Stage therefore should not be treated as a nuisance covariate when developmental exposure is being connected to adult physiology. The same strain can plausibly occupy different positions in the host–microbe system before and after metamorphosis because the host environment receiving its products has changed.

These observations motivate a state-space interpretation rather than a fixed microbiome-effect label. The proposed state space has two interacting axes: microbial functional availability, determined partly by strain composition and transmission, and host responsiveness, determined partly by genotype and life stage. Nutritional or immune environment then constrains which combinations become phenotypically consequential. A high-function microbial state can produce little detectable host effect when the host pathway is unresponsive or the relevant resource is nonlimiting; conversely, modest microbial activity can matter strongly when a susceptible developmental or physiological state creates dependence.

The figure is needed to distinguish these combinations visually because identical microbial abundance can occupy different biological states depending on genotype, stage, and environmental need.

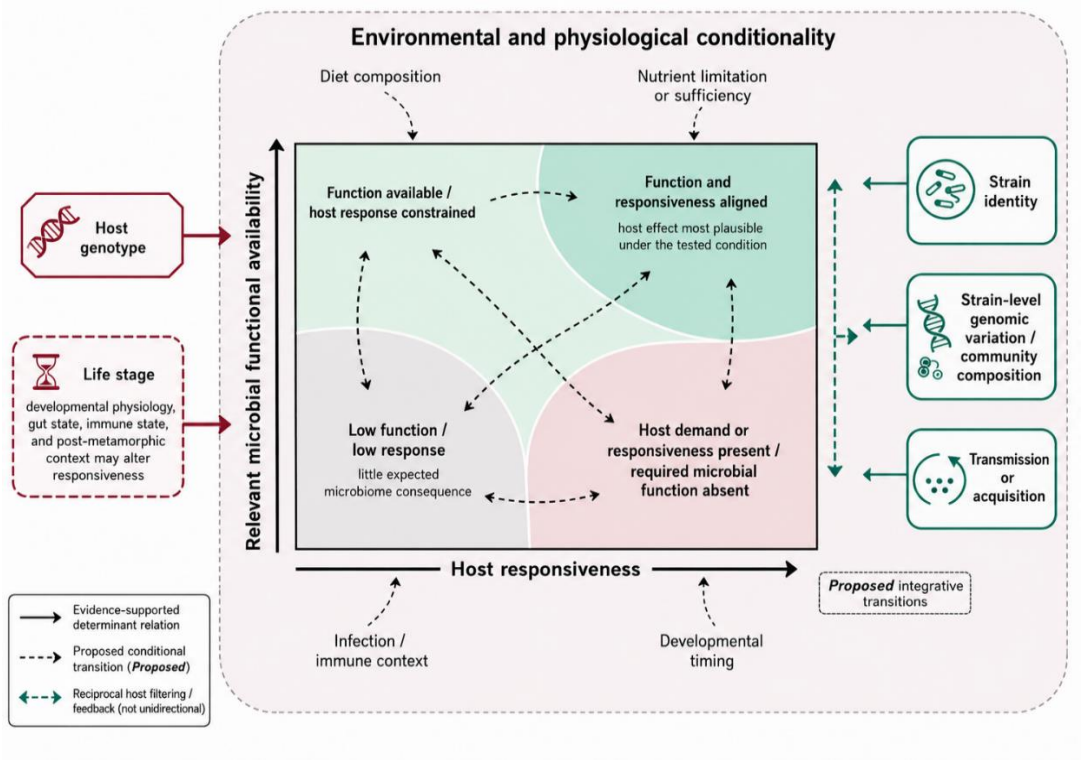


Figure 1. Genotype- and life-stage-dependent state space separating microbial functional availability from host responsiveness

Diet and environmental dependence

Diet is not merely a substrate on which a microbiome operates; it can change the microbial partner itself. Experimental evolution in the *Drosophila–Lactobacillus* association showed that bacterial adaptation to the host diet can shape symbiosis, demonstrating that diet can alter microbial traits that subsequently affect host interaction [30]. Thus, transferring a strain between diets may change both the resources supplied to the microbe and the biological meaning of its presence.

At broader scales, host species and geography differentiate honey bee gut bacterial communities by changing the relative contribution of community assembly processes [31]. Geographic variation therefore cannot automatically be interpreted as evidence for locally adapted host benefit, but it does indicate that environmental and host filters alter which communities assemble.

Developmental systems with environmentally acquired microbiota add further heterogeneity. In black soldier fly larvae, intestinal bacterial communities change dynamically and are associated with insect growth and development, linking community succession to a host stage that is simultaneously experiencing major dietary and physiological change [32]. In disease-transmitting vectors, metabolic interactions with microbiota likewise depend on the biochemical ecology of both host and microorganisms, emphasizing that microbial metabolism is embedded in the host's nutritional environment [33].

These observations separate at least four environmental roles: diet can supply substrates for microbial products, remove the need for microbial supplementation, select microbial genotypes, or change community assembly. Geography can additionally alter exposure pools and assembly processes. Consequently, replication across diets or locations tests more than robustness; it tests whether the inferred mechanism survives changes in the ecological conditions that generate both microbial state and host demand.

A comparative adjudication matrix is useful here because apparently conflicting microbiome effects can reflect different environmental questions rather than incompatible results.

