



UNDERSTANDING INSECT-MICROBE INTERACTIONS FOR SUSTAINABLE PEST MANAGEMENT

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ABSTRACT

Due to their enormous diversity, small body weight, flight and shorter lifecycles, insects thrive in almost all macro- and microhabitats. A plethora of microorganisms interact with insects as symbionts. Insect-microbial symbiont interaction can be either mutualistic, commensalism or pathogenic. The entry of a microbe mounts immune defenses in the insect at the local or systemic level in order to mitigate the damage inflicted. Microbes, on the other hand, synthesize various molecules/ toxins or develop various strategies to evade or counter insect defenses, allowing them to utilize the host resources for reproduction, coexistence or transmission. This review provides a comprehensive understanding of these insect-microbe interactions including bacteria, fungi and virus. Attempt has also been made to highlight the tripartite interactions between insects, microbes and plants in view of the need for sustainable pest management

Key words: Insect-microbe interactions, insect gut symbionts, immunity, insect-microbe-plant interactions, IPM, ectosymbionts, endosymbionts, Wolbachia, transmission

Insects infest plants and also transmit human diseases. Their ability to thrive in all kinds of microhabitats and microclimatic conditions makes their association with microbes inevitable. Upto 10% of the insect's biomass comprises of microbiota. The insect-microbe interactions are mostly presented separately as insect-bacterial, insect-fungal, or insect-viral interactions. Further, in natural ecological settings, insect-microbe-plant interactions are predominant which emphasizes the need to explore the cumulative and complex role of these tripartite interactions. The current review documents the association of insects with microorganisms including bacteria, fungi, and virus and also emphasize on the multitrophic interactions between insects, microbes, and plants in view of the need for effective ecofriendly pest management strategies.

1. Insect-bacterial interactions

a. Ectosymbionts

Insect cuticle forms a robust barrier against microbial pathogens. However, certain bacteria that colonize the exoskeleton act as ectosymbionts and offer protection against various entomopathogenic fungi. Cultivable bacteria, *Lactiplantibacillus plantarum* was isolated from the body surface of *Drosophila melanogaster* (Hong et al., 2022). Females of solitary digger wasp tribe, *Philanthini*, known as the beewolves, harbour *Streptomyces* sp. on their exoskeleton

(Goettler et al., 2022). Fungus-growing ants retain actinobacteria *Pseudonocardia* that produce secondary metabolites against the fungus (Goldstein et al., 2020). *Burkholderia* strain of bacterial symbionts inhabits the cuticle of *Lagria villosa* beetle and produce an antifungal compound, lagriamide (Florez et al., 2018). *Bacillus pumilus* isolated from the cuticular surface of *Delphacodes* sp. inhibits *Beauveria bassiana* conidial germination (Fernandez-Marin et al., 2006). Insects trade-off this protection offered by bacterial ectosymbionts during moulting process. Intriguingly, the cuticular invaginations in *Lagria villosa* larvae prevent a complete elimination of symbionts during moulting. Similarly, *Oreophoetes peruana* nymphs retain the cuticular lining even after the moult.

b. Endosymbionts

The gut microflora of an insect is involved in nutritional provisioning, digestion, detoxification, reproduction, immunity and communication. The obligate and facultative gut bacteria are broadly categorized as endosymbionts and free-living symbionts, respectively. The obligate bacteria are localized in specialized cells known as bacteriocytes and mostly exhibit mutualistic association with the insect and offers fitness advantage to the host. The characteristic feature of the bacterial partner in the obligate relation with its host is its genome size reduction and maternal transmission

(Singh et al., 2021). Many insects with bacteriocyte symbioses are pests of agricultural importance. *Buchnera aphidicola* is an obligate symbiont of aphids and a well characterized model system. The bacteria are indispensable for the survival and fecundity of the insect host. Also, *B. aphidicola* genome size is reduced such that it is deficient in branched-chain amino acid synthesis and therefore dependent on the insect host for its nutrition (Moran, 2021).

Facultative microbes could be a mutualist, commensal or a pathogen that are either vertically or horizontally transmitted. Facultative symbionts predominantly assist their insect hosts in digestion and/or xenobiotic detoxification. *Pseudomonas* sp.-*Spodoptera frugiperda* interaction provides pesticide resistance to the host. *Wolbachia* sp. is yet another well cited example of facultative endosymbiont that colonizes the mosquito gut and functions either as mutualist or pathogen. *Wolbachia* endosymbionts can manipulate the host's reproductive fitness and either enhances female fertility or cause male sterility (Singh et al., 2021). Insect-bacterial pathogenic interactions include *Bacillus thuringiensis* or *Bacillus cereus* with lepidopterans, coleopterans, and dipterans; *Pseudomonas entomophila* and *Serratia marcescens* with *Drosophila* sp.; *Yersinia pestis*-*Xenopsylla cheopiseas*; *Photorhabdus* and *Xenorhabdus* species with tobacco hornworm, *Manduca sexta*; *Serratia entomophila* with the grass grub, *Costelytra zealandica* (Vallet-Gely et al., 2008).

Nematobacterial complexes are widely used in the agricultural systems as insect biocontrol agents. The nematodes *Heterorhabditis* and *Steinernema* sp. symbiotically associate with bacteria in the genera *Photorhabdus* and *Xenorhabdus* sp. These nematobacterial complexes detect the insect host, attaches to the cuticle, penetrates through natural openings, invades into the insect body cavity and establishes in the hemolymph. Thereafter, the symbiotic bacteria that are released out of the nematodes rapidly proliferate in the hemolymph, secrete toxins and virulence factors to kill the host. Within the insect cadaver, the nematodes reproduce by feeding on the bacteria (Eleftherianos et al., 2016). Filarial nematodes including *Brugia* sp., *Onchocerca volvulus* and *Wuchereria bancrofti*, are thread-like roundworms that cause filariasis. In the mammalian host, the sexual stage gives rise to microfilarial larvae. Insects ingest the microfilariae from the mammalian blood which penetrates the midgut epithelium to migrate to the

thoracic musculature through hemolymph and invade the flight muscles. In the muscle cells, the microfilariae undergo two molts to transform into 3rd instar infective larvae. The infective larvae migrate to proboscis from where they are again transmitted to the subsequent human host. Table 1 provides the list of well-established insect-bacterial symbiotic associations.

