

1 **The complex interactions between nutrition, immunity and infection in insects**

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11 **Summary**

12 The field of nutritional immunology captures the complexity of the connections between the
13 nutritional environment, infection and immunity. Here, we discuss recent research that links
14 the nutritional environment with insect health.

15

16 **Abstract**

17 Insects are the most diverse animal group on the planet. Their success is reflected by the
18 diversity of habitats in which they live. However, these habitats have undergone great changes
19 in recent decades; understanding how these changes affect insect health and fitness is an
20 important question for insect conservation. In this Review, we focus on the research that links
21 the nutritional environment with infection and immune status in insects. We first discuss about
22 the research from the field of nutritional immunology, and we then investigate how factors
23 such as intra- and extra-cellular symbionts, sociality and transgenerational effects may interact
24 with the connection between nutrition and immunity. We show that the interactions between
25 nutrition and resistance can be highly specific to insect species and/or infection type – this is
26 almost certainly due to the diversity of insect social interactions and life cycles, and the varied
27 environments in which insects live. Hence, these connections cannot be easily generalised
28 across insects. We finally suggest that other environmental aspects – such as the use of
29 agrochemicals and climatic factors – might also influence the interaction between nutrition and
30 resistance, and highlight how research on these is essential.

31

32 **Introduction**

33 Insects are the most diverse lineage of multicellular organisms on the planet (Engel and
34 Grimaldi, 2004). Insects are found in nearly all ecosystems and are essential to ecosystem
35 functioning. For these reasons, understanding the effects of environmental changes on insect
36 populations – effects that have been quite dramatic in the last few centuries – can be considered
37 a defining challenge for entomological and ecological research in the 21st century (Boggs,
38 2016; Halsch et al., 2021). Changes in the environment include modifications of the nutritional
39 landscape that can have important implications for insect populations.

40 The field of nutritional immunology captures the complexity of the relationships between the
41 nutritional environment, infection and immunity (Ponton et al., 2013). Nutrition is a multi-
42 dimensional problem. Food sources can be abundant, scarce, diverse, unique, easy or difficult
43 to access, balanced, unbalanced or contaminated. Responses to infection are also complex.
44 Innate immune responses have been traditionally described as broad and non-specific to
45 pathogen strains; however, recent research suggests that insect innate immunity (see Glossary)
46 is also capable of providing highly specific immune responses to fight infections in a similar
47 way to adaptive immune responses found in vertebrates (Cooper and Eleftherianos, 2017;
48 Schulenburg et al., 2007). Responses to infections also include processes such as tolerance (see
49 Glossary), which allows individuals to maintain their fitness while infected (Ayres and
50 Schneider, 2012). In this Review, we focus on the recent research and questions that link the
51 nutritional environment with individual and population health, as well as the different factors
52 that may define the framework of nutritional immunology in insects. We explore the links (i.e.,
53 connections) and relationships (i.e., the manner in which components may be connected)
54 between dietary composition and innate immunity, resistance and tolerance of insects when
55 confronted with different types of parasites. Intra- and extracellular symbionts can interfere
56 with host metabolism and immunity, and we discuss how they affect the relationship between
57 nutrition and immunity. Insects successfully occupy multiple ecological niches thanks to the
58 different morphological and physiological phases they express during their development. Here,
59 we consider the links between nutrition and immunity throughout development but also across
60 generations. Finally, the very diverse lifestyles of insects, from solitary to eusocial, adds
61 another layer of complexity with implications for the interactions between nutrition and
62 immunity. Understanding how changes in the nutritional environment affect insect health and
63 fitness is a complex question, but it is relevant to issues such as pest management, disease

64 vector control, insect conservation, and insects as food and feed. Although most of the work in
65 eco-immunology has made use of insect model species, in the future it will be important to
66 explore other systems to obtain a wider and more integrative understanding of this field of
67 research. Further, understanding the importance of experimental nutritional conditions is
68 essential, since it can influence the outcome of experiments as well as their reproducibility.

69

70 **Nutritional effects on infection, and plastic nutritional responses**

71 **Nutrition, immunity and resistance**

72 Insects are rather uniform in their nutritional requirements because their chemical compositions
73 and metabolic capabilities are broadly similar (Chapman, 2013). However, there is still
74 variation in nutritional requirements among insect species that arises from adaptations to
75 specific nutritional environments. For example, plant-feeding insect species generally require
76 approximately equal amounts of protein and carbohydrates as adults, with larvae usually
77 requiring a high protein intake to support their growth. By contrast, predatory insects have high
78 protein and fat requirements relative to carbohydrates. Insects feeding on high-carbohydrate
79 foods, such as grains, have a high requirement for carbohydrates relative to proteins.

80 An insect's nutritional state influences its immune status and resistance to infection. Table 1
81 summarises the studies that have investigated the interactions between immunity and resistance
82 in insects. These studies have generally investigated the effects of food restriction and
83 starvation on the expression of immune and life history traits (i.e. reproduction and
84 longevity/survival) in the absence of infection (i.e. immuno-competence) and post-infection.
85 Starvation and limited food accessibility can both have negative effects on fitness and immune
86 parameters (however, see discussion on positive effects of caloric restriction in Partridge et al.,
87 2005). When food limitation is severe, humoral and cellular immunity (see Glossary) are
88 altered, and mortality post infection is increased (Kangassalo et al., 2015; Ariani et al., 2015;
89 Adamo et al., 2016; Kutzer and Armitage, 2016; McKay et al., 2016; Ebrahimi and
90 Ajamhassani, 2020; Meshrif et al., 2022). However, total food limitation is not always what
91 individuals face in nature, as some nutrients might be more limited than others, leading to
92 imbalanced diets. In this context, the immune effects of deficiencies in specific macro- or
93 micro-nutrients (see Glossary) – such as protein, alkaloids, ascorbic acid or selenium – have
94 been studied in different insect species (Popham et al., 2005; de Roode et al., 2008; Popham

95 and Shelby, 2009; Howich and Lazzaro, 2014; Anthony et al., 2015; Rochardson et al., 2015;
96 Unckless et al., 2015; Tritschler et al., 2017; Kelly and Bowers, 2018; Vogel et al., 2018).

97 Over the last 10 years, and following the pioneering work of Simpson and Raubenheimer
98 (2012), studies have employed geometric approaches to investigate the effects of dietary
99 macronutrient composition on insect physiology (Box 1). Protein and carbohydrates are two of
100 the main energy-yielding nutrients for insects, and the ratio of dietary protein to carbohydrates
101 has important effects on insect physiology, modulating longevity and reproduction (e.g. Lee et
102 al. 2008). There is a general trend for dietary protein being the primary regulatory
103 macronutrient of immunity in insect larval stages. When larvae do not have access to enough
104 protein, their immunity is usually negatively affected as well as their resistance to pathogenic
105 bacteria, fungi or macro-parasites (Lee et al., 2006; Povey et al., 2009; Povey et al., 2014;
106 Tritschler et al., 2017; Danihlik et al., 2018, Wilson et al., 2019; Wilson et al., 2020; Gomez-
107 moracho et al., 2021). The nutritional optima of larvae and adults can however differ
108 significantly. For instance, in *Drosophila melanogaster*, larvae require a diet high in protein to
109 optimise growth, whereas a diet with a more balanced composition of protein and
110 carbohydrates optimises lifetime egg production in adults (Jang and Lee, 2018). This might
111 explain why the results of studies exploring the interactions between nutrition and immunity in
112 adult insects differ from the ones in larval stages (as seen in Table 1). Different nutritional
113 optima between adult and juvenile stages have been mainly observed in holometabolous insects
114 (see Glossary) in which development includes a complete metamorphosis; nutritional optima
115 might be less marked between life stages of hemimetabolous insects (see Glossary), yet there
116 is a lack of data to fully support this conclusion.

117 In adult insects, the interaction between resistance and nutrition can also depend on the host
118 species and the type of infection. When *Drosophila* females are infected with the bacterium
119 *Micrococcus luteus*, a carbohydrate-biased diet (i.e. a diet that contains a greater concentration
120 of carbohydrates than what naïve flies usually select) promotes the expression of antimicrobials
121 and survival after infection (Ponton et al., 2020). Similar results were observed in the
122 Queensland fruit fly, *Bactrocera tryoni*. When infected with the bacterium *Serratia*
123 *marcescens*, adult females restricted to a carbohydrate-biased diet harbour a lower pathogen
124 load during the first few hours post-infection than those on a balanced diet (i.e. a diet with
125 approximately similar concentrations of protein and carbohydrates; Dinh et al., 2019). In
126 contrast, in adult honeybees, an increase in total dietary protein lowers mortality after viral

127 infection but increases the infection load of microsporidia (see Glossary, Tritschler et al.,
128 2017). There is no evidence of an increase in immuno-competence when the diet is rich in
129 protein, but a decrease in immune responses is seen when the diet does not contain protein (see
130 Brunner et al., 2014). Dietary fat (and not protein) also stimulates viral immunity in honeybees
131 (Alshukri and Al-Esawy, 2021). Diet diversity (i.e. when individuals are offered a choice
132 between different sources of food/nutrients) also influences immune parameters and resistance
133 to fungal pathogens in bees (Alaux et al., 2010; Foley et al., 2012, see also in other insect
134 species Vogelweith et al., 2016; Krams et al., 2017). Further, it has been shown that when
135 *Bombus terrestris* individuals are fed a diet with a low protein and a high carbohydrate
136 concentration, they harbour the greatest quantity of parasites but live the longest compared to
137 individuals fed a high-protein diet (Gomez-moraco et al., 2021). This result suggests that a
138 carbohydrate-biased diet in adult bees might increase their tolerance to infection (see Glossary;
139 Ayres and Schneider, 2012) but not their resistance to infection. This might illustrate that not
140 all immune parameters respond in the same way to the nutritional composition of the diet. For
141 instance, Cotter et al. (2010, 2019) have shown that when caterpillars of the Egyptian cotton
142 leafworm, *Spodoptera littoralis*, are fed diets varying in their protein-to-carbohydrate ratio,
143 functional immune traits – such as the lytic and phenoloxidase activities (see Glossary) –
144 increase as the protein content of the diet increases; however, immune gene expression was
145 much less predictable in the study. The activation of immunity can also be costly through
146 causing self-damage or immunopathology (Sadd and Siva-Jothy, 2006), with the physiological
147 costs carried across life stages (DeBlock and Stoks, 2008). Food availability might be an
148 important factor in mediating these effects (Stahlschmidt et al., 2015). More research is,
149 however, needed to produce a clearer picture of how nutrition may decrease these negative
150 effects of immune activation.

151 Host nutrition not only influences immunity but it also influences the resources that are
152 available to pathogens (Smith and Holt, 1996). For example, some specific nutrients, such as
153 iron, are required by pathogens to develop, and host supply can limit their access. Pike et al.
154 (2019) have published a meta-analysis where they investigated how nutrition influences
155 pathogen virulence (see Glossary) across vertebrates and invertebrates. Their analysis suggests
156 that host nutrition does not influence pathogen virulence; however, more research targeting
157 these specific questions is needed, since the resources required by the pathogens might be
158 species/strain-specific. It is also important to note that most studies, where the dietary protein
159 composition is manipulated, solely used yeast as a main protein source. Yeast is however not

160 only a major source of amino acids, but also a source of other miscellaneous components.
161 Therefore, protein restriction or supplementation through modulating yeast intake
162 inadvertently causes variation in other elements in the diet (Bruce et al., 2013). Further, most
163 studies assume that the food provided to insects is standardized; however, this is not always
164 true. Laboratory experimental settings do not always use defined or holidic diets (see Glossary),
165 as these might be either too challenging to prepare or too expensive to use routinely. Food
166 deprivation is also not always well defined in protocols, and – in natural environments – insects
167 can find themselves in diverse, nutritionally challenging situations that would affect their life
168 history traits differently (see Zhang et al., 2019). To be able to compare the results of the
169 different studies investigating the effects of nutritional manipulations on immunity and
170 resistance, protocols will need to be standardized.

171 **The proximate mechanisms modulating innate immunity through the diet**

172 The exploration of the proximate mechanisms of the interaction between metabolism and
173 immunity has produced some fascinating findings. Nunes et al. (2021) review the hormonal
174 regulation of cellular and humoral immunity in insects. The developmental hormones 20-
175 hydroxyecdysone (20E) and juvenile hormone (JH) have an important role in insect immunity.
176 20E stimulates the proliferation, differentiation and action of haemocytes (see Glossary),
177 induces phagocytosis and nodulation (see Glossary) and increases the expression of
178 antimicrobial genes (which code for antimicrobial peptides; AMP), such as dipterin, cecropin
179 and attacin, through the ecdysone receptor (Schwenke et al., 2015). 20E may also influence the
180 duration of immune responses (Garbuzov and Tatar, 2010). In *Manduca sexta* and *Tenebrio*
181 *molitor*, JH modulates the prophenoloxase cascade and encapsulation (see Glossary) (Hiruma
182 and Riddiford, 1988; Rantala et al. 2003; Rolff and Siva-Jothy, 2002). Overall, 20E acts as a
183 positive regulator of immunity, whereas JH acts as an immune suppressor (Nunes et al., 2021,
184 Schwenke et al., 2015). Nutrient-sensing pathways, JH and 20E signaling may interact.
185 Blockage of the two highly evolutionarily conserved nutrient sensors, insulin-like signalling
186 pathway (IIS) and target of rapamycin (TOR, sensing amino acids level), induces a decrease in
187 JH biosynthesis (e.g. Abrisqueta et al., 2014 and Leyria et al., 2023) and in ecdysone production
188 (Kemirembe et al., 2012). Further, infections can also lead to a decrease in fat and glycogen
189 stores through an impairment of insulin signaling decreasing JH biosynthesis (Dionne et al.,
190 2006). The effects of JH on immunity may be highly dependent on the insect's developmental
191 stage, and the type of host and pathogen, with contrasting effects in different species (Amaro-

192 Sánchez et al., 2023, Remolina and Hughes, 2008). More work is therefore needed to clearly
193 understand how nutrition and macronutrients modulate insect immunity through the JH and
194 20E pathways.

195 The central immunomodulators of insect immunity are molecules such as cytokines (i.e.,
196 signaling proteins), DAMPs (i.e., damage-associated molecular pattern molecules), PAMPs
197 (i.e., pathogen-associated molecular patterns) and biogenic amines (i.e., nitrogen compounds).
198 Metabolic signaling pathways are also involved in the activation of systemic immunity
199 (Adamo, 2021; Lee and Lee, 2018, Figure 1). In both insect and mammalian systems, IIS
200 regulates the transcription factor forkhead box O (FOXO; Ahlers et al., 2019), with the insulin–
201 FOXO pathway controlling glucose and lipid metabolism (see Figure 1 for more details).
202 FOXO is associated with longevity and nutritional signaling, as it induces the insulin-like
203 receptor (InR, DiAngelo and Birnbaum, 2009). FOXO also regulates the expression of
204 antimicrobial peptides in the fat body (see Glossary; Becker et al., 2010; Figure 1), and has
205 another immune role through its induction of RNA interference (RNAi)-specific genes that
206 mediate antiviral immunity (Galiana-Arnous et al., 2006; Trammell and Goodman, 2019;
207 Wang et al., 2006).