Table 2. Adjudicating diet- and environment-dependent microbiome effects by the source of conditionality

Focal distinction			
Evidence	**Interpretive consequence**	**Limits and uncertainty · Research or test**	**Evidential standing · Biological setting**

Diet as microbial substrate			
Microbial metabolism changes with available dietary substrates	Host effect may arise because diet enables production of a relevant microbial metabolite	Substrate concentration and food chemistry may differ among laboratories or habitats Manipulate substrate while holding microbial genotype constant	Evidence-derived synthesis Drosophila-associated bacteria and other nutritional symbioses
Diet as selective environment			
Bacterial adaptation occurs in relation to host diet	A strain's effect cannot be assumed stable across dietary histories	Evolutionary history may be confounded with immediate physiological response Compare ancestral and diet-adapted strains across reciprocal diets	Evidence-derived synthesis Drosophila–Lactobacillus association
Diet as replacement of microbial function			
Nutritionally permissive conditions can reduce apparent microbial dependence	Null microbiome effects may reflect environmental provision of the required function	Requires identification of the replaced biochemical function Test nutrient or metabolite rescue independently of live-cell rescue	Evidence-derived synthesis Nutrient-dependent developmental systems
Geographic assembly filter			
Host species and geography alter community assembly contributions	Community differences may reflect dispersal and filtering rather than a single host-selected optimum	Geography combines climate, flora, management, and exposure history Replicate host genotypes across locations and characterize source pools	Evidence-derived synthesis Honey bee gut communities
Stage-linked community turnover			
Gut bacterial communities change during larval growth	Microbial associations can shift while host diet and physiology also change	Direction of causation is unresolved by community dynamics alone Pair longitudinal community profiling with controlled perturbation	Evidence-derived synthesis Black soldier fly larvae
Contextual metabolic coupling			
Host and microbial metabolic interactions vary with physiological environment	Metabolic consequence depends on resources, tissue state, and microbial function	Transferability across vector species is uncertain Measure metabolites and host pathways under matched environmental conditions	Evidence-derived synthesis Disease-vector systems
Environmental conditionality gate			
Diet, geography, exposure, and host state jointly alter microbial function and demand	Proposed — environmental context can switch the same association among beneficial, neutral, or detrimental outcomes	Integrated gate is not yet validated as a universal model Use factorial, cross-environment gnotobiotic designs	Proposed synthesis Cross-system interpretation

Conditional host–microbiome model

The evidence supports construction of a conditional model, but not a universal microbiome rule. The proposed model contains four sequential requirements. First, a microbial function must be present: a strain must produce, transform, consume, or expose a molecule relevant to the host. Second, the product must be accessible in the correct compartment and developmental window. Third, the host must be responsive through an appropriate metabolic, immune, epithelial, or neurophysiological pathway. Fourth, the environment must create a condition in which activation of that pathway changes an organismal outcome.

Failure at any requirement predicts attenuation or absence of the expected phenotype. A bacterial growth-promoting function can become inconsequential when nutrients are sufficient; a host pathway can be competent

while the relevant microbial product is absent; and microbial activity can persist while immune or developmental state alters the host response. The negative mosquito-development evidence is especially informative because it demonstrates that an observed requirement for microbiota can disappear when live bacteria are experimentally separated from the biochemical conditions they ordinarily modify [26].

The model also predicts sign reversal. Microbial metabolism that is beneficial under nutrient limitation need not remain beneficial when the same product drives damaging redox activity or imposes another physiological cost. Lactate-dependent Nox activation in *Drosophila* illustrates that a microbiota-derived metabolite can shorten lifespan through host reactive-oxygen signaling [8]. The proposed framework therefore treats "beneficial," "commensal," and "detrimental" as context-dependent outcomes rather than immutable microbial properties.

This architecture is intended as an inference model, not a taxonomic classification. Its value lies in converting a broad association into testable conditional statements: which microbial function, where and when it is available, which host sensor or pathway receives it, and under which environmental state that response becomes phenotypically consequential. Each element can fail independently, creating experimentally distinguishable explanations for heterogeneous findings.

Causal tests and experimental standards

Causal inference requires experimental systems that separate microbial cells, microbial products, host pathways, and environmental conditions. Axenic and gnotobiotic technologies provide the principal toolkit for constructing insects with absent, defined, or manipulated microbial communities, while also introducing methodological challenges that must be controlled [34]. Sterility verification, inoculum definition, diet composition, rearing environment, developmental timing, and contamination surveillance are therefore components of the causal design rather than ancillary technical details.

A strong test of the conditional model should proceed beyond conventional-versus-axenic comparisons. Defined microbial strains can identify functional specificity; metabolite or nutrient rescue can test whether living cells are required; host genetic perturbation can identify sensing pathways; and reciprocal diets can determine whether the phenotype depends on environmental demand. Stage-restricted colonization can separate developmental exposure from adult persistence. Where possible, microbial abundance should be distinguished from microbial activity because equivalent cell counts need not generate equivalent molecular outputs.

The most informative experiments will deliberately seek boundary failure. A proposed microbial signal should lose its effect when its biosynthetic function is disrupted, regain it through appropriate rescue, and change predictably when the host response pathway or environmental requirement is altered. Such designs would test individual edges of the proposed architecture without presuming that the complete model is already validated. Cross-genotype, cross-diet, cross-stage, and cross-taxon replication would then establish which relationships transfer and which remain system-specific.

Conclusion

Insect microbiome effects are best interpreted as conditional biological events rather than consequences of microbial presence alone. Nutritional, immune, and developmental phenotypes can emerge when microbial functions, spatial and temporal access, host responsiveness, and environmental demand coincide. The same architecture also explains why associations can be weak, absent, or reversed when one component changes.

The proposed model does not imply that all insects require resident microbiomes, that particular bacterial taxa carry fixed host effects, or that mechanisms demonstrated in *Drosophila*, mosquitoes, or honey bees transfer unchanged across insects. Its contribution is instead an inference structure for distinguishing microbial membership from molecular function and molecular function from host consequence. Future causal tests should manipulate those components independently and determine the biological boundaries within which specific host–microbe signals matter.

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