c. Insect immune responses

Insects initiate an immune response against the pathogenic bacteria however symbiont bacteria evade the immune system and co-exist with the host. Peptidoglycan (PGN) is the main component of the bacterial cell wall that triggers an innate immune response in insects. Peptidoglycan recognition proteins (PGRPs) expressed by insects bind to these PGNs. The PGRP-SA and PGRP-SD-mediated recognition of Lys-type PGN in Gram-positive bacteria mainly activates the Toll signaling pathway. Gram-negative bacteria recognize the DAP-type PGN through specific PGRPs (e.g., PGRP-LC and PGRP-LE) to activate the immunodeficiency (Imd) pathway (Liehl et al., 2006; Zhang et al., 2021). Antibacterial responses are well characterized in *D. melanogaster*. The presence of bacteria in the insect gut activates local reactive oxygen species (ROS) and initiates antimicrobial peptide (AMP) production. ROS is generated by the dual oxidase (Duox) enzyme. An extracellular immune-regulated catalase (IRC) maintains the homeostatic redox balance that is altered by the bacterial ingestion. ROS-mediated protection against microorganisms constitutes the first line of defense (Ha et al., 2005). ROS tolerant bacteria elicit either Toll or Imd pathway leading to AMP and other effector molecule synthesis.

The insect AMPs include cecropins, defensins, attacins, dipterins, ponerins, and metchnikowins (Lemaitre et al., 2007). AMP production such as dipterin is active against a range of bacteria. Dipterins constitute a family of glycine-rich antibacterial peptides isolated from the dipteran haemolymph (Akbari et al., 2018). Cecropins were initially detected in the hemolymph of *Hyalophora cecropia*. Cecropins are active against both gram-positive and gram-negative bacteria (Eleftherianos et al., 2021). Insect defensins isolated from various insect orders including Coleoptera, Diptera, Hemiptera, Lepidoptera, Hymenoptera, and Trichoptera selectively target gram-positive bacteria (Wu et al., 2018). Silkworm AMPs including cecropins, defensins, moricins, gloverins, lebecins and attacins exhibit antimicrobial activity against a broad range of bacteria, such as *Klebsiella*

Table 1. List of symbionts, hosts, transmission mode, and their association

Symbiont	Association	Host	Transmission mode	References
<i>Buchnera</i> spp.	Obligate mutualism	Aleyrodidae	Transovarial	(Morin et al., 1999)
<i>Carsonella ruddii</i>	Obligate mutualism	<i>Psyllids</i>	Transovarial	(Thao et al., 2011)
<i>Candidatus Westeberhardia cardiocondylae</i>	Obligate mutualism	Formicidae	Horizontal and maternal	(Oliver et al., 2003)
<i>Buchnera aphidicola</i>	Obligate mutualism	Aphidoidea	Transovarial	(Baumann, 2005)
<i>Sulcia muelleri</i>	Obligate mutualism	Proconiini	Transovarial	(Moran et al., 2005)
<i>Baumannia cicadellinicola</i>	Obligate mutualism	Proconiini	Transovarial	(Wu et al., 2006)
<i>Ishikawaella capsulata</i>	Obligate mutualism	<i>Megacopta cribraria</i> , <i>Halyomorpha halys</i>	Capsule	(Nikoh et al., 2011)
<i>Tremblaya princeps</i>	Obligate mutualism	<i>Phenacoccus solenopsis</i>	Transovarial	(Lopez-madriral et al., 2013)
<i>Moranella endobia</i>	Obligate mutualism	<i>Phenacoccus solenopsis</i>	Maternal	(Lopez-madriral et al., 2013)
<i>Portiera aleyrodidarum</i>	Obligate mutualism	Aleyrodidae	Transovarial	(Santos-garcia et al., 2015)
<i>Rosenkranzia clausaccus</i>	Obligate mutualism	<i>Halyomorpha halys</i>	Egg smearing	(Hayashi et al., 2015)
<i>Blochmannia floridanus</i>	Obligate mutualism	<i>Camponotus pennsylvanicus</i>	Transovarial	(Kupper et al., 2016)
<i>Nardonella</i> spp.	Obligate mutualism	Curculionoidea, Coleoptera	Ovaries	(Anbutusu et al., 2017)
<i>Stammera</i> spp.	Obligate mutualism	<i>Cassida rubiginosa</i>	Egg-caplet	(Salem et al., 2014)
<i>Wigglesworthia glossinidia</i>	Obligate mutualism	<i>Glossina</i> spp.	Transovarial	(Bing et al., 2017)
<i>Wigglesworthia</i> spp., <i>Sodalis glossinidia</i>	Obligate mutualism	<i>Glossina</i> spp.	Maternal	(Griffith et al., 2018; Zaidman-Remy et al., 2018)
<i>Acetobacter thailandicus</i> , <i>Lactobacillus plantarum</i>	Facultative symbionts	<i>Dosophila melanogaster</i>	NA	(Pais et al., 2018; Storelli et al., 2018)
<i>Acetobacter tropicalis</i> , <i>Erwinia dadicola</i>	Facultative symbionts	<i>Bactrocera oleae</i>	Maternal	(Estes et al., 2009; Kounatidies al., 2009; Ben-yosef et al., 2010)
<i>Candidatus</i> , <i>Arsenophomus arthropodicus</i>	Facultative commensalism	Hippoboscidae	Transovarial	(Novakova et al., 2015)
<i>Candidatus liberibacte</i> <i>psyllaureus</i>	Facultative commensalism	<i>Bactericera cockerelli</i>	Vector	(Hansen et al., 2008)
<i>Cardinium</i> sp.	Facultative parasite	Fulgoroidea	Transovarial	(Gonella et al., 2011)
<i>Enterococcus</i> spp., <i>Enterobacter</i> spp., <i>Serratia</i> spp.	Facultative symbionts	<i>Plutella xylostella</i>	Vertical	(Xia et al., 2018)
<i>Enterococcus</i> spp., <i>Erwinia</i> spp., <i>Rahnella</i> spp., <i>Serratia</i> spp.	Facultative symbionts	<i>Hylobius abietis</i>	Food substrate	(Berasatagui et al., 2017)
<i>Gilliamella apicola</i> , <i>Snodgrassiella</i> spp.	Facultative symbionts	<i>Apis mellifera</i>	Maternal	(Martinson et al., 2012)
<i>Gilliamella bombicola</i> , <i>Snodgrassiella</i> spp.	Facultative symbionts	<i>Bombus</i> spp.	Maternal	(Koch et al., 2011; Zhang et al., 2016)
<i>Hamiltonella defensa</i>	Facultative commensalism	Aphidoidea, Aleyrodidae	Horizontal & maternal	(Marubayashi et al., 2014)
<i>Klebsiella</i> , <i>Stenotrophomonas</i> , <i>Microbacterium</i> , <i>Bacillus</i> , <i>Enterococcus</i>	Facultative symbionts	<i>Diatraea saccharalis</i>	NA	(Kucuk et al., 2020)