208 Generally speaking, immunity against fungi and Gram-positive bacteria is mediated by the
209 Toll-Dif/Dorsal pathway and immunity against Gram-negative bacteria is mediated by the Imd-
210 Relish pathway in insects, leading to the expression of antimicrobial peptide genes (see
211 Galenza and Foley, 2019 for details). Interestingly, Becker et al. (2010) have shown that
212 starvation can induce AMP production through the FOXO pathway, independently of the
213 evolutionary conserved immune pathways Toll or Imd (Figure 1). This might illustrate that
214 when food is not available, some insects (at least *Drosophila*) show an anticipatory increase in
215 AMP production (also see for early melanisation in Pan et al., 2018). Further, Toll-like receptor
216 activation induces the inactivation of the pathogen-induced phosphoinositide 3-kinase (PI3K)-
217 Akt pathway (Figure 1). Pathogen-induced Toll activation is upstream of the insulin signaling
218 inactivation (Lee and Lee, 2018). More investigation is still needed to clarify the exact
219 molecular relationship between the Toll and insulin signaling pathways during immune
220 responses (Lee and Lee, 2018)

221 Another signaling pathway involved in immunity against viruses, JAK/STAT, is connected to
222 IIS, which might again indicate that insects have evolved immune mechanisms that are
223 responsive to nutritional acquisition (see discussion in Trammell and Goodman, 2019). The

224 regulatory hormone adipokinetic hormone (AKH) – which is also involved in physiological,
225 metabolic and homeostatic processes, such as carbohydrate and lipid metabolism – also
226 regulates innate immunity (Toprak, 2020). For instance, the principal role of AKH is to initiate
227 lipid/carbohydrate mobilisation from the fat body, and its expression is elevated upon infection;
228 this might induce immune responses (Ibrahim et al., 2017). There is some indication that AKH
229 also activates the prophenoloxidase cascade, among other immune responses (Goldsworthy et
230 al., 2003; Mullen and Goldsworthy, 2006).

231 Only a few studies have investigated the effects of the dietary nutrient balance on innate
232 immunity components. Studies have generally shown that the balance of dietary protein and
233 carbohydrates influences the expression of immune genes and other immune markers in naïve
234 and infected insects with contrasting effects in larvae and adults (instance.g. Cotter et al., 2019;
235 Ponton et al., 2020). The number of studies is, however, too limited; more investigation is
236 needed to draw general conclusions. For instance, the two nutrient sensors TOR and AMPK
237 might respond not only to the concentration of circulating nutrients (with TOR being stimulated
238 and AMPK depressed either directly or indirectly by increasing concentrations of nutrients),
239 but to the amino acid/carbohydrate balance of the diet (Simpson and Raubenheimer, 2009). A
240 low ratio of dietary protein to carbohydrates would decrease TOR activity, whereas a high
241 protein to carbohydrate ratio would increase TOR activity. Whether these responses are directly
242 linked to immune pathways needs to be confirmed. Finally, it is worth noting that although
243 research to date has largely focused on the effects of nutrients on host immunity (i.e. ‘top-
244 down’ regulation of pathogens), the nutrients may directly or indirectly impact the pathogen
245 through (‘bottom-up’) non-immunological mechanisms. For example, it has recently been
246 shown that dietary protein has a direct negative impact on the growth of bacteria in the
247 haemolymph by altering haemolymph solute concentration, creating a significant osmotic
248 stress for the pathogens (Wilson et al., 2020).

249

250 **Self-medication**

251 Insects have evolved medication behaviours that occur either in response to an active infection
252 or to prevent an infection (prophylaxis). This is often referred to as ‘self-medication’, which is
253 defined as animals using molecules such as secondary plant compounds or other non-nutritive
254 substances with antiparasitic activity (de Roode et al., 2013; Raubenheimer and Simpson,

255 2009). Research investigating the role of macronutrients in nutritional immunology has also
256 demonstrated that self-medication can involve the modulation of macronutrient selection (i.e.
257 ingestion of a different ratio of macronutrients for infected individuals compared to non-
258 infected ones) to compensate for the negative effects of the infection on fitness traits. (Abbott,
259 2014; Bashir-Tanoli and Tinsley, 2014; Galenza et al., 2016; Ponton et al., 2011; Povey et al.,
260 2014). Self-medication can also stimulate immune responses. For example, modulation in
261 macronutrient intake was measured in adult *D. melanogaster*, injected with the bacterium
262 *Micrococcus luteus*. Infected flies ingested a diet that was two times more concentrated in
263 carbohydrate during the first six days post-infection (Ponton et al., 2020), compared to non-
264 infected flies. However, they decreased their total food intake. This shift in nutritional
265 behaviour increases the flies' survival after infection supposedly through an increase
266 expression of immune genes (Ponton et al., 2020). Furthermore, the diet selected by infected
267 flies is specifically beneficial during infection and is not optimal for non-infected individuals'
268 fitness (see discussion in de Rood and Hunter. 2019; Ponton et al. 2013; Ponton et al. 2011).
269 Similar self-medication responses have been observed in a range of insect–pathogen
270 interactions, including in larvae of moths from the genus *Spodoptera* infected with bacteria or
271 viruses. Details of these studies are given in Table 1.

272

273 **The role of symbionts in the relationship between nutrition and immunity**

274 Most insects have mutualistic relationships with microbes, which provide benefits to their hosts
275 such as immune priming (see Glossary) and stimulating immunity against pathogens (Buchner,
276 1965; Snyder, et al., 2012), facilitating digestion (Rio et al., 2006, Simonet et al., 2016) and
277 supplementing host diets with micronutrients (Chomicki et al., 2020; Gil et al., 2003). Host
278 diet is a key driver of the abundance and diversity of symbionts, and can modulate the role of
279 mutualistic microbes in immune responses. Here, we review empirical studies on the
280 interaction between insect nutrition, immunity and the microbiota.

281 **Gut microbiota**

282 The digestive tract harbours a high diversity (i.e. a high number of strains/species) and quantity
283 (i.e. high number of individuals) of microbes, and most of these microbes are dependent on
284 their host's nutrition (see Engl et al., 2020; Harris et al., 2019 for a recent review; Herren et al.,
285 2014; Mason, 2020; Pernice et al., 2014; Wilkinson et al., 2007; Wong et al., 2015). In wood-

286 feeding termites, changes in diet are accompanied by shifts in the dominance of protist species
287 (Tarayre et al., 2015), and in flies, the gut microbiota composition varies with plant and food
288 type, and diet shifts (see for instance Chandler et al., 2011, Fink et al., 2013; Vacchini et al.,
289 2017). More recently, it has been shown that black soldier fly (*Hermetia illucens*) larvae fed a
290 high-fibre diet harbour a gut microbiota with greater bacterial richness (i.e. total number of
291 bacterial strains/species) and diversity (i.e. amount of bacteria from each of the bacterial
292 strains/species present) compared to individuals fed protein-rich and fat-rich diets (Greenwood
293 et al., 2021). Although there is strong evidence that the nutritional conditions influence the gut
294 microbiota composition at both larval and adult stages, the physiological significance and
295 fitness consequences of this variation remain to be fully understood (see Harris et al., 2019 for
296 discussion).

297 Microbiota diversity correlates with insect immunity and resistance to pathogens. In
298 bumblebees, Mockler et al. (2018) found that individuals with high microbiota diversity have
299 lower infection loads of *Crithidia bombi*, which is a common bumblebee gut parasite. A more
300 diverse insect microbiota could intensify the competition experienced by pathogens when
301 colonising their insect hosts (Engel and Moran, 2013), and this may be the case for insects that
302 acquire most of their microbes from the environment (Boissière et al., 2012; Hammer et al.,
303 2017). Also, in honeybees, the gut bacterium *Snodgrassella alvi* enhances survival after
304 pathogen challenge, through an upregulation of antimicrobial genes (i.e. abaecin, apidecin and
305 hymenoptaecin; Horak et al., 2020). The gut bacteria might also directly produce antimicrobial
306 compounds, such as antimicrobial peptides and antibiotics, involved in protecting the host
307 against infections (Daisley et al., 2020; Horak et al., 2020, see Jang and Kikuchi, 2020 for
308 review; Osborne et al., 2012). Although the microbiome influences immunity across a large
309 number of insect species, its influence in insects that have minimal symbiotic communities,
310 such as lepidoptera (Hammer et al., 2017), needs to be investigated.

311 **Intracellular symbionts**

312 In addition to the gut microbiota, insects harbour specific bacterial symbionts that live
313 intracellularly, mostly within specialised organs known as bacteriocytes (Douglas, 2011). Most
314 intracellular symbionts have limited metabolic functions, with their growth and abundance
315 being dependent on the host's nutrition (see Whittle et al 2021 for review). For instance, high
316 levels of nitrogen in the diet of the pea aphid (*Acyrtosiphon pisum*), increase the density of
317 the obligate bacterial symbiont *Buchnera aphidicola* (Wilkinson et al., 2007), whereas in the

318 tsetse fly, thiamine dietary supplementation results in reduced numbers of the obligate
319 symbiont *Wigglesworthia morsitans* (Snyder et al., 2012). Some insects may indeed reduce the
320 supply of nutrients to their symbionts to provide additional nutrients to host functions (Whittle
321 et al. 2021). However, it remains to be fully explored how the host nutritional conditions
322 regulate intracellular symbiont populations based on how obligative or facultative (see
323 Glossary) their relationship with the host is.

324 Intracellular symbionts can have a substantial impact on host immunity. For example,
325 mosquitoes are susceptible to viral infections due to their blood-feeding behaviour, and they
326 rely heavily on the anti-viral function of the symbiont *Wolbachia* (Lu et al., 2012; Osborne et
327 al., 2012). Mechanistically, *Wolbachia* induces an increase in immune gene expression
328 (antimicrobial peptides, melanisation, Toll pathway constituents, C-type lectins, serine
329 proteases and transferrin) when mosquitoes are infected by pathogens such as dengue virus
330 (Rancès et al., 2012). As another example, the pea aphid hosts an obligate primary symbiont,
331 but can also host one or more facultative endosymbionts (see Glossary) that can challenge the
332 immune system through increasing immune cell counts (i.e. granulocytes and plasmatocytes;
333 Laughton et al., 2016). The results above suggest that intracellular symbionts are generally, but
334 not always (e.g. Graham et al., 2012; Sinotte et al., 2018) beneficial to the immunity of their
335 insect hosts. Indeed, the presence of symbionts at varying densities may involve a trade-off
336 between their impact on host immunity and metabolic resources (Whittle et al., 2021).

337 **Fungal symbionts**

338 Insects generally also have fungal symbionts, which may reside extra- or intra-cellularly
339 (Gibson and Hunter, 2010). Despite being neglected in many earlier studies on insect
340 symbioses, there has been an emerging interest in the role of insect–fungal symbioses in
341 immunity (Brentassi et al., 2017; Cappelli et al., 2014; Gibson and Hunter, 2010; Meriggi et
342 al., 2019; Tauber et al., 2019). Symbiotic fungi provide some developmental and survival
343 benefits to their hosts (Brentassi et al., 2017), and can produce antimicrobial molecules
344 (Cappelli et al., 2014). In the paper wasp (*Polistes dominula*) infected by *Escherichia coli*
345 bacteria, yeast strains reduced the *E. coli* load in foundresses but not in workers (Meriggi et al.,
346 2019). Associated with their enhanced immunity, wasp foundresses with prior yeast treatment
347 show increased diversity and changes in the composition of their gut bacterial communities,
348 but without changes in their fungal communities (Meriggi et al., 2019). Further, when
349 honeybees are exposed to the pathogenic fungus *Nosema ceranae*, the growth of the bacterial

350 symbiont *Lactobacillus Firm-5* is supported when young individuals are fed *Wickerhamomyces*
351 *anomalus* yeast, which contributes to the honeybee's immune health (Tauber et al., 2019).
352 Fungi might have caste- and developmental stage-specific direct involvement in immunity, or
353 may be involved indirectly by supporting the growth of other important symbionts.

354 **Symbionts as a link between insect host nutrition and immunity**

355 Understanding the direct effect of symbionts on immunity and resistance to infection is
356 challenging. The first challenge is to define a healthy composition of the symbiont communities
357 inhabiting the host. Studies usually compare the symbiont composition of treated animals to
358 control ones, and, in parallel, measure some physiological and life history traits to inform on
359 the health status of the individuals. The composition of the symbiont communities also changes
360 with physiological parameters such as age and developmental stage (Wang et al., 2020),
361 implying that parameters need to be well controlled during experiments. Diet can influence the
362 composition of the symbiont communities. 16S rRNA sequencing of *Hermetia illucens* gut
363 microbiota showed, for instance, strong differences between soybean and insect diet groups in
364 both type and relative abundance of microbial species (Zhineng et al., 2021). Some recent
365 studies have attempted to explore the impact of insect diet on their immunity in relation to their
366 microbiota. In greater wax moth (*Galleria mellonella*) larvae, a more diverse diet is associated
367 with a higher number of Enterococci in the microbiota, which may be linked to a greater
368 expression of AMP genes (Krams et al., 2017). A greater expression level of AMPs is also
369 induced when soldier fly larvae have a high inhibition of Gram-negative bacteria linked to
370 high-protein diets (Vogel et al., 2018). In another study, Maes et al. (2016) demonstrated that
371 aged diet (i.e. when hive frames were housed with 500 adult bees at 50% humidity and 35 °C
372 until bees reached an average of 14 and 21 days old) leads to a dysbiosis of the gut microbiota
373 (see Glossary), involving a reduction in the numbers of the core symbiont, *S. alvi*, but an
374 increase in the amount of the pathogenic bacteria *Frischella perrara* and *Parasacharibacter*
375 *apium* (Cariveau et al. 2014; Engel et al. 2015). Gut dysbiosis in honeybees results in decreased
376 survival and colonisation by another pathogenic fungus, *Nosema*; this can be prevented by the
377 core symbiont *S. alvi* taking up residence in the gut in early development (Maes et al., 2016).
378 Castelli et al. (2020) examined whether nutritional stress simultaneously affects honeybee gut
379 microbiota, immunity and infection by *Nosema*. Honeybees fed a nutritionally poor diet (i.e.
380 *Eucalyptus grandis* pollen) showed a lower abundance of *Lactobacillus Firm-4*, *Firm-5* and
381 *Bifidobacterium spp.* in their gut, and a higher abundance of *Bartonella apis* compared to bees

382 fed a polyfloral pollen. They also observed a decrease in the expression levels of vitellogenin
383 and genes associated with immunity (glucose oxidase, hymenoptaecin and lysozyme).