(contd.)

(contd. Table 1)

<i>Lactococcus</i> spp., <i>Dysgonomonas</i> spp., <i>Serratia</i> spp.	Facultative symbionts	<i>Cyrtotrachelus dux</i>	NA	(Luo et al., 2019)
<i>Promicromonospora</i> <i>pachnodae</i>	Facultative	<i>Pachnoda marginata</i>	NA	(Cazemier et al., 2023)
<i>Proteus vulgaris</i> , <i>Klebsiella pneumoniae</i> , <i>Citrobacter freundii</i> , <i>Pseudomonas fluorescens</i> , <i>Erwinia</i>	Facultative	<i>Bombyx mori</i>	NA	(Anand et al., 2010)
<i>Providencia</i> spp., <i>Morganella</i> spp., <i>Vagococcus</i> spp., <i>Proteus</i> spp., <i>Koukoulia</i> spp., <i>Serratia</i> spp.	Facultative symbionts	<i>Nicrophorus</i> sp.	Maternal	(Wang et al., 2017; Shukla et al., 2018; Heise et al., 2019)
<i>Pseudomonas</i> spp., <i>Cellulosimicrobium</i> spp., <i>Ochrobacterium</i> spp.	Facultative symbionts	<i>Holotrichia parallela</i>	NA	(Huang et al., 2012)
<i>Pseudomonas</i> spp., <i>Pantoea</i> spp.	Facultative symbionts	<i>Hypothenemus hampei</i>	Deposited on eggs	(Ceja-Navarro et al., 2015)
<i>Regiella insecticola</i>	Facultative commensalism	Aphidoidea	Transovarial	(Vorburger et al., 2010)
<i>Rhodococcus rhodnii</i>	Facultative mutualism	Reduviidae	Coprophagy	(Kikuchi, 2009)
<i>Rickettsia</i> sp.	Facultative parasite	Various insects	Transovarial	(Behar et al., 2010)
<i>Rickettsia</i> sp., <i>Cardinium</i> sp., <i>Wolbachia</i> sp.	Facultative parasites	Cicadellidae	Transmitted via food	(Nakamura et al., 2009)
<i>Serratia marcescens</i>	Facultative symbiont	<i>Hematophagous insects</i>	Adhere to eggs surface, colonize ovipositional site	(Bando et al., 2013)
<i>Serratia</i> spp.	Facultative	<i>Spodoptera litura</i>	NA	(Subhashini, 2015)
<i>Serratia symbiotica</i>	Facultative commensalism	Aphidoidea	Horizontal transmission	(Pons et al., 2019)
<i>Sodalis glossinidius</i>	Secondary facultative	<i>Glossina</i>	Milk gland, transovarial, & mating	(De vooght et al., 2015)
<i>Spiroplasma</i> sp.	Facultative parasite	Various insects	Transovarial	(Bove, 1997)
<i>Streptococcus faecalis</i> , <i>Enterococcus mundii</i>	Facultative symbiont	<i>Galleria mellonella</i>	NA	(Johnston et al., 2015)
<i>Streptomyces</i> spp.	Facultative symbiont	<i>Sirex noctilio</i>	NA	(Adams et al., 2011)
<i>Wolbachia</i> sp.	Facultative parasite	Various insects	Transovarial	(Miller, 2013)

sp., *Shigella* sp., *Staphylococcus aureus*, *Enterococcus faecalis*, *B. bombysepticus*, *B. subtilis*, *P. aeruginosa* and *Xanthomonas campestris*. Pyrrhocoricin is a proline-rich peptide isolated from the sap-sucking bug, *Pyrrhocoris apterus* (Nesa et al., 2022).

Systemic immune responses are triggered when the PGN fragments are translocated from the gut lumen into the haemolymph. Haemolymph consists of haemocytes including plasmatocytes, granulocytes, oenocytoids/crystal cells, lamellocytes and spherulocytes. Cellular immune responses to bacterial infection include nodulation, phagocytosis and clotting of haemolymph

by plasmatocytes; melanization by crystal cells and/or oenocytoids; and encapsulation by lamellocytes. Both haemocytes and the fat body play an important role in the prophenoloxidase (PPO) cascade activation (Sadekuzzaman et al., 2018). Figures 1 and 2 summarize the insect humoral and cell-mediated immune responses against bacteria, fungal and viral pathogens

e. Immunity-reproduction tradeoffs

Insects rely solely on innate immunity to protect themselves from pathogens. In many female insects, there is a tradeoff observed between immune defenses and reproduction as both are physiologically and

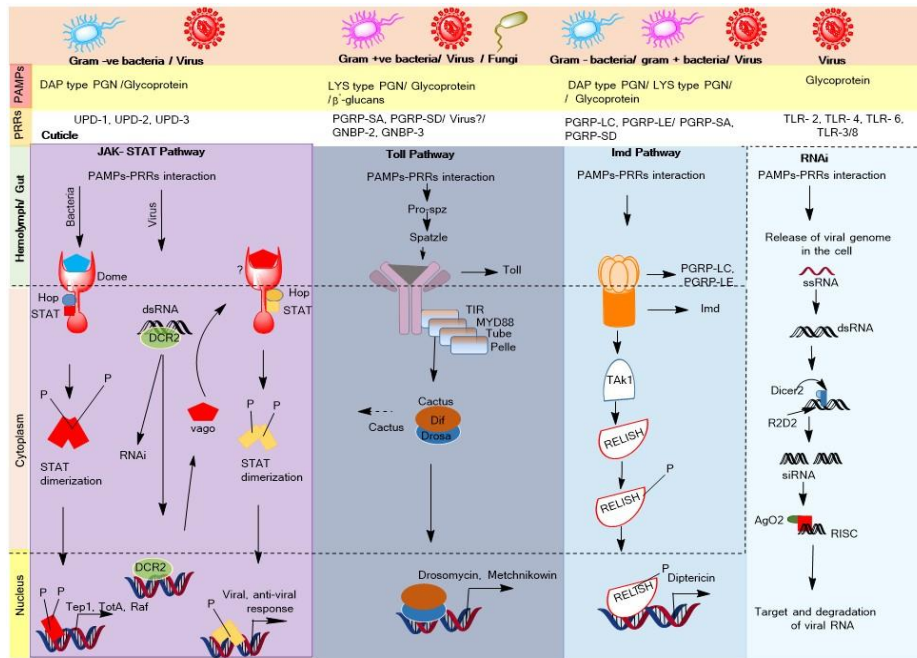


Fig. 1. Insect innate immune responses

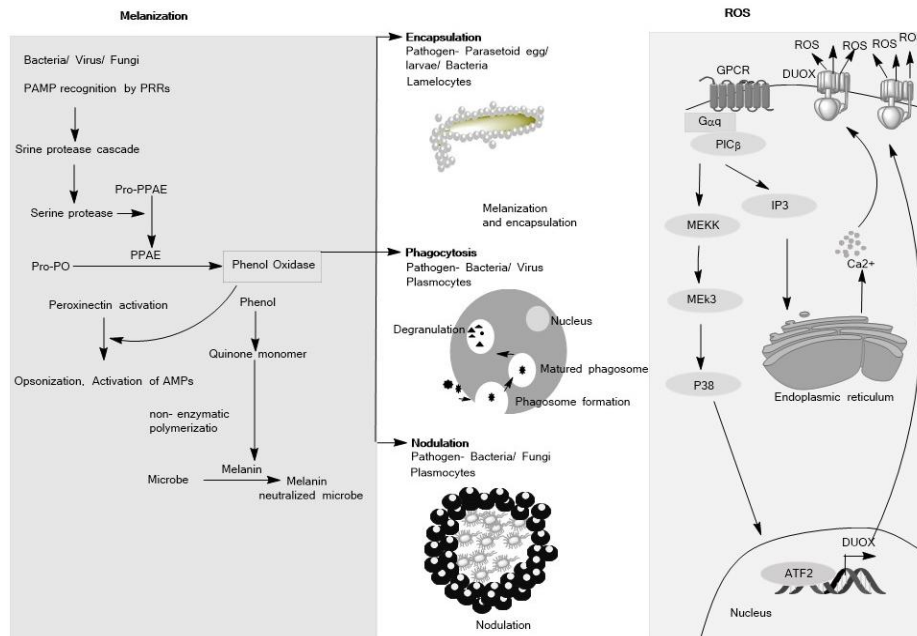


Fig. 2. Insect cell-mediated immunity

energetically demanding processes. The molecular mechanism of the tradeoff is mediated by those proteins that are involved in both immunity and/or fertility. For eg., *Anopheles gambiae* thioester-containing protein-1 (TEP-1) alleles are associated with higher fertility. But at the same time, these alleles are also responsible for the increased susceptibility to *Plasmodium* sp. The tradeoff between mating and immunity is evident only when the infection is pathogenic (Baxter et al., 2017).

f. Bacterial evasion strategies

Bacteria employ multiple evasion strategies against insect defenses for its successful colonization or transmission. Catalase expression in *Salmonella* or *E. coli* sp. allow these bacteria to tolerate ROS generation in the gut (Ha et al., 2005). Gut persistence is a prominent strategy employed by few bacteria. *Yersinia pestis* proliferates in *Xenopsylla cheopis* (rat flea) midgut and colonizes the proventriculus with the aid of *Yersinia*

murine toxin (Ymt). Ymt offers protection against a cytotoxic digestion product of blood plasma in the gut (Hinnebusch et al., 2002). *Mycobacterium ulcerans* ensure proliferation by migrating from the digestive tract to salivary gland with the assistance of virulence factor, mycolactone (Marsollier et al., 2005). *Erwinia carotovora* strain (Ecc15) colonizes the *Drosophila* gut by the accumulation of *Erwinia* virulence factor (Evf) (Acosta Muniz et al., 2007). Few bacteria alter insect gut physiology for successful immune evasion. For eg., *Serratia entomophila* antifeeding prophage (Afp) forms a bullet-shaped virus-like structure which serves as toxin-delivery apparatus in the New Zealand grass grub, *Costelytra zealandica* to induce amber coloration of the gut and decline digestive enzyme levels (Jackson et al., 2001). Two main strategies employed by bacterial pathogens to escape the systemic immune responses are to i) evade detection due to absence of immune elicitors on their cell surfaces, and ii) suppress the immune response by proteases/toxins/virulence factors. In weevil, *Sitophilus zeamais*, bacteriocytes express IMD-dependent PGN amidase that degrades the immunogenic PGN fragments (Anselme et al., 2006). *Pseudomonas aeruginosa* suppresses *D. melanogaster* defenses by limiting AMP gene expression (Apidianakis et al., 2005). The Dlt operon of gram-positive bacteria encodes enzymes that incorporate D-alanine in the teichoic acids on the surface of the bacteria to neutralize their negative charge and confer resistance to cationic AMPs. Further, AprA, a metalloprotease produced by *P. entomophila* provides protection against *Drosophila* AMPs, particularly, Diptericin (Liehl et al., 2006).