384 Work on the African armyworm, *Spodoptera exempta*, also shows the importance of the
385 microbiota in immunity. When larvae of this species were brought into the laboratory and fed
386 a semi-synthetic diet (i.e. a wheatgerm-based diet including a broad-spectrum antibiotic), their
387 gut microbial diversity was reduced and this led to a reduction in their capacity to resist
388 infection with the baculovirus *Spodoptera exempta* nucleopolyhedrovirus (Donkersley et al.,
389 2023). The capacity to resist the virus was greatly improved when the gut microbiota was
390 restored following a shift onto a diet supplemented with field-collected armyworm faeces.

391 Overall, studies on the interplay between nutrition, symbionts and infection in insects
392 convincingly show that a healthy microbiota corresponds to effective immune responses, which
393 in turn depends on host dietary conditions. Immune responses of insects are affected by their
394 nutrition, with the microbiota modulating this interaction. Although high microbiota diversity
395 seems to have immunological benefits generally, this is not always the case (Yoon et al., 2019).
396 Within the symbionts inhabiting the insect body, multiple taxa may interact to either
397 compromise insect host immunity (Fast et al., 2020) or synergistically enhance the capability
398 of individuals to fight infections (Consuegra et al., 2020; Oliver et al., 2014; Xie et al., 2014),
399 making the combined transient and resident symbionts important. Apart from bacterial
400 communities and yeasts, other kingdoms such as viruses, archaea and protozoa might also be
401 important (Gurung et al., 2019) and may be influenced by nutrition. Only a small number of
402 studies in insects have investigated the combined effects of food quality on symbiont
403 communities, immunity and resistance. Hence, the functional relationships between symbionts,
404 diet and infection remain to be fully explored.

405

406 **How nutrition affects disease resistance throughout development and across generations**

407 There is extensive evidence across taxa that diet quality and access to specific nutrients, both
408 during early development and in the parental generation, affects the development and
409 performance of the immune system. Nutrition in early development plays a key role in the
410 maturation of the immune system (Calder et al., 2006). If nutritional needs are not met during
411 the critical period of early development, the immune system may be ineffective upon infection

412 or even over-sensitised against innocuous and beneficial antigens (Calder et al., 2006; Nwaru
413 et al., 2010; Vassallo and Camargo Jr, 2010).

414 We know from studies on mammalian species that nutrition may also have effects on the
415 immune system across generations. Individuals may be more susceptible to diseases if relatives
416 from previous generations have suffered from malnutrition (Barker, 2004; Bateson et al., 2004;
417 De Boo and Harding, 2006). In general, the effects of diet and nutrition during development or
418 across generations can be considered under two alternative (but not necessarily exclusive)
419 hypotheses. On the one hand, these could be seen as ‘silver spoon effects’, whereby high-
420 quality diet enhances the immune response of the adult (in terms of developmental effects) or
421 offspring (for transgenerational effects; Monaghan, 2008). On the other hand, such effects can
422 also be seen as a form of ‘predictive adaptive response’ (PAR) or ‘immune priming’, whereby
423 low-quality diet is indicative of a more pathogenic environment; thus, individuals exposed to
424 a low-quality diet during development or in the parental generation show a heightened immune
425 response (Gluckman et al., 2005; Little et al., 2003). Whether empirical findings fit one
426 hypothesis or another depends on the type of dietary manipulation, the immune assay
427 conducted and the life history of the species in question. Here, we highlight how studies in
428 insects provide unique insights into the evolution and mechanisms by which nutrition affects
429 immunity through development and across generations. This section also proposes methods to
430 further test alternative hypotheses explaining the immunological impact of insect nutrition.

431 **Nutrition impacts insect immunity during development**

432 In insects, nutrition during juvenile stages has a significant impact on the development of adults
433 (Koyama et al., 2013; Mirth and Shingleton, 2012; Nijhout, 2003; Nijhout et al., 2014). For
434 example, when larvae of the greater wax moth are experimentally provided with a low-nutrition
435 diet (i.e. diluted diet), they develop into adults with lower body mass and require longer to
436 develop (Kangassalo et al., 2018). The immune development of insects is negatively affected
437 by poor nutrition during larval development with affected adults showing a lower encapsulation
438 strength (Kangassalo et al, 2018; Wilson et al., 2019).

439 Priming effects have also been observed, whereby larvae experience low nutritional conditions
440 but, as a result, develop into adults with enhanced immune responses in anticipation of
441 suboptimal conditions (Wang et al., 2016). For example, when mosquito larvae are reared with
442 nutrient limitation caused by higher food competition, the resulting adults show reduced

443 immune responses (i.e. melanisation and antibacterial responses) when exposed to the
444 insecticide permethrin (Hauser and Koella, 2020). Such priming effects may be more prevalent
445 in holometabolous insects in comparison to hemimetabolous species, given that the larval stage
446 requires greater adaptive plasticity compared to the later adult stage, as larvae tend to show a
447 reduced ecological range relative to the adults. This means that they have less opportunity to
448 alter their nutritional state through their diet and modulate their immune system in this manner
449 (English and Barreaux, 2020). Further, predicting the effect of larval diet in adults is likely
450 dependent on reproductive strategies (e.g. some adults do not feed, live for only a few days and
451 then die); further investigation is needed to explore this.

452 **Transgenerational effects of nutrition on insect immunity**

453 The experimental studies cited above highlight how nutrition in development is important for
454 later immunity at adulthood. However, these effects can also occur across generations in the
455 form of a carry-over or priming effect (Uller et al., 2013). Parental nutrition in insects affects
456 offspring immunity: poor nutrition has been shown to have negative effects across generations.
457 For example, in a study on Indian meal moths (*Plodia interpunctella*), offspring immune
458 reactivity is reduced when either parent received poor nutrition, with further reduction in
459 immunity when both parents receive poor nutrition (Triggs and Knell, 2012). By contrast,
460 parental nutrition effects can also influence offspring responses in potentially adaptive ways.
461 In the greater wax moth, a maternal low-nutrition diet increases the survival of offspring when
462 exposed to the pathogenic fungus *Beauveria bassiana* (Kangassalo et al., 2015). The results
463 from Kangassalo et al. (2015) support the hypothesis that poor parental nutrition is being used
464 as an indication of the resources that are likely to be available to the offspring. If the offspring
465 have fewer resources to fuel their immune systems, then selection may favour parents that give
466 their offspring an immunological ‘helping hand’. This mechanism may also provide the
467 offspring with a predictive cue to allow them to adapt and maximise their fitness in a poor
468 environment (Uller et al., 2013).

469 When the parental diet also includes pathogenic agents, this can affect offspring immunity
470 through a phenomenon known as ‘transgenerational immune priming’ (TGIP), which is likely
471 to be an adaptive effect whereby parents prepare their offspring’s immune system for
472 encounters with common pathogens (e.g. Futo et al., 2017; Little et al., 2003; Moret, 2006).
473 For example, when female larvae of the greater wax moth are provided diets containing
474 pathogenic bacteria, the eggs deposited by the developed females show an induced expression

475 of various immunity-related genes (Freitak et al., 2014). The transmission of dietary bacteria
476 was detected from the gut of mothers to their haemocoel, followed by the ovary and lastly in
477 the outer membrane of the laid eggs (Freitak et al., 2014).

478 In the context of TGIP, microbes that are consumed may be considered as nutritional
479 supplements, akin to probiotics in foods. These ‘probiotics’ are known to enhance immunity
480 across a wide range of insect orders (Grau et al., 2017; Maruščáková et al., 2020; Msaad
481 Guerfali et al., 2021; Rossoni et al., 2017). Ideally, ‘dietary pathogens’ and nutrition should be
482 studied separately: for example, in a study of cabbage looper moths (*Trichoplusia ni*), Shikano
483 et al. (2015) separated the factors of dietary pathogens and nutritional quality in parental diets.
484 When moth offspring are fed the same bacterial pathogen than their parents, the offspring’s
485 resistance to the pathogen and antibacterial activity increase tremendously in comparison to
486 those of offspring whose parents are not exposed to the pathogen. This enhanced immunity is
487 not observed when offspring are exposed to a pathogen that had not been encountered by their
488 parents (Shikano et al., 2015). By contrast, when parents consume diets of lower nutritional
489 quality, the nutritional stress tolerance of their offspring is increased, as is their resistance to
490 both pathogens (Shikano et al., 2015). Moreover, when both pathogenic and nutritional
491 stressors are applied, the cross-generation transfer of pathogen resistance takes precedence over
492 nutritional stress tolerance (Shikano et al., 2015). Taken together, these results emphasise the
493 potential trade-offs between TGIP and the transfer of nutritional stress tolerance. This trade-
494 off may be environment dependent as, for example, TGIP would confer greater fitness
495 advantages in an environment where disease risk is high compared to a resource-depleted
496 environment.

497 The effects of parental diet and nutrition can be sex-specific, although the results from some
498 studies can be complex. In some cases, the diet of one parent but not the other has an effect. In
499 the greater wax moth example discussed above (Kangassalo et al., 2015), the effects on
500 offspring survival during pathogen exposure are evident only when the maternal diet is
501 manipulated, but there was no effect of paternal diet. In a study by Zirbel and Alto (2018) on
502 mosquitoes, both maternal and paternal effects were shown to interact and significantly
503 enhance the survival of their larval offspring when infected by the dengue virus. Specifically,
504 there was a greater positive effect on offspring immunity when diets differed between fathers
505 and mothers (which received a low and high quantity of food, respectively), compared to
506 offspring from parents that were both fed a high quantity of food (Zirbel and Alto, 2018). In

507 the cabbage looper moth, TGIP has been shown to be provided by not just mothers, but also by
508 fathers (Freitak et al., 2009). When both parents are reared on diets containing bacteria,
509 offspring upregulate their immune enzymatic activities, immune protein expression and
510 immune gene transcription when immune-challenged by a bacterial injection (Freitak et al.,
511 2009). Most insects provide relatively little paternal care and resources to their offspring;
512 fathers may compensate for this by priming their sperm following bacterial exposure, to
513 transmit epigenetic factors that enhance the offspring's resistance to diseases and parasitism
514 (Ashe and Whitelaw, 2007).

515 Although studies have shown both positive and negative effects of parental diet on offspring
516 immunity, there are also several studies showing no effect. For example, in the Queensland
517 fruit fly, there was no significant effect of either parental diet on offspring immunity when the
518 offspring were infected by the pathogenic bacterium *Serratia marcescens* (Dinh et al., 2021).
519 Given the mixed results and interpretations, the transgenerational effects of insect nutrition on
520 immunity can indeed be complex and depend on factors determining the mechanistic link
521 between nutrition and immunity (e.g. the type of diet manipulation and infection assay) and the
522 potential adaptive nature of such effects (e.g. whether a diet cue in the parental generation
523 indicates a likely pathogen threat). Hence, future studies may further explore the effects of
524 parental diet on insect immunity across several generations, focusing on a broad range of
525 immune-related measurements.

526 In summary, insect nutrition impacts immunity both developmentally and across generations,
527 although the effects are complex. To elucidate the mechanisms and test potential adaptive
528 explanations, further experimental studies could incorporate diverse experimental systems
529 exhibiting a high likelihood of adaptive effects, such as insects with short generation times and
530 those that display a clear link between infection with a pathogen and the subsequent
531 measurement of pathogen load. As a result, comparative work could be carried out to identify
532 general patterns of insect nutrition on immunity, while highlighting the life history of different
533 insects and types of nutritional manipulation and immune assay across empirical studies. As
534 also discussed above, dietary microbes seem to closely interact with the insect host microbiota
535 to affect immunity (Ponton et al., 2011; Tetreau et al., 2019). Given the crucial role of the
536 microbiota, future studies may investigate whether developmental or parental nutrition effects
537 act directly on the immune system, or whether the immune system operates indirectly through
538 nutritional effects on the microbiota.

539 **Nutritional immunology and sociality**

540 Animals do not exist in isolation, and how they interact with other individuals can impact: i)
541 their nutrition, through how and what they eat; ii) their immunity, through variable exposure
542 to types and abundances of parasites, and through the direct or environmental social transfer of
543 immune molecules (Masri and Cremer, 2014); and iii) their microbiome, which plays a role in
544 both nutrition and immunity (see above), through direct or indirect transfer of symbionts.

545 Insects cover all levels of sociality; from solitary, where adults interact only during mating,
546 through various forms of semi-social and social interactions, including species with biparental
547 care and cooperative breeders, through to fully eusocial, where there is a strict division of
548 labour, sterile castes and overlapping generations (West et al., 2006). In addition, many species,
549 although not social in the evolutionary sense, occur at high densities, in aggregates or
550 gregarious groups, where many individuals gather to access resources or increase survival.

551 Parasite transmission is typically density dependent (McCallum et al., 2001); therefore,
552 sociality can influence the level of individual exposure to parasites. In solitary individuals, the
553 risk of parasite exposure is usually stochastic, but it is likely to be lower than that experienced
554 by social individuals due to less frequent interactions with conspecifics (except for ‘solitary’
555 species that occur at very high densities, as commonly it occurs in many lepidoptera (e.g.
556 viruses in African armyworm; Rose et al., 2000). Beyond parasites, an organism’s sociality can
557 also impact the microbiota they are exposed to at various life stages. The exchange and
558 maintenance of symbionts through sociality facilitates the sharing of characteristic and
559 beneficial microbiota, including those required for nutrition and pathogen defense (Engel et al.,
560 2012). Although solitary individuals still have some methods and opportunities to transfer
561 microbial symbionts (discussed in Engel and Moran, 2013; Voulgari-Kokota et al., 2019), they
562 are comparatively limited.

563 The social environment in which an individual lives and grows will also influence how it
564 forages, and the type of food it consumes. In solitary species, individuals may be entirely
565 independent in their choice of food (e.g. Auerbach and Simberloff, 1989), or constrained in
566 their dietary choices (Austin and Gilbert, 2021). Social species will always control offspring
567 diet to some degree but offspring can signal their needs (Hendriksma et al., 2019; Lihoreau et
568 al., 2015; Royle et al., 2012; Dussutour and Simpson, 2008; Kraus et al., 2019; Pernal and
569 Currie, 2002). These differing levels of nutritional control mean that the ability of an individual

570 to adjust its intake in response to infection may be dependent on changing the foraging
571 behaviour of others (but see Simpson and Raubenheimer, 2012 for ingestional mechanisms to
572 modify the nutrients digested, absorbed and assimilated).

573 Sociality can also play a role in an individual's immunological investment. First, in
574 'outbreking' species, where population density fluctuates across time and space, many species
575 have evolved plastic investment responses, whereby immunity is ramped up in the presence of
576 conspecifics to combat the increased risk of parasite transmission; this is known as density-
577 dependent prophylaxis (DDP, Wilson and Cotter, 2009; 2013; Wilson and Reeson, 1998). We
578 might therefore expect that group-living species would invest more heavily in their immune
579 systems than those that typically live alone (but see Wilson et al., 2003).