2. Insect-fungal associations

a. Ectosymbionts

Insect members belonging to the orders Coleoptera, Diptera, Lepidoptera, Hemiptera, Hymenoptera and Blattodea are involved in mutualistic fungal associations with Ascomycetes (Microascales, Botryosphaeriales, Eurotiales, Helotiales, Capnodiales, Chaetothyriales, Hypocreales, Saccharomycetales, Ophiostomatales, Xylariales) or Basidiomycetes (Agaricales, Russulales, Polyporales, Boletales, Septobasidiales). Insect-fungus mutualisms include fungal cultivation by ambrosia and bark beetles, fungus-farming leaf-cutter ants, and fungus-farming termites. All these three are the examples of ectosymbiotic associations (Biedermann et al., 2020).

b. Endosymbionts

Few yeast species are localized in specialized

fat body cells called mycetocytes of certain insect species belonging to the Coleoptera and Hemiptera orders (Malassigne et al., 2021). However, yeasts predominantly colonize the gut to offer nutrients and protection against pathogens and toxic compounds. Yeast species located in the mycetocytes of the planthopper, *Nilaparvata lugens* (Hou et al., 2013) and the aphid, *Cerataphis brasiliensis* (Vogel et al., 2013) are primary symbionts. Endosymbiotic yeasts associated with bacterial species act as secondary symbionts. For eg., *Metschnikowia pimensis* of the planthopper, *Hishimonus phycitis* are associated with bacterial endosymbionts belonging to *Sulcia* and *Nasuia* species (Hemmati et al., 2017). Similarly, in several cicada species including *Cryptotympana facialis*, *Hyalessa maculaticollis*, *Graptopsaltria nigrofusca* and *Meimuna opalifera*, Ophiocordyceps fungi is associated with the primary bacterial endosymbiont, *Sulcia* (Matsuura et al., 2018).

Entomopathogenic fungi include species belonging to genera *Beauveria*, *Metarhizium*, *Ophiocordyceps*, *Basidiobolus* & *Conidiobolus* and species *Cordyceps militaris*, *Hirsutella thompsonii*, *Isaria fumosorosea*, *Aschersonia aleyrodis*, *Lecanicillium lecanii*, *Sporothrix sectorum*, *Ascosphaera apis* & *Tolypocladium inflatum* (Vlisidou et al., 2010). Fungal conidia adhere to the insect cuticle, detoxify the cuticle, penetrate inside, develop within the hemocoel and sporulate when released from the insect cadaver (Kim et al., 2005; Park et al., 2004; Shrestha et al., 2007). *Metarhizium* species encoded MAD1 molecule contributes to fungal virulence by facilitating spore adhesion to the insect cuticle. Fungal G protein-coupled receptors are involved in insect-host recognition and subsequent downstream activation of mitogen-activated protein kinase (MAPK) and protein kinase A pathways to activate the formation of the appressorium structure, which is pivotal for the host recognition (Miyoshi and Shinoda, 2000).

c. Insect behavioral responses against fungi

Social insects such as ants, bees and termites sense the presence of distant virulent fungi using olfactory cues (de Roode et al., 2012; Feng et al., 2015). Termite, *Macrotermes michaelseni*, differentiates the degree of virulence among strains of *M. anisopliae* and *B. bassiana* based on the volatile emissions emanated by these fungi (Mburu et al., 2009; Ugelvig et al., 2007). Further, honeybee workers identify and remove the larvae infected with the fungus *A. apis* by detection of phenethyl acetate originated from the pathogen. Few insects secrete out antifungal compounds by

either salivary glands or metathoracic gland to protect themselves and their nest mates (Mburu et al., 2013). For eg., termicin and GNBP2, secreted by termite salivary glands possess antifungal activity (Tragust et al., 2013). In certain ant species, fungicidal secretion is released from the glands within a short span of fungal infection (Swanson et al., 2009). When these glands were blocked, infected ants died eventually. Similarly, bed bug glandular secretions, (E)-2-hexenal and (E)-2-octenal, inhibited *M. anisopliae* (Bulmer et al., 2009). Few insects including locusts (eg., *Schistocerca gregaria*) bask in the sun to raise their body temperature to fight *Metarhizium* infection (Lamberty et al., 2001). *Tribolium castaneum* secretes out benzoquinones to defend itself against the *B. bassiana* infection (Ulrich et al., 2015).

d. Insect immune responses against fungi

In insects, serine protease, persephone, activated by fungal Pr1 protease, and gram-negative bacteria-binding protein-3 (GNBP-3) act exclusively to detect antifungal infection by binding specifically to fungal α - and β -glycan structures and trigger downstream signalling pathways/effector molecules (Blanford et al., 1999; Toledo et al., 2011). Fungal infection triggers the toll signalling pathway to produce antifungal peptides. So far, eight insect antifungal peptides have been reported (Pedrini et al., 2015). Fungal infection induced the expression of AMPs, drosomycin and metchnikowin in *Drosophila* (Gottar et al., 2006). *Bombyx mori* Cecropin A and Gloverin 2 demonstrated antifungal activity against *B. bassiana* (Mao et al., 2021). Other well characterized insect antifungal peptides include heliomicin from *Heliothis virescens* (Faruck et al., 2016), termicin from termites (Kurata et al., 2006), and gallerimycin from *Galleria mellonella* (Lu et al., 2017). A recent study in *Drosophila* revealed the defensive role of TEPs against entomopathogenic fungi by activation of toll pathway (Da Silva et al., 2003; Mireille Lamberty et al., 1999). *Beauveria bassiana* infection resulted in elevated levels of fungal recognition protein, CLSP2 in *A. aegypti* (Schuhmann et al., 2003). The antifungal defense in *A. aegypti* is also mediated through JAK-STAT pathway (Dostalova et al., 2017).

Fungal penetration of the cuticle activates the PPO pathway in epidermal cells to synthesize melanin, a highly fungitoxic compound which deposits on the fungal surface and not only limits the pathogen development by melanic sheath encapsulation but also prevents cuticle-degrading enzyme synthesis (Dong et al., 2012; Wang et al., 2015). In *Drosophila*, transglutaminase anchors

the fungi to microclots to facilitate the action of AMPs and haemocytes in the haemolymph (Binggeli et al., 2014). The insect transferrin binds to iron and impede the pathogen survival. Upon infection with *B. bassiana* and *M. anisopliae*, transferrin levels are elevated in *Mastotermes darwiniensis* and *G. mellonella* (Geiser et al., 2012; Sowa-Jasilek et al., 2014). Insects can counter fungal infection employing microRNAs to silence virulence-related genes. Mosquitoes enhance the expression of let-7 and miR-100 miRNAs for specific silencing of the virulent fungal genes, sec2p and C6TF (Dubovskiy et al., 2013).

e. Fungal evasion strategies

To up the ante in the arms race, fungi exhibit various invasive strategies to counteract the immune responses and successfully colonize the insect haemocoel. Fungal cells belonging to the genus *Metarhizium* upregulate MOS1 osmosensor to adapt to the osmotic pressure of the insect haemolymph (Thompson et al., 2003). Cell wall remodelling coupled with cell surface camouflaging enables the fungi to escape haemocyte encapsulation. In the host haemolymph, *B. bassiana* demonstrate carbohydrate epitope shielding to immune recognition and propagate as single yeast-like cells with thin cell walls known as blastopores (Wang et al., 2008; Wang et al., 2021c). These shifts to blastospores minimize the number of PAMPs on the cell surface to reduce host PRR recognition in *G. mellonella* (Wanchoo et al., 2009). *Metarhizium* sp. blastospores evade haemocytes by secreting a hydrophilic collagen (Mcl-1) coat to mask antigenic beta-glucans of the fungal cell wall (Hou et al., 1985). A non-hydrophobic cell wall protein (CWP-10) and a conidial protein (CP-15) of *B. bassiana* are also involved in the escape mechanism and insect virulence (Vertyporokh et al., 2020).

Certain fungi use yeast-type budding strategy to rapidly proliferate as hyphal bodies in the haemocoel. The quick propagation of fungal cells facilitates nutrient deprivation to expedite the insect death (Wang et al., 2006a). For instance, acid trehalase (Brivio et al., 2020) and phosphoketolase genes (Xu et al., 2015) in *Metarhizium* are switched on to degrade the insect haemolymph trehalose thereby contributing to the fungal virulence. An insect-like sterol carrier protein in *Metarhizium* is involved in the hyphal body formation in the haemocoel (Jin et al., 2015). Compared to fungal conidia or hyphae, hyphal bodies possess fewer sugar epitopes which permit them to avoid recognition (Duan et al., 2009). Downregulation or suppression of AMPs produced via toll or Imd pathways is yet another

evasive mechanism by which entomopathogenic fungi evade the host immune responses. Certain *Metarhizium* and *Beauveria* strains are resistant to the antifungal peptide, drosomycin (Zhao et al., 2014). In *B. bassiana*, the dysbiosis of gut microbiota in infected mosquitoes downregulated AMPs including attacin, cecropin 1, defensin 1, Gambicin 1, and FBN9 which resulted in accelerated mosquito death (Pendland et al., 1993). In a different study, oosporein secreted by *B. bassiana* downregulated the expression of gallerimycin in *G. mellonella* (Tzou et al., 2002). Other immune evasive strategies employed by entomopathogenic fungi include immune modulation to disrupt the host immune responses and repression of proteases involved in the activation of PPO cascade. Entomopathogenic fungi secrete a variety of virulent factors/toxins during invasion, including bassianin, bassiacridin, cyclosporine and cyclic destruxins (Chen et al., 2014; Gibson et al., 2014; Matskevich et al., 2010; Molnar et al., 2010; Wang et al., 2012; Wei et al., 2017) which are responsible for host specificity, virulence and suppression of immune response. Further, destruxins also block phagocytosis by inhibiting V-ATPase and thereby alter the pH within insect lysosomes and vacuoles (Kissing et al., 2018). The Pr1 protease produced during the fungal penetration also activates the PPO pathway. Few entomopathogenic fungi suppress this protease to diminish the insect PO activity (Wang et al., 2021a).

3. Insect-viral interactions

The acquisition of virus by insects is through blood feeding, sap sucking or foliage feeding. Plant RNA viruses including Caulimovirus, Crinivirus, Luteovirus, Geminiviridae, marafiviruses, tospoviruses, tenuiviruses, reoviruses, and Rhabdoviruses replicate within insect vectors including aphids, thrips, whiteflies, leafhoppers and planthoppers. Based on the length of the period the vector harbours infectious particles, insect transmission of plant viruses can be non-persistent, semi-persistent and persistent. Non-persistent viruses are retained in the stylet of the vector for few hours. Insects can hold semi-persistent viruses in their foregut for few days. Persistent plant viruses initially infect gut epithelial cells of Hemiptera insects and subsequently invade other tissues and organ systems including hemocytes, salivary glands, nervous and reproductive systems (Luplertlop et al., 2011). On the other hand, most arboviruses that impact human health are categorized under three viral families including Alphaviridae, Flaviviridae, and Bunyaviridae. *Drosophila* is an ideal model to study arbovirus transmission. Natural pathogens of *Drosophila* include

Drosophila C virus (DCV), nora virus and sigma virus (Kissing et al., 2018; Matskevich et al., 2010).