580 As discussed above, solitary species have been shown to alter their intake of nutrients to fight
581 infections, but how would such a response be achievable on a collective scale? We know that
582 within social insect systems there is often some form of feedback between the larvae and the
583 adults in terms of nutritional requirements (especially in progressively provisioning systems
584 where adults feed larvae directly after hatching until complete development). Honeybee
585 individuals, for example, show the ability to forage differentially to make up for nutrient
586 deficiencies (Hendriksma and Shafir, 2016). Adult social bees also show different foraging
587 behaviours when infected by certain parasites (e.g. Ferguson et al., 2018; Table 1), and both
588 honeybees and bumblebees can adapt at the colony level to changes in nutrient requirements
589 (Hendriksma et al., 2019, see also in ants: Dussutour and Simpson, 2009). It stands to reason,
590 then, that social insects could also alter their colony-level foraging behaviour in response to
591 infection, because an individual's nutrition has a direct impact on its ability to respond
592 immunologically (Danihlik et al., 2018). Furthermore, nutrition can affect group-level defenses
593 (Kay et al., 2014). Thus, there is scope for colonies to self-medicate, not simply altering
594 individual-level immune responses, but social immune responses too. More research is needed
595 to understand how sociality may interact with the interplay between immunity and nutrition in
596 invertebrates.

597

598 **Conclusion and perspectives**

599 For a long time, the immune system of insects has been considered as non-complex and non-
600 specific. Yet, studies in recent decades have shown that insect immunity can be trained and

601 primed (see for recent review Lanz-Mendoza and Contreras-Garduno, 2021), and that it is
602 influenced by a variety of biotic and abiotic factors. In this Review, we have shown that the
603 nutritional environment of insects is an essential factor influencing their immunity and
604 resistance/tolerance to infections. It is interesting to note that although the metabolic pathways
605 and innate immunity are highly conserved across invertebrates, their interactions can be highly
606 specific to individual groups/species. This is certainly due to the large diversity of social forms,
607 life cycles and environments in which insects live, leading to specific responses that may or
608 may not be evolutionarily adaptive. Investigating the factors that interact with the interplay
609 between nutrition and resistance gives a more comprehensive and integrative understanding of
610 the complex field of nutritional immunology. In the future, pathogen exposure, nutrition,
611 immune function, sociality and the gut microbiome should be considered individually and in
612 combination when attempting to understand an individual's nutritional immunology. The next
613 research exploring the depths, intricates and mechanisms of these components and their
614 impacts in more detail will advance our understanding of nutritional immunology.

615 In terms of the bigger picture, understanding how changes in the environment influence the
616 fitness costs associated with infections is essential when deploying conservation measures for
617 insect populations that have been steeply declining in the last few years (Seibold et al., 2019).
618 For instance, the recent development of natural probiotic treatments (i.e. using native
619 microbiome strains) is a promising route for protecting insect health and, more particularly,
620 pollinators' health (Motta et al., 2022). The development of this field of research directly results
621 from knowledge regarding the interactions between metabolism, gut microbiota, immunity,
622 resistance and the food sources that insects forage on. Other fields that may benefit from a
623 greater understanding of nutritional immunological interactions include novel approaches to
624 insect pest management (e.g. Qadri et al., 2020; Xu et al. 2020, 2022), disease vector control
625 (Caragata et al., 2013; Kho et al., 2016; Hoffmann et al., 2011), insect conservation (van Rijn
626 and Wackers, 2016; Vaudo et al., 2015;), and insects as food and feed (Qian et al., 2022;
627 Rumpold and Schluter, 2013). In this Review, we have focused our discussion on a few factors
628 influencing the interaction between nutrition and resistance; however, other environmental
629 conditions – such as temperature and pesticides– might also be of importance to nutrition and
630 resistance, and further discussion is needed. The field of eco-immunology may, in the future,
631 offer solutions to help insect populations to survive our changing world.

632

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637

638 **Table and Figure legend**

639 **Table 1:** List of the studies that have investigated the effects of nutritional manipulation
640 immune traits, resistance and tolerance to infection in insects.

641 **Figure 1: Framework of some of the proximate mechanisms modulating innate**
642 **immunity through the diet.** Akt, Protein kinase B; Dif, Dorsal-related immunity factor;
643 FOXO, Forkhead box; ILS, Insulin-like signaling; Imd, Immune deficiency signaling; InR,
644 Insulin-like receptor; MEF2, Myocyte enhancer factor-2; TOR, Target of rapamycin; S6K, S6
645 kinase; Toll, Toll signaling pathway. Not all connections between molecules and pathways
646 are shown on the figure.

Model system	Immune challenge or immune measurements	Developmental stage	Nutritional treatment (how the diet was manipulated)	Results	Reference
Hymenoptera					
European honeybee, <i>Apis mellifera</i>	Challenged naturally with deformed wing virus (DWV) and infection with the microsporidian <i>Nosema ceranae</i>	Adult	Diet with or without pollen	Diet with pollen decreased mortality due to DWV but increase the number of <i>Nosema</i> spores.	Tritschler et al., 2017
	Measure immuno-competence, no infection	Adult	Mono or polyfloral pollen diet	Pollen diversity but not quantity increased immuno-competence levels.	Alaux et al., 2010
	Infection with the fungal parasites <i>Aspergillus flavus</i> , <i>Aspergillus phoenicis</i> and <i>A. fumigatus</i>	Larva	Mono or polyfloral pollen diet	Polyfloral pollens feeding enhanced resistance to parasitic fungi.	Foley et al., 2012
	Infection with the deformed wing virus (DWV)	Adult	Dietary ratio of protein-to-fat	DWV concentration decreased as the fat content in the diet increased.	Alshukri and Al-Esawy, 2021
	Immuno-competence, no infection	Adult	Dietary pollen composition	Lowest expression level of antimicrobials in bees fed no pollen and varied with pollen type.	Danihlik et al., 2018
Common Eastern bumblebee, <i>Bombus impatiens</i>	Infection with the gut parasite <i>Crithidia bombi</i>	Adult	Dietary concentration of anabasine (a nectar alkaloid)	High-anabasine diet decreased parasitic load but did not influence survival time.	Anthony et al., 2015

	Infection with the gut parasite <i>Crithidia bombi</i>	Adult	Diet varying in eight naturally occurring nectar chemicals	Secondary metabolites reduced parasitic load, but did not influence survival time.	Richardson et al., 2015
Buff-tailed bumblebee, <i>Bombus terrestris</i>	Infection with the microsporidia <i>Nosema ceranae</i>	Adult	Dietary protein-to-carbohydrate ratio (P:C)	Insects fed low P:C diet showed the highest parasite prevalence but lived the longest.	Gomez-moracho et al., 2021
	Infection with the gut parasite <i>Crithidia bombi</i>	Adult	Dietary pollen concentration	Insects fed no pollen showed reduced immune responses to infection.	Brunner et al., 2014
Lepidoptera					
Monarch butterfly, <i>Danaus plexippus</i>	Infection with the protozoan <i>Ophryocystis elektroscirrha</i>	Caterpillar	Fed two milkweed species that differed in their levels of cardenolides: toxic chemicals involved in predator defence	Parasite infection, replication and virulence were affected by host plant species. Greater reduction in lifespan on low-cardenolide vs. the high-cardenolide host plant.	de Roode et al., 2008
Fall armyworm, <i>Spodoptera frugiperda</i> ; beet armyworm, <i>Spodoptera exigua</i> ; corn earworm, <i>Helicoverpa zea</i>)	Infection with the bacterium <i>Serratia marcescens</i>	Caterpillar	Total quantity of nutrients	Low nutrient diet increased mortality from infection for beet armyworm and corn earworm but not for fall armyworm.	Kangassalo et al., 2015
African armyworm, <i>Spodoptera exempta</i>	Infection with the bacterium <i>Bacillus subtilis</i> .	Caterpillar	Dietary protein and carbohydrate ratio (P:C)	Survival after infection increased with increasing P:C. Increase in antibacterial activity, phenoloxidase	Povey et al., 2009

				activity and protein levels in the haemolymph as dietary protein level increased.	
African armyworm, <i>Spodoptera exempta</i>	Infection with the nucleopolyhedrovirus SpexNPV	Caterpillar	Dietary protein and carbohydrate ratio (P:C)	Survival after infection increased with increasing P:C. Increase in antibacterial activity, phenoloxidase activity, haemocyte density and protein levels in the haemolymph as dietary protein level increased.	Povey et al., 2014
	Infection with the nucleopolyhedrovirus SlittMNPV	Caterpillar	Dietary protein and carbohydrate ratio (P:C)	Greater influence of dietary protein on resistance and constitutive immunity function than carbohydrate.	Lee et al., 2006
Egyptian cotton leafworm, <i>Spodoptera littoralis</i>	Infection with the bacterium <i>Micrococcus lysodeikticus</i> (lyophilised cells)	Caterpillar	Dietary protein and carbohydrate ratio (P:C)	Neither constitutive or induced immune responses were limited by the total quantity of nutrients consumed and different immune traits responded differently to variation in P:C (diet quality).	Cotter et al., 2010
	Infection with live or dead bacterium <i>Xenorhabdus nematophila</i>	Caterpillar	Dietary protein and carbohydrate ratio (P:C)	Immune gene expression peaked at moderate protein and high carbohydrate after infection. Gene expression and functional immune	Cotter et al., 2019

	Infection with the bacterium <i>Xenorhabdus nematophila</i>	Caterpillar	Dietary protein and carbohydrate ratio (P:C)	responses were generally only correlated on diets with relatively high levels of protein. Bacteria grew slower and caterpillars died slower on high protein diets.	Wilson et al., 2020
Greater wax moth, <i>Galleria mellonella</i>	Immuno-competence, no infection	Caterpillar	Diets of high and average nutritional quality	Greatest encapsulation response on the low-energy food.	Krams et al., 2015
Tobacco budworm, <i>Heliothis virescens</i>	Infection with <i>Autographa californica</i> multiple nucleopolyhedrovirus AcMNPV	Caterpillar	Dietary ascorbic acid concentration	Larvae fed an ascorbic acid-free diet showed signs of infection much earlier than larvae fed control levels of ascorbic acid, as well as greater mortality post-infection.	Popham and Shelby, 2009
Cabbage looper, <i>Trichoplusia ni</i>	Infection with <i>Autographa californica</i> multiple nucleopolyhedrovirus AcMNPV	Caterpillar	Dietary selenium concentration	Larvae fed selenium in the final instars were more resistant to viral infection than larvae not fed selenium.	Popham et al., 2005
Tobacco hornworm, <i>Manduca sexta</i>	Infection with the bacterium <i>Serratia marcescens</i> or the fungus <i>Beauveria bassiana</i>	Caterpillar	Food limitation	Food limitation altered immunity and reduced resistance to bacteria but appeared to have less effect on resistance to fungal infection.	Adamo et al., 2016
	Immuno-competence, no infection	Caterpillar	Variation in dietary protein and carbohydrate content	Immune components varied in response to interactions between carbohydrates,	Wilson et al., 2019

				protein, and intake, but protein reductions had the largest impacts—mostly detrimental.	
Anicia checkerspot, <i>Euphydryas anicia</i> infection	Immuno-competence, no	Caterpillar	Plant secondary metabolites	Plant secondary metabolites in the diet decreased immuno-competence.	Kelly and Bowers, 2018
Grapevine pest, <i>Eupoecilia ambiguella</i>	Infection with the heat-killed bacterium <i>Arthrobacter globiformis</i>	Caterpillar	Addition of berries from different grape varieties in diet	Total concentration of haemocytes was influenced by grape variety. Grape variety affected differently the concentration of specific haemocytes.	Vogelweith et al., 2016
Monarch butterfly, <i>Danaus plexippus</i>	Infection with the protozoan parasite, <i>Ophryocystis elektroscirrha</i>	Caterpillar and adult	Food restriction	Food restriction lowered haemocyte concentration at larval stage and phenoloxidase activity at larval and adult stage. Food restriction did not increase parasite infection.	McKay et al., 2016
Greater wax moth, <i>Galleria mellonella</i>	Immuno-competence, no infection	Caterpillar	Dietary nutritional value and diversity	Parasitic load and expression of some antimicrobials increased in response to a diverse diet, which in turn decreased encapsulation rate.	Krams et al., 2017

Velvetbean caterpillar, <i>Anticarsia gemmatalis</i>	Infection with the virus <i>Baculovirus anticarsia</i>	Caterpillar	Plant-based vs. artificial diet	More haemocytes and greater survival post-infection for larvae fed the artificial diet.	Costantin et al., 2022
Indian meal moth, <i>Plodia interpunctella</i>	Immuno-competence, no infection	Caterpillar	Diet restriction and four diets including walnut, pistachio, pea and raisin, and artificial diets.	Declining total haemocyte count and phenoloxidase activity with increasing starvation duration. The type of diet also influenced the number of immune cells and phenoloxidase activity.	Ebrahimi and Ajamhassani, 2020
Diptera					
Mosquito, <i>Anopheles coluzzii</i>	Infection with <i>Plasmodium berghei</i>	Larva and adult	Three fish larval diets	Composition of the larval diet influenced the prevalence and intensity of the infection in adults.	Linenberg et al., 2016
Mosquito, <i>Aedes aegypti</i>	Infection with the filarial nematode, <i>Brugia malayi</i>	Adult	Nutrient limitation	Following a fructose diet susceptibility to <i>B. malayi</i> decreased with age; however, after frequent blood meals, the decline in susceptibility with age was considerably less.	Ariani et al., 2015
Vinegar fly, <i>Drosophila melanogaster</i>	infection with the bacterium <i>Providencia rettgeri</i>	Adult	Dietary sugar quantity	Genotype-by-diet interactions shaped tolerance but not resistance. Diet-dependent positive	Howich and Lazzaro, 2014

				relationship between resistance and tolerance.	
	Infection with bacterium <i>Micrococcus luteus</i>	Adult	Dietary protein-to-carbohydrate ratio (P:C)	Survival post-infection and antimicrobial expression in naïve flies greater when flies were fed a low P:C (carbohydrate-biased diet).	Ponton et al., 2020
	Infection with bacterium <i>Pectobacterium carotovorum</i>	Larva and adult	Food restriction	Dietary protein restriction induced a decrease in survivorship post-infection and antimicrobials.	Meshrif et al., 2022
	Infection with the bacteria <i>Escherichia coli</i> and <i>Lactococcus lactis</i>	Adult	Protein restriction	Diet did not affect resistance to any bacterial strain. Evidence for diet-induced and time-dependent variation in host tolerance to <i>E. coli</i> , but not to <i>L. lactis</i> .	Kutzer and Armitage, 2016
	Infection with the bacterium <i>Providencia rettgeri</i>	Adult	High-glucose versus low-glucose diet	Elevated dietary glucose resulted in higher pathogen loads.	Unckless et al., 2015
Queensland fruit fly, <i>Bactrocera tryoni</i>	Infection with the bacterium <i>Serratia marcescens</i>	Adult	Protein-to-carbohydrate ratio (P:C)	Flies fed a carbohydrate-biased diet had a greater survival post-infection and a lower bacterial load.	Dinh et al., 2019

Black soldier fly, <i>Hermetia illucens</i>	Infection with the bacteria <i>Escherichia coli</i> , <i>Micrococcus luteus</i> , <i>Pseudomonas fluorescens</i> and <i>Bacillus subtilis</i> (added to the diet)	Larva	The addition of sulfonated lignin, cellulose, chitin, brewer's grains or sunflower oil in the diet	Highest levels of antimicrobials expression on diets supplemented with protein or sunflower oil.	Vogel et al., 2018
Orthoptera					
Australian plague locust, <i>Chortoicetes terminifera</i>	Challenge with fungus <i>Metarhizium acridum</i>	Adult	Protein-to-carbohydrate ratio (P:C)	Highest survival but lowest haemolymph protein, haemocyte density and antimicrobial activity on low P:C diet.	Graham et al., 2014
Coleoptera					
Burrying beetle, <i>Nicrophorus vespilloides</i>	Infection with the bacterium <i>Photorhabdus luminescens</i>	Adult	Fat-to-protein ratio (F:P)	Survival much higher on diets with high F:P; phenoloxidase activity increased with increasing dietary fat.	Miller and Cotter, 2017

649

650

651 **Box 1**

652 **The Geometric Framework for Nutritional Immunology**

653 There is now clear evidence that the diet composition influences the immune state and the
654 resistance to infection. Dietary manipulations have typically focused on modulating the
655 quantity of single food components, which results in not only varying the caloric content but
656 also the ratio of nutrients in the diet, simultaneously. Hence, these protocols do not allow
657 measuring the effects of specific food components or their ratios on immunity. There is
658 however growing evidence that taking into account the interactive effects of diet components
659 is important to give a better ecological understanding of how nutrition interacts with
660 immunity and resistance to infection (Cotter et al., 2019, 2011; Simpson & Raubenheimer,
661 2012). This can be achieved by manipulating the ratio of nutrients in experimental diets (at a
662 constant caloric content), and measuring the effects of imbalanced foods, where the ratio of
663 ingested nutrients deviates from the usual diet ingested by the organisms (the so-called intake
664 target, Simpson and Raubenheimer, 2012).

665

666 **Glossary**

667 Cellular immunity: Immune responses mediated by cell responses, including nodulation,
668 encapsulation and phagocytosis.

669 Dysbiosis: An imbalance or a disruption in the gut microbial community. Dysbiosis includes
670 both a gain or loss of community members and a change in the relative abundance of the
671 different members.

672 Encapsulation: A cellular immune response used against pathogens. This immune response is
673 activated when the pathogens are too large to be engulfed. Haemocytes (immune cells) react
674 by creating a multi-layered cellular capsule around the foreign body. Endosymbionts:
675 Symbionts that are found inside host cells or specialized organs sometimes called bacteriome.

676 Facultative symbionts: Symbionts that are not generally required for the survival or
677 reproduction of their host. These symbionts can play beneficial, neutral or detrimental roles
678 in shaping the biological and ecological traits of their hosts.

679 Fat body: A dynamic tissue that is involved in multiple metabolic functions. One of these
680 functions is to store and release energy in response to the energy demands of the insect.

681 Haemocytes: Immune effector cells that participate in cellular and humoral defenses.

682 Hemimetabolous insects: Insects that transition directly from larva to adult, without a pupal
683 stage.

684 Holidic diets: Diets that consist of entirely chemically defined ingredients.

685 Holometabolous insects: Insects that transition from larva to adult through a metamorphosis
686 (i.e. pupal stage).

687 Humoral immunity: Immune responses mediated by molecules, including the production of
688 antimicrobial peptides, activation of prophenoloxidase (proPO) and production of reactive
689 oxygen species.

690 Immune priming: The ability to resist infections if previously exposed to a sub-lethal
691 inoculum or a stress event. Innate immunity: Innate immune responses are the first line of
692 defence against intruding pathogens. The mechanisms of innate immunity are highly
693 evolutionary conserved between invertebrates and vertebrates.

694 Lytic activity: Immune response driven by proteolytic and hydrolytic enzymes that hydrolyse
695 peptide bonds.

696 Micro-nutrient: Nutrients that are usually needed by the body in very small quantities, such as
697 vitamins and minerals.

698 Macro-nutrient: Nutrients that are usually needed by the body in large quantities, such as
699 carbohydrates, fat and proteins.

700 Microsporidia: Microsporidia form a group of spore-forming unicellular
701 parasites. Nodulation: An immune process that involves the aggregation of cells to entrap
702 microorganisms.

703 Obligate symbionts: Symbionts essential for the survival and/or reproduction of their host.

704 Pathogen virulence: The ability of a pathogen to infect and/or to cause damage to its host
705 tissues.

706 Phagocytosis: An immune cellular process where large particles are ingested and eliminated.

707 Phenoloxidase activity: A defense system that ultimately leads to the melanization of
708 pathogens and damaged tissues.

709 Tolerance to infection: A defence strategy that does not have a direct negative effect on the host
710 pathogen load, but relies on the control of the mechanisms involved in tissue damage during
711 an infection.

712 **References**

- 713 Abbott, J. (2014). Self-medication in insects: current evidence and future perspectives. *Ecol.*
714 *Entomol.* 39(3), 273-280.
- 715 Abrisqueta, M., Süren-Castillo, S. and Maestro, J.L. (2014). Insulin receptor-mediated
716 nutritional signalling regulates juvenile hormone biosynthesis and vitellogenin production in
717 the German cockroach. *Insect Biochem Mol. Biol.* 49, 14-23.
- 718 Adamo, S.A., Davies, G., Easy, R., Kovalko, I. and Turnbull, K.F. (2016). Reconfiguration of
719 the immune system network during food limitation in the caterpillar *Manduca sexta*. *J. Exp.*
720 *Biol.* 219(5), 706-718.
- 721 Adamo, S.A. (2021). How insects protect themselves against combined starvation and
722 pathogen challenges, and the implications for reductionism. *Comp. Biochem. Physiol. B:*
723 *Biochem. Mol. Biol.* 255, 110564.
- 724 Ahlers, L.R., Trammell, C.E., Carrell, G.F., Mackinnon, S., Torre Villas, B.K., Chow, C.Y.,
725 Luckhart, S. and Goodman, A.G. (2019). Insulin potentiates JAK/STAT signaling to broadly
726 inhibit flavivirus replication in insect vectors. *Cell Rep.* 29(7), 1946-1960.
- 727 Alaux, C., Ducloz, F., Crauser, D. and Le Conte, Y. (2010). Diet effects on honeybee
728 immunocompetence. *Biol. Lett.* 6, 562-565.
- 729 Alshukri, B.M. and Al-Esawy, M.T. (2021). Reduced deformed wing virus of *Apis mellifera*
730 *L.* nurses by high fat diets under laboratory conditions. *J. Plant Protect. Res.* 61.
- 731 Amaro-Sánchez, T., Ruiz-Guzmán, G., Hernández-Martínez, S., Krams, I., Rantala, M.J. and
732 Garduño, J.C. (2023). Effect of juvenile hormone on phenoloxidase and hemocyte number:
733 The role of age, sex, and immune challenge. *Comp. Biochem. Physiol. B: Biochem. Mol. Biol.*
734 110827.
- 735 Anthony, W.E., Palmer-Young, E.C., Leonard, A.S., Irwin, R.E. and Adler, L.S. (2015).
736 Testing dose-dependent effects of the nectar alkaloid anabasine on trypanosome parasite loads
737 in adult bumble bees. *PLoS One* 10, 0142496.
- 738 Ariani, C.V., Juneja, P., Smith, S., Tinsley, M.C. and Jiggins, F.M. (2015). Vector competence
739 of *Aedes aegypti* mosquitoes for filarial nematodes is affected by age and nutrient limitation.
740 *Exp. Gerontol.* 61, 47-53.
- 741 Ashe, A. and Whitelaw, E. (2007). Another role for RNA: a messenger across generations.
742 *Trends Genet.* 23(1), 8-10.
- 743 Auerbach, M. and Simberloff, D. (1989). Oviposition site preference and larval mortality in a
744 leaf-mining moth. *Ecol Entomol* 14, 131-140.
- 745 Austin, A. J. and Gilbert, J. D. (2021). Solitary bee larvae prioritize carbohydrate over protein
746 in parentally provided pollen. *Func. Ecol.* 35, 1069-1080.

- 747 Ayres, J.S. and Schneider, D.S. (2012). Tolerance of infections. *Ann. Rev. Immun.* 30, 271-
748 294.
- 749 Barker, D.J.P. (2004). The developmental origins of adult disease. *J. Am. Coll. Nutri.* 23, 588S-
750 595S.
- 751 Bashir-Tanoli, S. and Tinsley, M.C. (2014). Immune response costs are associated with
752 changes in resource acquisition and not resource reallocation. *Funct. Ecol.* 28(4), 1011-1019.
- 753 Bateson, P., Barker, D., Clutton-Brock, T., Deb, D., D'Udine, B., Foley, R.A., Gluckman, P.,
754 Godfrey, K., Kirkwood, T., Lahr, M.M. and McNamara, J. (2004). Developmental plasticity
755 and human health. *Nature* 430, 419-421.
- 756 Becker, T., Loch, G., Beyer, M., Zinke, I., Aschenbrenner, A.C., Carrera, P., Inhester, T.,
757 Schultze, J.L. and Hoch, M. (2010). FOXO-dependent regulation of innate immune
758 homeostasis. *Nature* 463(7279), 369-373.
- 759 Boissière, A., Tchioffo, M.T., Bachar, D., Abate, L., Marie, A., Nsango, S.E., Shahbazkia,
760 H.R., Awono-Ambene, P.H., Levashina, E.A., Christen, R. and Morlais, I. (2012). Midgut
761 microbiota of the malaria mosquito vector *Anopheles gambiae* and interactions with
762 *Plasmodium falciparum* infection. *PLoS Pathog.* 8(5), e1002742.
- 763 Boggs, C. L. (2016). The fingerprints of global climate change on insect populations. *Curr.*
764 *Op. Ins. Sci.* 17, 69–73.
- 765 Brentassi, M.E., Maciá, A., de la Fuente, D., Cano, M.E. and Marino de Remes Lenicov, A.M.
766 (2017). Food quality affects wing-form, demographic traits and number of yeast-like symbionts
767 (YLS) in the planthopper vector, *Delphacodes kuscheli* (Hemiptera: Delphacidae). *Stud.*
768 *Neotrop.* 52(1), 25-36.
- 769 Bruce, K.D., Hoxha, S., Carvalho, G.B., Yamada, R., Wang, H-D., Karayan, P., He, S.,
770 Brummel, T., Kapahi, P. and Ja, W.W. (2013). High carbohydrate-low protein consumption
771 maximizes *Drosophila* lifespan. *Exp. Gerontol.* 48, 1129–1135.
- 772 Brunner, F.S., Schmid-Hempel, P. and Barribeau, S. M. (2014). *Proc. R. Soc. B* 281, 20140128.
- 773 Buchner, P. (1965). Endosymbiosis of animals with plant microorganisms. New York, NY:
774 Interscience Publishers.
- 775 Calder, P. C., Krauss-Etschmann, S., Jong, E. C. de, Dupont, C., Frick, J.-S., Frokiaer, H.,
776 Heinrich, J., Garn, H., Koletzko, S., Lack, G., Mattelio, G., Renz, H., Sangild, P. T.,
777 Schrezenmeir, J., Stulnig, T. M., Thymann, T., Wold, A. E. and Koletzko, B. (2006). Early
778 nutrition and immunity – progress and perspectives. *Br. J. Nutr* 96(4), 774–790.
- 779 Cappelli, A., Ulissi, U., Valzano, M., Damiani, C., Epis, S., Gabrielli, M.G., Conti, S.,
780 Polonelli, L., Bandi, C., Favia, G. and Ricci, I. (2014). A *Wickerhamomyces anomalus* killer
781 strain in the malaria vector *Anopheles stephensi*. *PloS One* 9(5), e95988.
- 782 Caragata, E.P., Rancès, E., Hedges, L.M., Gofton, A.W., Johnson, K.N., O'Neill, S.L. and
783 McGraw, E.A. (2013). Dietary cholesterol modulates pathogen blocking by *Wolbachia*. *PLoS*
784 *Pathog.* 9(6), e1003459.

- 785 Cariveau, D.P., Elijah Powell, J., Koch, H., Winfree, R. and Moran, N.A. (2014). Variation in
786 gut microbial communities and its association with pathogen infection in wild bumble bees
787 (*Bombus*). *ISME J* 8(12), 2369-2379.
- 788 Castelli, L., Branchiccela, B., Garrido, M., Invernizzi, C., Porrini, M., Romero, H., Santos, E.,
789 Zunino, P. and Antúnez, K. (2020). Impact of nutritional stress on honeybee gut microbiota,
790 immunity, and *Nosema ceranae* infection. *Microb. Ecol.* 80, 908-919.
- 791 Chandler, J.A., Morgan Lang, J., Bhatnagar, S., Eisen, J.A. and Kopp, A. (2011). Bacterial
792 communities of diverse *Drosophila* species: ecological context of a host–microbe model
793 system. *PLoS Genet.* 7(9), e1002272.
- 794 Chapman, R.F. (2013). *The insects: structure and function*. Fifth edition. Cambridge university
795 press.
- 796 Chomicki G., Werner, G.D., West, S.A. and Kiers, E.T. (2020). Compartmentalization drives
797 the evolution of symbiotic cooperation. *Phil. Trans. R. Soc. B* 375, 20190602.
- 798 Consuegra, J., Grenier, T., Akherraz, H., Rahioui, I., Gervais, H., Da Silva, P. and Leulier, F.
799 (2020). Metabolic cooperation among commensal bacteria supports *Drosophila* juvenile
800 growth under nutritional stress. *IScience* 23(6), 101232.
- 801 Cooper, D. and Eleftherianos, I. (2017). Memory and Specificity in the Insect Immune System:
802 Current Perspectives and Future Challenges. *Front. Immunol.* 8, 539.
- 803 Costantin, E.C., Viol, D.L., Del Puppo, N.P. and Elliot, S.L. (2022). Realism in Immune
804 Ecology Studies: Artificial Diet Enhances a Caterpillar's Immune Defense but Does Not Mask
805 the Effects of a Plastic Immune Strategy. *Front. Ins. Sci.* 1, 20.
- 806 Cotter, S. C., Simpson, S. J., Raubenheimer, D. and Wilson, K. (2011). Macronutrient balance
807 mediates trade-offs between immune function and life history traits. *Funct. Ecol.* 25, 186–198.
- 808 Cotter, S.C., Reavey, C.E., Tummala, Y., Randall, J.L., Holdbrook, R., Ponton, F., Simpson,
809 S.J., Smith, J.A. and Wilson, K. (2019). Diet modulates the relationship between immune gene
810 expression and functional immune responses. *Ins. Biochem. Mol. Biol.* 109, 128-141.
- 811 Daisley, B.A., Chmiel, J.A., Pitek, A.P., Thompson, G.J. and Reid, G. (2020). Missing
812 microbes in bees: how systematic depletion of key symbionts erodes immunity. *Trends*
813 *Microbiol.* 28(12), 1010-1021.
- 814 Danihlík, J., Škrabišová, M., Lenobel, R., Šebela, M., Omar, E., Petřivalský, M., Crailsheim,
815 K. and Brodschneider, R. (2018). Does the pollen diet influence the production and expression
816 of antimicrobial peptides in individual honey bees? *Insects* 9, 79.
- 817 DeBlock, M. and Stoks, R. (2008). Short-term larval food stress and associated compensatory
818 growth reduce adult immune function in a damselfly. *Ecol. Entomol.* 33(6), 796-801.
- 819 De Boo, H.A. and Harding, J.E. (2006). The developmental origins of adult disease (Barker)
820 hypothesis. *ANZJOG* 46(1), 4-14.