a. Insect antiviral responses

Antiviral response in the insects is primarily mediated by small interfering RNA (siRNA) pathway. Viral dsRNA that is synthesized as a result of viral RNA genome replication is cleaved by endonuclease, Dicer-2 (Dcr-2), and subsequently incorporated into the RNA-induced silencing complex (RISC). The dsRNA is eventually processed into a single strand that binds to the viral RNA genomes and targets them for degradation. The antiviral function of siRNA pathway has been validated in *Drosophila* using loss of function studies and knockdown experiments of RNAi machinery including Dcr-2, Ago-2 or R2D2 (Galiana-Arnoux et al., 2006; Wang et al., 2006b). Similarly, knockdown of the core siRNA pathway components resulted in enhanced arbovirus replication in *Anopheles* and *Aedes* mosquitoes and decreased arboviral transmission efficiency (Franz et al., 2006; Keene et al., 2004) suggesting the indispensable role of siRNA-mediated antiviral defense.

Toll, Imd, JAK-STAT and JNK pathways are implicated in antiviral innate immunity in insects. The DExD/H helicase domain of insect DCR2 acts as a PRR which during viral infection recognize viral nucleic acids and viral glycoproteins (PAMPs) (Deddouche et al., 2008; Rosendo Machado et al., 2021) to activate the immune pathways. Toll pathway is implicated in the inhibition of *Drosophila X virus* (DXV) replication in *Drosophila*. Imd signaling pathway genes, Relish (Rel) and the peptidoglycan recognition protein-LC (PGRP-LC) displayed antiviral role in the flies infected with cricket Paralysis virus (CrPV) (Costa et al., 2009). The *Drosophila* Imd pathway is also implicated in the antiviral activity against alphavirus. DENV infection in *A. aegypti* elicits immune components of the Imd pathway (Luplertlop et al., 2011). Further, knockdown of the midgut Imd components resulted in enhanced infection in *A. gambiae* with O'nyong'nyong virus (ONNV) (Carissimo et al., 2015). Activation of JAK-STAT pathway is attributed to antiviral response against DENV, *Drosophila C virus*, SINV, and West Nile virus (WNV) (Dostert et al., 2005; Souza-Neto et al., 2009). Knockdown of JAK-STAT component, dome, in *Drosophila* enhanced sigma viral load significantly (Liao et al., 2019). *Drosophila* Dcr-2 triggers the expression of Vago, which is a cytokine with interferon-like activity. Subsequently, vago binds to an unidentified cellular receptor on the adjacent cells to activate the JAK-STAT

pathway and induce AMP expression downstream (Paradkar et al., 2012). A robust transcriptional activation of the JNK pathway components, Hemipterous, Gadd45, Jra, Kay, Puckered and Rab-30 was demonstrated in *Drosophila* during DCV infection (Merkling et al., 2015; Swevers et al., 2018).

The direct role of AMPs, attacin C and dipterin B, in the regulation of viral replication is demonstrated in flies (Huang et al., 2013). In *Ae. aegypti*, knockdown of cecropin N, defensin C, defensin D, and lysozyme C increased DENV-2 infection (Ramirez et al., 2012; Xiao et al., 2014). The insect cellular immunity in antiviral defense is mediated by apoptosis or autophagy. Viral activation of apoptosis is induced either by pro-apoptotic genes or inhibitors of apoptosis proteins (IAPs). Flock house virus infection in *Drosophila* triggers p53 activation that induces pro-apoptotic gene, Reaper to block IAPs activity (Byers et al., 2016; Liu et al., 2013). Insect humoral immunity components also contribute in antiviral immunity. In *Helicoverpa armigera*, SP41/cSP1/cSP6 cascade converts PPO into active phenoloxidase to block baculovirus infection (Wang et al., 2020). The whitefly protein, Tid, interacts with the TYLCV coat protein. Inhibition of Tid enhanced TYLCV replication (Zhao et al., 2020). In insects, *Wolbachia* offers protection against RNA viruses. The protection is density-dependent which varies among strains. Flies infected with *Wolbachia* are less sensitive against infection by the DCV, FHV and Nora virus (Teixeira et al., 2008). *Wolbachia* also blocks DENV replication in mosquitoes (Pimentel et al., 2020). Further, *Wolbachia* stimulates the ROS production which provides antiviral protection mediated by ERK signalling pathway (Wong et al., 2016).

b. Viral evasion mechanisms

Counter viral mechanisms for insect survival are primarily through RNA interference (RNAi) and IAPs. Certain viruses produce proteins known as virus suppressor of RNAi (VSRs) to evade the RNAi-mediated cleavage. VSRs, B2 and 1A produced by members of the Nodaviridae and Dicistroviridae respectively are well characterized (Ding et al., 2011). VSRs including IIV6-340R, DCV-1A, VP3 and FHV-B2 that are characterized from *Drosophila* X virus (DXV) and *Culex* Y virus (CYV) directly bind to long dsRNA and thereby block Dcr-2 processing (Fareh et al., 2018; van Cleef et al., 2014). Nora virus VSRs, CrPV-1A and VP1, bind to AGO-2 and inhibit slicing of the target (Schuster et al., 2019). NS4B protein isolated from dengue virus 2 (DENV-2) inhibits the siRNA

pathway in mosquito cells (Elrefaey et al., 2021). Some viruses encode specific factors to counter the immune responses in the insect gut. The flavivirus nonstructural protein-1 (NS-1) facilitates infection of DENV and ZIKV in mosquito gut epithelial cells by suppressing the enzymes involved in ROS synthesis and JAK-STAT pathway (Liu et al., 2016; Liu et al., 2017). Virus-induced *Drosophila* protein, *Diedel*, acts as an inhibitor of the IMD pathway for successful establishment of SINV infection (Lamiabile et al., 2016).