- 821 De Roode, J.C. and Hunter, M.D. (2019). Self-medication in insects: when altered behaviors
822 of infected insects are a defense instead of a parasite manipulation. *Curr. Op. Ins. Sci.* 33, 1-6.
- 823 De Roode, J.C., Lefèvre, T. and Hunter, M.D. (2013). Self-medication in animals. *Science*,
824 340(6129), 150-151.
- 825 De Roode, J.C., Pedersen, A.B., Hunter, M.D. and Altizer, S. (2008). Host Plant Species
826 Affects Virulence in Monarch Butterfly Parasites. *J. Anim. Ecol.* 77, 120–26.
- 827 DiAngelo, J.R. and Birnbaum, M.J. (2009). Regulation of fat cell mass by insulin in *Drosophila*
828 *melanogaster*. *Mol. Cell Biol.* 29, 6341–52.
- 829 Dinh, H., Nguyen, B., Morimoto, J., Lundback, I., Kumar, S.S. and Ponton, F. (2021).
830 Transgenerational effects of parental diet on offspring development and disease resistance in
831 flies. *Front. Ecol. Evol.* 9, 606993.
- 832 Dinh, H., Mendez, V., Tabrizi, S.T. and Ponton, F. (2019). Macronutrients and infection in
833 fruit flies. *Ins. Biochem. Mol. Biol.* 110, 98-104.
- 834 Dionne, M.S., Pham, L.N., Shirasu-Hiza, M. and Schneider, D.S. (2006). Akt and FOXO
835 dysregulation contribute to infection-induced wasting in *Drosophila*. *Curr. Biol.* 16(20), 1977-
836 1985.
- 837 Donkersley, P., Rice, A., Graham, R.I. and Wilson, K. (2023). Gut microbial community
838 supplementation and reduction modulates African armyworm susceptibility to a baculovirus.
839 *FEMS Microb. Ecol.* 99(1), fiac147.
- 840 Douglas, A.E. (2011). Lessons from studying insect symbioses. *Cell Host Micr.* 10(4), 359-
841 367.
- 842 Dussutour, A. and Simpson, S. J. (2009). Communal nutrition in ants. *Curr. Biol.* 19, 740-744.
- 843 Dussutour, A. and Simpson, S. J. (2008). Carbohydrate regulation in relation to colony growth
844 in ants. *J. Exp. Biol.* 211, 2224-2232.
- 845 Ebrahimi, M. and Ajamhassani, M. (2020). Investigating the effect of starvation and various
846 nutritional types on the hemocytic profile and phenoloxidase activity in the Indian meal moth
847 *Plodia interpunctella* (Hübner)(Lepidoptera: Pyralidae). *Inv. Surv. J.* 175-185.
- 848 Engel, M. and Grimaldi, D. (2004). New light shed on the oldest insect. *Nature* 427, 627–630.
- 849 Engel, P., Bartlett, K.D. and Moran, N.A. (2015). The bacterium *Frischella perrara* causes
850 scab formation in the gut of its honeybee host. *MBio* 6(3), e00193-15.
- 851 Engel, P. and Moran, N.A. (2013). The gut microbiota of insects—diversity in structure and
852 function. *FEMS Microbiol. Rev.* 37(5), 699-735.
- 853 Engel, P., Martinson, V. G. and Moran, N. A. (2012). Functional diversity within the simple
854 gut microbiota of the honey bee. *PNAS* 109, 11002-11007.

- 855 Engl, T., Schmidt, T.H., Kanyile, S.N. and Klebsch, D. (2020). Metabolic cost of a nutritional
856 symbiont manifests in delayed reproduction in a grain pest beetle. *Insects* 11(10), 717.
- 857 English, S. and Barreaux, A.M. (2020). The evolution of sensitive periods in development:
858 insights from insects. *Curr. Op. Behav. Sci.* 36, 71-78.
- 859 Fast, D., Petkau, K., Ferguson, M., Shin, M., Galenza, A., Kostiuik, B., Pukatzki, S. and Foley,
860 E. (2020). *Vibrio cholerae*-symbiont interactions inhibit intestinal repair in *Drosophila*. *Cell*
861 *rep.* 30(4), 1088-1100.
- 862 Ferguson, J. A., Northfield, T. D. and Lach, L. (2018). Honey bee (*Apis mellifera*) pollen
863 foraging reflects benefits dependent on individual infection status. *Microbial Ecol.* 76, 482-
864 491.
- 865 Fink, C., Staubach, F., Kuenzel, S., Baines, J. F. and Roeder, T. (2013). Noninvasive analysis
866 of microbiome dynamics in the fruit fly *Drosophila melanogaster*. *Appl. Environ. Microbiol.*
867 79: 6984–6988.
- 868 Foley, K., Fazio, G., Jensen, A.B. and Hughes, W.O. (2012). Nutritional limitation and
869 resistance to opportunistic *Aspergillus* parasites in honey bee larvae. *J. Invert. Pathol.* 111, 68-
870 73.
- 871 Freitak, D., Heckel, D.G. and Vogel, H. (2009). Dietary-dependent trans-generational immune
872 priming in an insect herbivore. *Proc. R. Soc. B.* 276(1667), 2617-2624.
- 873 Freitak, D., Schmidtberg, H., Dickel, F., Lochnit, G., Vogel, H. and Vilcinskas, A. (2014). The
874 maternal transfer of bacteria can mediate trans-generational immune priming in insects.
875 *Virulence* 5(4), 547-554.
- 876 Futo, M., Sell, M.P., Kutzer, M.A. and Kurtz, J. (2017). Specificity of oral immune priming in
877 the red flour beetle *Tribolium castaneum*. *Biol. Lett.* 13(12), 20170632.
- 878 Galenza, A. and Foley, E. (2019). Immunometabolism: insights from the *Drosophila* model.
879 *Dev. Comp. Immunol.* 94, 22-34.
- 880 Galenza, A., Hutchinson, J., Campbell, S.D., Hazes, B. and Foley, E. (2016). Glucose
881 modulates *Drosophila* longevity and immunity independent of the microbiota. *Biol. Open* 5(2),
882 165-173.
- 883 Garbuzov, A. and Tatar, M. (2010). Hormonal regulation of *Drosophila* microRNA let-7 and
884 miR-125 that target innate immunity. *Fly* 4, 306-311.
- 885 Gibson, C.M. and Hunter, M.S. (2010). Extraordinarily widespread and fantastically complex:
886 comparative biology of endosymbiotic bacterial and fungal mutualists of insects. *Ecol. Lett.*
887 13(2), 223-234.
- 888 Gil, R., Silva, F.J., Zientz, E., Delmotte, F., González-Candelas, F., Latorre, A., Rausell, C.,
889 Kamerbeek, J., Gadau, J., Hölldobler, B. and Van Ham, R.C. (2003). The genome sequence of
890 *Blochmannia floridanus*: comparative analysis of reduced genomes. *PNAS* 100, 9388-9393.

- 891 Gluckman, P.D., Hanson, M.A. and Spencer, H.G. (2005). Predictive adaptive responses and
892 human evolution. *TREE* 20(10), 527-533.
- 893 Goldsworthy, G., Chandrakant, S. and Opoku-Ware, K. (2003). Adipokinetic hormone
894 enhances nodule formation and phenoloxidase activation in adult locusts injected with bacterial
895 lipopolysaccharide. *J. Ins. Physiol.* 49(8), 795-803.
- 896 Gómez-Moracho, T., Durand, T., Pasquaretta, C., Heeb, P. and Lihoreau, M. (2021). Artificial
897 diets modulate infection rates by *Nosema ceranae* in bumblebees. *Microorganisms* 9(1), 158.
- 898 Graham, R.I., Deacutis, J.M., Pulpitel, T., Ponton, F., Simpson, S.J. and Wilson, K. (2014).
899 Locusts increase carbohydrate consumption to protect against a fungal biopesticide. *J. Ins.*
900 *Physiol.* 69, 27-34.
- 901 Graham, R.I., Grzywacz, D., Mushobozi, W.L. and Wilson, K. (2012). Wolbachia in a major
902 African crop pest increases susceptibility to viral disease rather than protects. *Ecol. Lett.* 15,
903 993-1000.
- 904 Greenwood, M.P., Hull, K.L., Brink-Hull, M., Lloyd, M. and Rhode, C. (2021). Feed and host
905 genetics drive microbiome diversity with resultant consequences for production traits in mass-
906 reared black soldier fly (*Hermetia illucens*) larvae. *Insects* 12(12), 1082.
- 907 Gurung, K., Wertheim, B. and Falcao Salles, J. (2019). The microbiome of pest insects: it is
908 not just bacteria. *Entomol. Exp. App.* 167(3), 156-170.
- 909 Grau, T., Vilcinskas, A. and Joop, G. (2017). Probiotic *Enterococcus mundtii* isolate protects
910 the model insect *Tribolium castaneum* against *Bacillus thuringiensis*. *Front. Microbiol.* 8,
911 1261.
- 912 Halsch, C.A., Shapiro, A.M., Fordyce, J.A., Nice, C.C., Thorne, J.H., Waetjen, D.P. and
913 Forister, M.L. (2021). Insects and recent climate change. *PNAS* 118(2), e2002543117.
- 914 Hammer, T.J., Janzen, D.H., Hallwachs, W., Jaffe, S.P. and Fierer, N. (2017). Caterpillars lack
915 a resident gut microbiome. *PNAS* 114(36), 9641-9646.
- 916 Harris, E.V., de Roode, J.C. and Gerardo, N.M. (2019). Diet–microbiome–disease:
917 Investigating diet’s influence on infectious disease resistance through alteration of the gut
918 microbiome. *PLoS Pathog.* 15(10), e1007891.
- 919 Hauser, G. and Koella, J.C. (2020). Larval exposure to a pyrethroid insecticide and competition
920 for food modulate the melanisation and antibacterial responses of adult *Anopheles gambiae*.
921 *Sci. rep.* 10(1), 1-8.
- 922 Hendriksma, H. P., Toth, A. L. and Shafir, S. (2019). Individual and colony level foraging
923 decisions of bumble bees and honey bees in relation to balancing of nutrient needs. *Front. Ecol.*
924 *Evol.* 7, 177.
- 925 Hendriksma, H. P. and Shafir, S. (2016). Honey bee foragers balance colony nutritional
926 deficiencies. *Behav. Ecol. Sociobiol.* 70, 509-517.

- 927 Herren, J.K., Paredes, J.C., Schüpfer, F., Arafah, K., Bulet, P. and Lemaitre, B. (2014). Insect
928 endosymbiont proliferation is limited by lipid availability. *Elife* 3, e02964.
- 929 Hiruma, K. and Riddiford, L.M. (1988). Granular phenoloxidase involved in cuticular
930 melanization in the tobacco hornworm: regulation of its synthesis in the epidermis by juvenile
931 hormone. *Dev. Biol.* 130(1), 87-97.
- 932 Hoffmann, A.A., Montgomery, B.L., Popovici, J., Iturbe-Ormaetxe, I., Johnson, P.H., Muzzi,
933 F., Greenfield, M., Durkan, M., Leong, Y.S., Dong, Y. and Cook, H. (2011). Successful
934 establishment of *Wolbachia* in *Aedes* populations to suppress dengue transmission. *Nature*
935 476(7361), 454-457.
- 936 Horak, R.D., Leonard, S.P. and Moran, N.A. (2020). Symbionts shape host innate immunity in
937 honeybees. *Proc. R. Soc. B.* 287(1933), 20201184.
- 938 Howick, V.M. and Lazzaro, B.P. (2014). Genotype and diet shape resistance and tolerance
939 across distinct phases of bacterial infection. *BMC Evol. Biol.* 14, 1-13.
- 940 Ibrahim, E., Hejníková, M., Shaik, H.A., Doležel, D. and Kodrík, D. (2017). Adipokinetic
941 hormone activities in insect body infected by entomopathogenic nematode. *J. Insect. Physiol.*
942 98, 347-355.
- 943 Jang, S. and Kikuchi, Y. (2020). Impact of the insect gut microbiota on ecology, evolution, and
944 industry. *Curr. Op. Ins. Sci.* 41, 33-39.
- 945 Jang, T. and Lee, K.P. (2018). Comparing the impacts of macronutrients on life-history traits
946 in larval and adult *Drosophila melanogaster*: the use of nutritional geometry and chemically
947 defined diets. *J. Exp. Biol.* 221(21), p.jeb181115.
- 948 Kangassalo, K., Valtonen, T.M., Sorvari, J., Kecko, S., Pölkki, M., Krams, I., Krama, T. and
949 Rantala, M.J. (2018). Independent and interactive effects of immune activation and larval diet
950 on adult immune function, growth and development in the greater wax moth (*Galleria*
951 *mellonella*). *J. Evol. Biol.* 31(10), 1485-1497.
- 952 Kangassalo, K., Valtonen, T.M., Roff, D., Pölkki, M., Dubovskiy, I.M., Sorvari, J. and Rantala,
953 M.J. (2015). Intra- and trans-generational effects of larval diet on susceptibility to an
954 entomopathogenic fungus, *Beauveria bassiana*, in the greater wax moth, *Galleria mellonella*.
955 *J. Evol. Biol.* 28, 1453-1464.
- 956 Kay, A. D., Bruning, A. J., van Alst, A., Abrahamson, T. T., Hughes, W. O. and Kaspari, M.
957 (2014). A carbohydrate-rich diet increases social immunity in ants. *Proc. R. Soc. B.* 281,
958 20132374.
- 959 Kelly, C.A. and Bowers, M.D. (2018). Host plant iridoid glycosides mediate herbivore
960 interactions with natural enemies. *Oecologia* 188, 491-500.
- 961 Kemirembe, K., Liebmann, K., Bootes, A., Smith, W.A. and Suzuki, Y. (2012). Amino acids
962 and TOR signaling promote prothoracic gland growth and the initiation of larval molts in the
963 tobacco hornworm *Manduca sexta*. *PLoS ONE* 7(9): e44429.

- 964 Kho, E.A., Hugo, L.E., Lu, G., Smith, D.D. and Kay, B.H. (2016). Effects of larval nutrition
965 on Wolbachia-based dengue virus interference in *Aedes aegypti* (Diptera: Culicidae). *J. Med.*
966 *Entomol.* 53(4), 894-901.
- 967 Koyama, T., Mendes, C.C. and Mirth, C.K. (2013). Mechanisms regulating nutrition-
968 dependent developmental plasticity through organ-specific effects in insects. *Front. Physiol.* 4,
969 263.
- 970 Krams, I.A., Kecko, S., Jõers, P., Trakimas, G., Elferts, D., Krams, R., Luoto, S., Rantala, M.J.,
971 Inashkina, I., Gudrā, D. and Fridmanis, D. (2017). Microbiome symbionts and diet diversity
972 incur costs on the immune system of insect larvae. *J. Exp. Biol.* 220(22), 4204-4212.
- 973 Krams, I., Kecko, S., Kangassalo, K., Moore, F.R., Jankevics, E., Inashkina, I., Krama, T.,
974 Lietuvietis, V., Meija, L. and Rantala, M.J. (2015). Effects of food quality on trade-offs among
975 growth, immunity and survival in the greater wax moth *Galleria mellonella*. *Ins. Sci.* 22, 431-
976 439.
- 977 Kraus, S., Gómez-Moracho, T., Pasquaretta, C., Latil, G., Dussutour, A. and Lihoreau, M.
978 (2019). Bumblebees adjust protein and lipid collection rules to the presence of brood. *Curr.*
979 *Zool.* 65, 437-446.
- 980 Kutzer, M.A. and Armitage, S.A. (2016). The effect of diet and time after bacterial infection
981 on fecundity, resistance, and tolerance in *Drosophila melanogaster*. *Ecol. Evol.* 6, 4229-4242.
- 982 Lanz-Mendoza, H. and Contreras-Garduño, J. (2022). Innate immune memory in invertebrates:
983 Concept and potential mechanisms. *Dev. Comp. Immunol.* 127, 104285.
- 984 Laughton, A.M., Garcia, J.R. and Gerardo, N.M. (2016). Condition-dependent alteration of
985 cellular immunity by secondary symbionts in the pea aphid, *Acyrtosiphon pisum*. *J. Insect.*
986 *Physiol.* 86, 17-24.
- 987 Lee, K.P., Simpson, S.J., Clissold, F.J., Brooks, R., Ballard, J.W.O., Taylor, P.W., Soran, N.
988 and Raubenheimer, D. (2008). Lifespan and reproduction in *Drosophila*: new insights from
989 nutritional geometry. *PNAS* 105(7), 2498-2503.
- 990 Lee, K.P., Cory, J.S., Wilson, K., Raubenheimer, D. and Simpson, S.J. (2006). Flexible diet
991 choice offsets protein costs of pathogen resistance in a caterpillar. *Proc. R. Soc. B.* 273(1588),
992 823-829.
- 993 Leyria, J., Benrabaa, S., Nouzova, M., Noriega, F.G., Tose, L.V., Fernandez-Lima, F., Orchard,
994 I. and Lange, A.B. (2023). Crosstalk between Nutrition, Insulin, Juvenile Hormone, and
995 Ecdysteroid Signaling in the Classical Insect Model, *Rhodnius prolixus*. *Int. J. Mol. Sci.* 24, 7.
- 996 Lee, K.A. and Lee, W.J. (2018). *Curr. Opin. Ins. Sci.* 29, 21–26.
- 997 Lihoreau, M., Buhl, J., Charleston, M. A., Sword, G. A., Raubenheimer, D. and Simpson, S. J.
998 (2015). Nutritional ecology beyond the individual: a conceptual framework for integrating
999 nutrition and social interactions. *Ecol. Lett.* 18, 273-286.

- 1000 Linenberg, I., Christophides, G.K. and Gendrin, M. (2016). Larval diet affects mosquito
1001 development and permissiveness to Plasmodium infection. *Sci. Rep.* 6, 1-10.
- 1002 Little, T.J., O'Connor, B., Colegrave, N., Watt, K. and Read, A.F. (2003). Maternal transfer of
1003 strain-specific immunity in an invertebrate. *Curr. Biol.* 13(6), 489-492.
- 1004 Lu, P., Bian, G., Pan, X. and Xi, Z. (2012). Wolbachia induces density-dependent inhibition to
1005 dengue virus in mosquito cells. *PLoS Neglect. Trop. Dis.* 6(7), e1754.
- 1006 McKay, A.F., Ezenwa, V.O. and Altizer, S (2016). Consequences of Food Restriction for
1007 Immune Defense, Parasite Infection, and Fitness in Monarch Butterflies. *Physiol. Biochem.*
1008 *Zool.* 89:5, 389-401.
- 1009 Meshrif, W.S., Elkayal, S.H., Soliman, M.A., Seif, A.I. and Roeder, T. (2022). Metabolic and
1010 immunological responses of *Drosophila melanogaster* to dietary restriction and bacterial
1011 infection differ substantially between genotypes in a population. *Ecol. Evol.* 12, e8960.
- 1012 Maes, P.W., Rodrigues, P.A., Oliver, R., Mott, B.M. and Anderson, K.E. (2016). Diet-related
1013 gut bacterial dysbiosis correlates with impaired development, increased mortality and Nosema
1014 disease in the honeybee (*Apis mellifera*). *Mol. Ecol.* 25(21), 5439-5450.
- 1015 Maruščáková, I.C., Schusterová, P., Bielik, B., Toporčák, J., Bíliková, K. and Mudroňová, D.
1016 (2020). Effect of application of probiotic pollen suspension on immune response and gut
1017 microbiota of honey bees (*Apis mellifera*). *Probiotics Antimicrob. Proteins* 12(3), 929-936.
- 1018 Mason, C.J. (2020). Complex relationships at the intersection of insect gut microbiomes and
1019 plant defenses. *J. Chem. Ecol.* 46(8), 793-807.
- 1020 Masri, L. and Cremer, S. (2014). Individual and social immunisation in insects. *Trends*
1021 *Immunol* 35, 471-482.
- 1022 McCallum, H., Barlow, N. and Hone, J. (2001). How should pathogen transmission be
1023 modelled? *TREE* 16, 295-300.
- 1024 Meriggi, N., Di Paola, M., Vitali, F., Rivero, D., Cappa, F., Turillazzi, F., Gori, A., Dapporto,
1025 L., Beani, L., Turillazzi, S. and Cavalieri, D. (2019). *Saccharomyces cerevisiae* induces
1026 immune enhancing and shapes gut microbiota in social wasps. *Front. Microbiol.* 10, 2320.
- 1027 Miller, C.V. and Cotter, S.C. (2017). Pathogen and immune dynamics during maturation are
1028 explained by Bateman's Principle. *Ecol. Entomol.* 42, 28-38.
- 1029 Mirth, C.K. and Shingleton, A.W. (2012). Integrating body and organ size in *Drosophila*: recent
1030 advances and outstanding problems. *Front. Endocri.* 3, 49.
- 1031 Mockler, B.K., Kwong, W.K., Moran, N.A. and Koch, H. (2018). Microbiome structure
1032 influences infection by the parasite *Crithidia bombi* in bumble bees. *App. Environ. Microbiol.*
1033 84(7), e02335-17.
- 1034 Monaghan, P. (2008). Early growth conditions, phenotypic development and environmental
1035 change. *Phil. Trans. R. Soc. B* 363(1497), 1635-1645.

- 1036 Moret, Y. (2006). Trans-generational immune priming: specific enhancement of the
1037 antimicrobial immune response in the mealworm beetle, *Tenebrio molitor*. *Proc. R. Soc. B.*
1038 273(1592), 1399-1405.
- 1039 Motta, E.V., Powell, J.E., Leonard, S.P. and Moran, N.A. (2022). Prospects for probiotics in
1040 social bees. *Phil. Trans. R. Soc. B* 377(1853), 20210156.
- 1041 Msaad Guerfali, M., Charaabi, K., Hamden, H., Djobbi, W., Fadhl, S., Mosbah, A. and Cherif,
1042 A. (2021). Probiotic based-diet effect on the immune response and induced stress in irradiated
1043 mass reared *Ceratitis capitata* males (Diptera: Tephritidae) destined for the release in the sterile
1044 insect technique programs. *Plos one* 16(9), e0257097.
- 1045 Mullen, L.M. and Goldsworthy, G.J. (2006). Immune responses of locusts to challenge with
1046 the pathogenic fungus *Metarhizium* or high doses of laminarin. *J. Insect. Physiol.* 52(4), 389-
1047 398.
- 1048 Nijhout, H.F. (2003). The control of body size in insects. *Dev. Biol.* 261(1), 1-9.
- 1049 Nijhout, H.F., Riddiford, L.M., Mirth, C., Shingleton, A.W., Suzuki, Y. and Callier, V. (2014).
1050 The developmental control of size in insects. *Wiley Interdiscip. Rev. Dev. Biol.* 3(1), 113-134.
- 1051 Nunes, C., Sucena, É. and Koyama, T. (2021). Endocrine regulation of immunity in insects.
1052 *FEBS J.* 288(13), 3928-3947.
- 1053 Nwaru, B.I., Ahonen, S., Kaila, M., Erkkola, M., Haapala, A.M., Kronberg-Kippilä, C.,
1054 Veijola, R., Ilonen, J., Simell, O., Knip, M. and Virtanen, S.M. (2010). Maternal diet during
1055 pregnancy and allergic sensitization in the offspring by 5 yrs of age: a prospective cohort study.
1056 *Pediatr. Allergy Immunol.* 21(1-Part-I), 29-37.
- 1057 Oliver, K.M., Smith, A.H. and Russell, J.A. (2014). Defensive symbiosis in the real world—
1058 advancing ecological studies of heritable, protective bacteria in aphids and beyond. *Func. Ecol.*
1059 28(2), 341-355.
- 1060 Osborne, S.E., Iturbe-Ormaetxe, I., Brownlie, J.C., O'Neill, S.L. and Johnson, K.N. (2012).
1061 Antiviral protection and the importance of *Wolbachia* density and tissue tropism in *Drosophila*
1062 *simulans*. *App. Environ. Microbiol.* 78(19), 6922-6929.
- 1063 Osborne, S.E., Iturbe-Ormaetxe, I., Brownlie, J.C., O'Neill, S.L. and Johnson, K.N. (2012).
1064 Antiviral protection and the importance of *Wolbachia* density and tissue tropism in *Drosophila*
1065 *simulans*. *App. Environ. Microbiol.* 78(19), 6922-6929.
- 1066 Pan, Y., Lu, P., Zhu, F.F., Li, C.J., He, Y.Q. and Chen, K.P. (2018). *Comp. Biochem. Physiol.*
1067 *B-Biochem. Mol. Biol.* 223, 50–57.
- 1068 Partridge, L., Piper, M.D. and Mair, W. (2005). Dietary restriction in *Drosophila*. *Mech. Ag.*
1069 *Dev.* 126(9), 938-950.
- 1070 Pernal, S. F. and Currie, R. W. (2002). Discrimination and preferences for pollen-based cues
1071 by foraging honeybees, *Apis mellifera* L. *Anim. Behav.* 63, 369-390.
- 1072 Pernice, M., Simpson, S.J. and Ponton, F. (2014). Towards an integrated understanding of gut
1073 microbiota using insects as model systems. *J. Ins. Physiol.* 69, 12-18.

- 1074 Pike, V.L., Lythgoe, K.A. and King, K.C. (2019). On the diverse and opposing effects of
1075 nutrition on pathogen virulence. *Proc. R. Soc. B.* 286(1906), 20191220.
- 1076 Ponton, F., Morimoto, J., Robinson, K., Kumar, S.S., Cotter, S.C., Wilson, K. and Simpson,
1077 S.J. (2020). Macronutrients modulate survival to infection and immunity in *Drosophila*. *J.*
1078 *Anim. Ecol.* 89, 460-470.
- 1079 Ponton, F., Wilson, K., Holmes, A.J., Cotter, S.C., Raubenheimer, D. and Simpson, S.J. (2013).
1080 Integrating nutrition and immunology: a new frontier. *J. Ins. Physiol.* 59, 130-137.
- 1081 Ponton, F., Lalubin, F., Fromont, C., Wilson, K., Behm, C. and Simpson, S.J. (2011). Hosts
1082 use altered macronutrient intake to circumvent parasite-induced reduction in fecundity. *Int. J.*
1083 *Parasitol.* 41(1), 43-50.
- 1084 Ponton, F., Wilson, K., Cotter, S.C., Raubenheimer, D. and Simpson, S.J. (2011). Nutritional
1085 immunology: a multi-dimensional approach. *PLoS Pathog.* 7, p.e1002223.
- 1086 Popham, H.J. and Shelby, K.S. (2009). Ascorbic acid influences the development and
1087 immunocompetence of larval *Heliothis virescens*. *Entomol. Exp. App.* 133(1), 57-64.
- 1088 Povey, S., Cotter, S.C., Simpson, S.J. and Wilson, K. (2014). Dynamics of macronutrient self-
1089 medication and illness-induced anorexia in virally infected insects. *J. Anim. Ecol.* 83(1), 245-
1090 255.
- 1091 Povey, S., Cotter, S.C., Simpson, S.J., Lee, K.P. and Wilson, K. (2009). Can the protein costs
1092 of bacterial resistance be offset by altered feeding behaviour? *J. Anim. Ecol.* 78(2), 437-446.
- 1093 Qian, L., Deng, P., Chen, F., Cao, Y., Sun, H. and Liao, H. (2022). The exploration and
1094 utilization of functional substances in edible insects: A review. *Food Product. Process. Nutri.*
1095 4(1), 1-15.
- 1096 Qadri, M., Short, S., Gast, K., Hernandez, J. and Wong, A.C.N. (2020). Microbiome innovation
1097 in agriculture: Development of microbial based tools for insect pest management. *Front.*
1098 *Sustain Food Syst.* 4, 547751.
- 1099 Rancès, E., Ye, Y.H., Woolfit, M., McGraw, E.A. and O'Neill, S.L. (2012). The relative
1100 importance of innate immune priming in Wolbachia-mediated dengue interference. *PLoS*
1101 *Pathog.* 8, e1002548.
- 1102 Rantala, M.J., Vainikka, A. and Kortet, R. (2003). The role of juvenile hormone in immune
1103 function and pheromone production trade-offs: a test of the immunocompetence handicap
1104 principle. *Proc. R. Soc. B.* 270, 2257-2261.
- 1105 Raubenheimer, D. and Simpson, S.J. (2009). Nutritional PharmEcology: doses, nutrients,
1106 toxins, and medicines. *Int. Comp. Biol.* 49(3), 329-337.
- 1107 Remolina, S.C. and Hughes, K.A. (2008). Evolution and mechanisms of long life and high
1108 fertility in queen honey bees. *Age* 30, 177-185.