Few insect viruses employ specific components to breach the peritrophic matrix and thereby establish virus infection in the midgut. Enhancin produced by baculoviruses is one such component with viral-enhancing activity. *Trichoplusia ni* granulovirus (TnGV) enhancin established NPV infectivity (Wang et al., 1994) by specifically degrading intestinal mucin proteins from the *T. ni* peritrophic matrix (Bischoff et al., 1997). Bacterium *Serratia marcescens* secretes 'Sm enhancin' that digests membrane-bound mucins and facilitates DENV infection (Wu et al., 2019). Peritrophic matrix in silkworm larvae is disrupted by fusolin secreted by entomopoxvirus spheroids of *Anomala cuprea* (Mitsuhashi et al., 2003). Baculovirus-infected insect cells inhibit translation by activating PK2, a homolog of eIF2 α kinase which prevents eIF2 α phosphorylation by competitive inhibition (Li et al., 2015). Lysine deacetylation of heat shock cognate protein, HSC70-4 accelerates *Bombyx mori* nucleopolyhedrovirus proliferation through proteasome-mediated nuclear import system (Mao et al., 2021). In silkworms infected with Cypovirus, increased levels of BmCPV-miR-1 and BmCPV-miR-3 inhibited host gene BmRan thereby promoting viral proliferation (Lin et al., 2021). Tomato yellow leaf curl virus (TYLCV) replicates efficiently in the whitefly vector via induction and recruitment of proliferating cell nuclear antigen (PCNA) (He et al., 2020; Marques et al., 2016).

4. Insect-microbe-plant tripartite interactions and pest management

Insect-associated microbes play an important role in determining insect-plant interactions. Insect-microbe interactions can be either beneficial to the plant or could help the insect to infest the plants as a monophagous or polyphagous pest. Piercing and sucking insects that belongs to the order Hemiptera transmit endophytes that promote plant growth and benefit the insect host with nutrition. Insect transmitted Rhizobacterium, *Klebsiella oxytoca*, induces jasmonic acid and ethylene defenses in the plant species against necrotrophic pathogens

and insects (Coolen et al., 2022). For eg., the root associated *Rhizobium* sp. induces systemic response in the plant that allows rapid and effective defense against *Pectobacterium*, a gut inhabitant of the larvae of cabbage root fly *Delia radicum* (van den Bosch et al., 2020). Few bacilli such as *Klebsiella* and *Enterobacter* sp. can directly produce sex pheromones using glucose and threonine as the substrates in the male Oriental fruit fly, *Bactrocera dorsalis*. These pheromones influence the mating behaviour of fruit fly which is a major pest of fruit bearing plants (Zhao et al., 2022).

Plant volatiles and phytochemicals act as chemical defenses against the herbivorous insects. In response, herbivorous insects with the help of their associated microbiota metabolize these detrimental substances and detoxify the phytochemicals. Oral secretions of *Leptinotarsa decemlineata* harbour bacteria including *Pseudomonas* and *Enterobacter* sp. repressed plant jasmonic acid mediated defenses. Whitefly *Bemisia tabaci* with its gut symbiont *Hamiltonella* induced salicylic acid responses while repressing the jasmonic acid defenses. *Staphylococcus epidermidis* in the saliva secretions of *Spodoptera litura* and *Pseudomonas syringae* in the cabbage looper moth *Trichoplusia ni* benefits from salicylic acid-jasmonic acid antagonism (Caarls et al., 2015). The generalist or specialist nature of insect pests is now known to be determined by their microbial composition. For eg., *Trichoplusia ni* gut was dominated by *Propionibacterium*, *Shinella*, *Terribacillus* that degraded plant glucosinolates when fed upon *Arabidopsis thaliana* leaves. On the other hand, the abundance of *Agrobacterium* and *Rhizobium* sp. prominently increases when fed on *Solanum lycopersicum* leaves which enabled degradation of alkaloids (Zhao et al., 2022). Similarly, a bean diet rich in cyanogenic glycosides caused mortality in *Spodoptera littoralis* insect larvae, however when the larvae were fed with barley-rich diet, the gut microbiota was revived (Mason et al., 2020).

In the agricultural or residential set up, insect pests are exposed to repellents or agrochemicals. Insect residing microbiota has developed the capabilities to detoxify these chemicals and subsequently generate insect resistance. In the urban pest *Aedes albopictus* that causes dengue and chikungunya, higher abundance of *Serratia oryzae* and *Acinetobacter junii* were observed in deltamethrin-resistant strains compared to the sensitive strains (Wang et al., 2021b). The insect gut symbionts of bean bug, *Cletus punctiger* and *Riptortus pedestris* were able to detoxify the

agrochemical fenitrothion and confer resistance to the insect host (Zhao et al., 2022). In cockroach *Blattella orientalis*, higher degradation rate of α -endosulfan was mediated by the gut bacteria *Pseudomonas aeruginosa* and *Acinetobacter lwoffii* which make these household pests difficult to control (Ozdal et al., 2016). The gut microbiota of the pollinator such as the honey bee *Apis mellifera*, upregulated the gene expression of detoxifying-related genes, CYP450s, GST, and catalase, and thus exhibited enhanced tolerance to thiacloprid or flumethrin (Wu et al., 2020).

Changing agriculture landscape and climate is reshaping the insect biodiversity worldwide. Rapid decline in many insect species that are beneficial to ecosystem is reported. The insect lifecycles and their patterns are affected such that many non-vector insects are gaining vector competence. Non-pest insects are transforming into agricultural pests and pest resistance to agrochemicals is often reported. Under this scenario, understanding natural adaptive mechanisms of plants, insects and their associated microbes is important to provide sustainable alternatives without negatively impacting the ecological footprint. Effective pest and plant disease management strategies require application of knowledge of multitrophic interactions between plants, insects and microbes. Further, since insects rely on their microbial services, insect-associated microbes would serve as ideal targets for pest control.

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AUTHOR CONTRIBUTION STATEMENT

Chaitanya, R.K. conceived the original idea and conceptualized the review. Alok collected, sorted and compiled the literature, contributed to manuscript writing and figure illustrations. Chaitanya, R.K. edited the manuscript, and supervised the work till completion.

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CONFLICT OF INTEREST

No conflict of interest.

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