- 1109 Richardson, L.L., Adler, L.S., Leonard, A.S., Andicoechea, J., Regan, K.H., Anthony, W.E.,
1110 Manson, J.S. and Irwin, R.E. (2015). Secondary metabolites in floral nectar reduce parasite
1111 infections in bumblebees. *Proc. R. Soc. B* 282, 20142471.
- 1112 Rio, R.V.M, Wu, Y.N., Filardo G. and Aksoy S. 2006. Dynamics of multiple symbiont density
1113 regulation during host development: tsetse fly and its microbial flora. *Proc. R. Soc. B* 273, 805-
1114 814.
- 1115 Rolff, J. and Siva-Jothy, M.T. (2002). Copulation corrupts immunity: a mechanism for a cost
1116 of mating in insects. *PNAS* 99(15), 9916-9918.
- 1117 Rose, J. W , Dewhurst, C. F. and Page, W.W. (2000). The African armyworm handbook: the
1118 status, biology, ecology, epidemiology and management of *Spodoptera exempta* (Lepidoptera:
1119 Noctuidae). Natural Resources Institute University of Greenwich.
- 1120 Royle, N. J., Smiseth, P. and Kölliker, M. (2012). The evolution of parental care: summary,
1121 conclusions and implications. In *The evolution of parental care*, pp. 327-345: Oxford
1122 University Press.
- 1123 Rossoni, R.D., Fuchs, B.B., De Barros, P.P., Velloso, M.D.S., Jorge, A.O.C., Junqueira, J.C.
1124 and Mylonakis, E. (2017). *Lactobacillus paracasei* modulates the immune system of *Galleria*
1125 *mellonella* and protects against *Candida albicans* infection. *PLoS One* 12(3), e0173332.
- 1126 Rumpold, B.A. and Schlüter, O.K. (2013). Nutritional composition and safety aspects of edible
1127 insects. *Mol. Nutr. Food Res.* 57(5), 802-823.
- 1128 Sadd, B.M. and Siva-Jothy, M.T. (2006). Self-harm caused by an insect's innate immunity.
1129 *Proc. R. Soc. B* 273(1600), 2571-2574.
- 1130 Schulenburg, H., Boehnisch, C. and Michiels, N.K. (2007). How do invertebrates generate a
1131 highly specific innate immune response? *Mol. Immunol.* 44, 3338-3344.
- 1132 Schwenke, R.A., Lazzaro, B.P. and Wolfner, M.F. (2016). Reproduction–immunity trade-offs
1133 in insects. *Ann. Rev. Entomol.*, 61, 239-256.
- 1134 Shikano, I., Oak, M.C., Halpert-Scanderbeg, O. and Cory, J.S. (2015). Trade-offs between
1135 transgenerational transfer of nutritional stress tolerance and immune priming. *Func. Ecol.*
1136 29(9), 1156-1164.
- 1137 Seibold, S., Gossner, M.M., Simons, N.K., Blüthgen, N., Müller, J., Ambarlı, D., Ammer, C.,
1138 Bauhus, J., Fischer, M., Habel, J.C. and Linsenmair, K.E. (2019). Arthropod decline in
1139 grasslands and forests is associated with landscape-level drivers. *Nature* 574(7780), 671-674.
- 1140 Simpson, S.J. and Raubenheimer, D. (2009). Macronutrient balance and lifespan. *Aging*
1141 (Albany NY) 1(10), 875.
- 1142 Simpson, S. J. and Raubenheimer, D. (2012). *The nature of nutrition – A unifying framework*
1143 *from animal adaptation to human obesity*. Princeton, NJ: Princeton University Press.
- 1144 Simonet, P., Duport, G., Gaget, K., Weiss-Gayet, M., Colella, S., Febvay, G., Charles, H.,
1145 Viñuelas, J., Heddi, A. and Calevro, F. (2016). Direct flow cytometry measurements reveal a

- 1146 fine-tuning of symbiotic cell dynamics according to the host developmental needs in aphid
1147 symbiosis. *Sci. Rep.* 6, 19967.
- 1148 Sinotte, V.M., Freedman, S.N., Ugelvig, L.V. and Seid, M.A. (2018). *Camponotus floridanus*
1149 ants incur a trade-off between phenotypic development and pathogen susceptibility from their
1150 mutualistic endosymbiont *Blochmannia*. *Insects* 9(2), 58.
- 1151 Smith, V.H. and Holt, R.D. (1996). Resource competition and within-host disease dynamics.
1152 *TREE* 11, 386-389.
- 1153 Snyder, A.K., McLain, C. and Rio, R.V. (2012). The tsetse fly obligate mutualist
1154 *Wigglesworthia morsitans* alters gene expression and population density via exogenous
1155 nutrient provisioning. *App. Environ. Microbiol.* 78(21), 7792-7797.
- 1156 Stahlschmidt, Z.R., Acker, M., Kovalko, I. and Adamo, S.A. (2015). The double-edged sword
1157 of immune defence and damage control: do food availability and immune challenge alter the
1158 balance? *Func. Ecol.* 29(11), 1445-1452.
- 1159 Stein, A.D. and Lumey, L.H. (2000). The relationship between maternal and offspring birth
1160 weights after maternal prenatal famine exposure: the Dutch Famine Birth Cohort Study. *Hum.*
1161 *Biol.*, 641-654.
- 1162 Tarayre, C., Bauwens, J., Mattéotti, C., Brasseur, C., Millet, C., Massart, S., Destain, J.,
1163 Vandenbol, M., De Pauw, E., Haubruge, E. and Francis, F. (2015). Multiple analyses of
1164 microbial communities applied to the gut of the wood-feeding termite *Reticulitermes flavipes*
1165 fed on artificial diets. *Symbiosis* 65, 143-155.
- 1166 Tauber, J.P., Nguyen, V., Lopez, D. and Evans, J.D. (2019). Effects of a resident yeast from
1167 the honeybee gut on immunity, microbiota, and *Nosema* disease. *Insects* 10(9), 296.
- 1168 Tetreau, G., Dhinaut, J., Gourbal, B. and Moret, Y. (2019). Trans-generational immune priming
1169 in invertebrates: current knowledge and future prospects. *Front. Immunol.* 10, 1938.
- 1170 Toprak, U. (2020). The role of peptide hormones in insect lipid metabolism. *Front. Physiol.*
1171 11, 434.
- 1172 Trammell, C.E. and Goodman, A.G. (2019). Emerging mechanisms of insulin-mediated
1173 antiviral immunity in *Drosophila melanogaster*. *Front. Immunol* 10, 2973.
- 1174 Triggs, A.M. and Knell, R.J. (2012). Parental diet has strong transgenerational effects on
1175 offspring immunity. *Funct. Ecol.* 26(6), 1409-1417.
- 1176 Tritschler, M., Vollmann, J.J., Yañez, O., Chejanovsky, N., Crailsheim, K. and Neumann, P.
1177 (2017). Protein nutrition governs within-host race of honey bee pathogens. *Sci. Rep.* 7, 1-11.
- 1178 Tu, M.P., Yin, C.M. and Tatar M. (2002). Impaired ovarian ecdysone synthesis of *Drosophila*
1179 *melanogaster* insulin receptor mutants. *Ag. Cell.* 1, 158-160.
- 1180 Uller, T., Nakagawa, S. and English, S. (2013). Weak evidence for anticipatory parental effects
1181 in plants and animals. *J. Evol. Biol.* 26(10), 2161-2170.

- 1182 Unckless, R.L., Rottschaefter, S.M. and Lazzaro, B.P. (2015). The complex contributions of
1183 genetics and nutrition to immunity in *Drosophila melanogaster*. *PLoS Gen.* 11, e1005030.
- 1184 Vacchini, V., Gonella, E., Crotti, E., Prosdocimi, E.M., Mazzetto, F., Chouaia, B., Callegari,
1185 M., Mapelli, F., Mandrioli, M., Alma, A. and Daffonchio, D. (2017). Bacterial diversity shift
1186 determined by different diets in the gut of the spotted wing fly *Drosophila suzukii* is primarily
1187 reflected on acetic acid bacteria. *Env. Microbiol. Rep.* 9(2), 91-103.
- 1188 van Rijn, P.C. and Wäckers, F.L. (2016). Nectar accessibility determines fitness, flower choice
1189 and abundance of hoverflies that provide natural pest control. *J. App. Ecol.* 53(3), 925-933.
- 1190 Vassallo, M.F. and Camargo Jr, C.A. (2010). Potential mechanisms for the hypothesized link
1191 between sunshine, vitamin D, and food allergy in children. *J. Allerg. Clin. Immunol.* 126(2),
1192 217-222.
- 1193 Vogel, H., Müller, A., Heckel, D.G., Gutzeit, H. and Vilcinskas, A. (2018). Nutritional
1194 immunology: diversification and diet-dependent expression of antimicrobial peptides in the
1195 black soldier fly *Hermetia illucens*. *Dev. Comp. Immunol.* 78, 141-148.
- 1196 Vogelweith, F., Moret, Y., Monceau, K., Thiéry, D. and Moreau, J. (2016). The relative
1197 abundance of hemocyte types in a polyphagous moth larva depends on diet. *J. Ins. Physiol.* 88:
1198 33-39.
- 1199 Vaudo, A.D., Tooker, J.F., Grozinger, C.M. and Patch, H.M. (2015). Bee nutrition and floral
1200 resource restoration. *Curr. Op. Insec. Sci.* 10, 133-141.
- 1201 Voulgari-Kokota, A., McFrederick, Q. S., Steffan-Dewenter, I. and Keller, A. (2019). Drivers,
1202 diversity, and functions of the solitary-bee microbiota. *Trend Microbiol.* 27, 1034-1044.
- 1203 Wang, Y., Kaftanoglu, O., Brent, C.S., Page Jr, R.E. and Amdam, G.V. (2016). Starvation
1204 stress during larval development facilitates an adaptive response in adult worker honey bees
1205 (*Apis mellifera* L.). *J. Exp. Biol.* 219(7), 949-959.
- 1206 Wang, S., Wang, L., Fan, X., Yu, C., Feng, L. and Yi, L. (2020). An Insight into Diversity and
1207 Functionalities of Gut Microbiota in Insects. *Curr Microbiol* 77, 1976-1986.
- 1208 West, S. A., Gardner, A. and Griffin, A. S. (2006). Altruism. *Curr. Biol.* 16, R482-R483.
- 1209 Whittle, M., Barreaux, A.M., Bonsall, M.B., Ponton, F. and English, S. (2021). Insect-host
1210 control of obligate, intracellular symbiont density. *Proc. R. Soc. B.* 288(1963), 20211993.
- 1211 Wilkinson, T.L., Koga, R. and Fukatsu, T. (2007). Role of host nutrition in symbiont
1212 regulation: impact of dietary nitrogen on proliferation of obligate and facultative bacterial
1213 endosymbionts of the pea aphid *Acyrtosiphon pisum*. *App. Environ. Microbiol.* 73(4), 1362-
1214 1366.
- 1215 Zirbel, K.E. and Alto, B.W. (2018). Maternal and paternal nutrition in a mosquito influences
1216 offspring life histories but not infection with an arbovirus. *Ecosphere* 9(10), e02469.

- 1217 Wilson, K., Holdbrook, R., Reavey, C.E., Randall, J.L., Tummala, Y., Ponton, F., Simpson,
1218 S.J., Smith, J.A. and Cotter, S.C., 2020. Osmolality as a novel mechanism explaining diet
1219 effects on the outcome of infection with a blood parasite. *Curr. Biol.* 30(13), 2459-2467.
- 1220 Wilson, J.K., Ruiz, L. and Davidowitz, G. (2019). Dietary protein and carbohydrates affect
1221 immune function and performance in a specialist herbivore insect (*Manduca sexta*). *Phys.*
1222 *Biochem. Zool.* 92, 58-70.
- 1223 Wilson, K. and Cotter, S. C. (2013). Host–Parasite interactions and the evolution of immune
1224 defense. In *Advances in the Study of Behavior*, vol. 45, pp. 81-174: Elsevier.
- 1225 Wilson, K. and Cotter, S. C. (2009). Density-dependent prophylaxis in insects. *Phenotypic*
1226 *plasticity of insects: mechanisms and consequences*, 381-420.
- 1227 Wilson, K., Knell, R., Boots, M. and Koch-Osborne, J. (2003). Group living and investment in
1228 immune defence: an interspecific analysis. *J. Anim. Ecol.* 72, 133-143.
- 1229 Wilson, K. and Reeson, A. F. (1998). Density-dependent prophylaxis: evidence from
1230 Lepidoptera-baculovirus interactions? *Ecol. Entomol.* 23, 100-101.
- 1231 Wong, A.C.N., Luo, Y., Jing, X., Franzenburg, S., Bost, A. and Douglas, A.E. (2015). The host
1232 as the driver of the microbiota in the gut and external environment of *Drosophila melanogaster*.
1233 *App. Environ. Microbiol.* 81(18), 6232-6240.
- 1234 Xie, J., Butler, S., Sanchez, G. and Mateos, M. (2014). Male killing *Spiroplasma* protects
1235 *Drosophila melanogaster* against two parasitoid wasps. *Heredity* 112(4), 399-408.
- 1236 Xu, P., Yang, L., Tang, X., Li, T., Graham, R.I., Wu, K. and Wilson, K. (2020). Novel partiti-
1237 like viruses are conditional mutualistic symbionts in their normal lepidopteran host, African
1238 armyworm, but parasitic in a novel host, Fall armyworm. *PLoS Pathog.* 16(6), e1008467.
- 1239 Xu, P., Rice, A. Li, T.; Wang, J. Yang, X., He Y., Graham, R.I. and Wilson, K. (2022). Partiti-
1240 like viruses from African armyworm increase larval and pupal mortality of a novel host: the
1241 Egyptian cotton leafworm. *Pest Manag. Sci.* 78(4), 1529-1537.
- 1242 Ye, Y.H., Woolfit, M., Rancès, E., O'Neill, S.L. and McGraw, E.A. (2013). Wolbachia-
1243 associated bacterial protection in the mosquito *Aedes aegypti*. *PLoS Neglect. Trop. Dis.* 7(8),
1244 e2362.
- 1245 Yoon, S.A.A., Harrison, J.G., Philbin, C.S., Dodson, C.D., Jones, D.M., Wallace, I.S., Forister,
1246 M.L. and Smilanich, A.M. (2019). Host plant-dependent effects of microbes and
1247 phytochemistry on the insect immune response. *Oecologia* 191(1), 141-152.
- 1248 Zhang, D.W., Xiao, Z.J., Zeng, B.P., Li, K. and Tang, Y.L. (2019). *Front. Physiol.* 10, 8.
- 1249 Zhineng, Y., Ying, M., Bingjie, T., Rouxian, Z. and Qiang, Z. (2021). Intestinal microbiota and
1250 functional characteristics of black soldier fly larvae (*Hermetia illucens*). *Ann. Microbiol.* 71,
1251 1-9.