

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

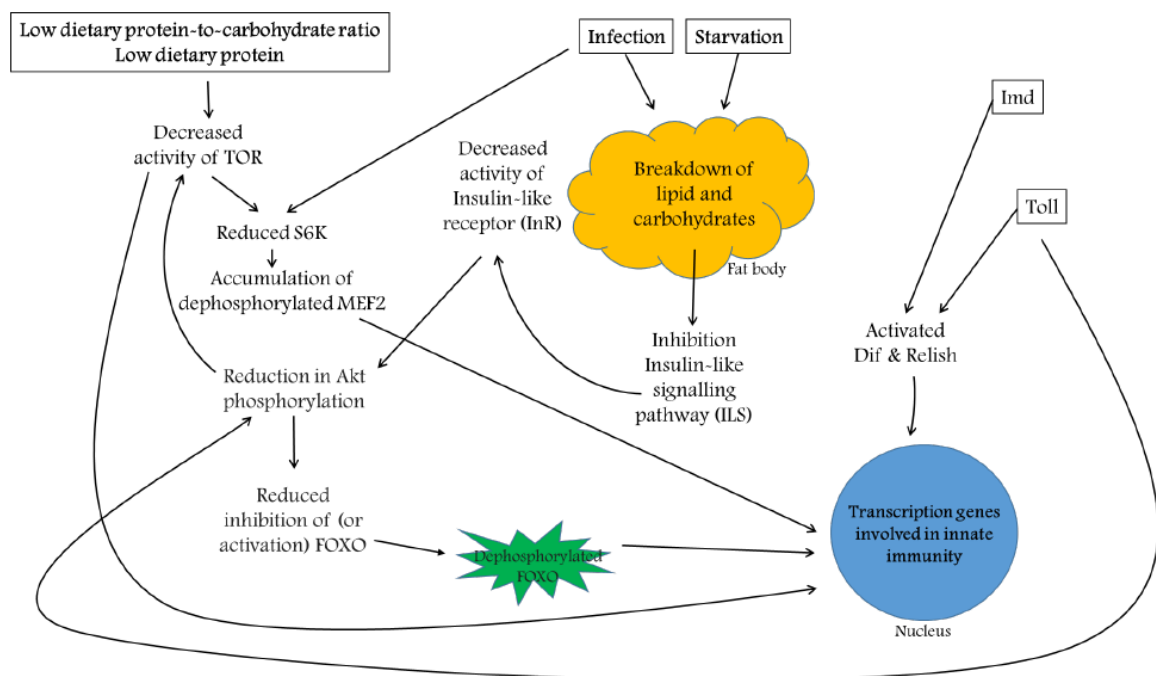
160 only a major source of amino acids, but also a source of other miscellaneous components.
161 Therefore, protein restriction or supplementation through modulating yeast intake
162 inadvertently causes variation in other elements in the diet (Bruce et al., 2013). Further, most
163 studies assume that 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
 209 **Figure 1:** Framework of potential connections between sociality and nutritional immunology

210

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

224 Another signaling pathway involved in immunity against viruses, JAK/STAT, is connected to
225 IIS, which might again indicate that insects have evolved immune mechanisms that are
226 responsive to nutritional acquisition (see discussion in Trammell and Goodman, 2019). The
227 regulatory hormone adipokinetic hormone (AKH) – which is also involved in physiological,
228 metabolic and homeostatic processes, such as carbohydrate and lipid metabolism – also
229 regulates innate immunity (Toprak, 2020). For instance, the principal role of AKH is to initiate
230 lipid/carbohydrate mobilisation from the fat body, and its expression is elevated upon infection;
231 this might induce immune responses (Ibrahim et al., 2017). There is some indication that AKH
232 also activates the prophenoloxidase cascade, among other immune responses (Goldsworthy et
233 al., 2003; Mullen and Goldsworthy, 2006).

234 Only a few studies have investigated the effects of the dietary nutrient balance on innate
235 immunity components. Studies have generally shown that the balance of dietary protein and
236 carbohydrates influences the expression of immune genes and other immune markers in naïve
237 and infected insects with contrasting effects in larvae and adults (instance.g. Cotter et al., 2019;
238 Ponton et al., 2020). The number of studies is, however, too limited; more investigation is
239 needed to draw general conclusions. For instance, the two nutrient sensors TOR and AMPK
240 might respond not only to the concentration of circulating nutrients (with TOR being stimulated
241 and AMPK depressed either directly or indirectly by increasing concentrations of nutrients),
242 but to the amino acid/carbohydrate balance of the diet (Simpson and Raubenheimer, 2009). A

243 low ratio of dietary protein to carbohydrates would decrease TOR activity, whereas a high
244 protein to carbohydrate ratio would increase TOR activity. Whether these responses are directly
245 linked to immune pathways needs to be confirmed. Finally, it is worth noting that although
246 research to date has largely focused on the effects of nutrients on host immunity (i.e. ‘top-
247 down’ regulation of pathogens), the nutrients may directly or indirectly impact the pathogen
248 through (‘bottom-up’) non-immunological mechanisms. For example, it has recently been
249 shown that dietary protein has a direct negative impact on the growth of bacteria in the
250 haemolymph by altering haemolymph solute concentration, creating a significant osmotic
251 stress for the pathogens (Wilson et al., 2020).

252

253 **Self-medication**

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

275

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

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

284 **Gut microbiota**

285 The digestive tract harbours a high diversity (i.e. a high number of strains/species) and quantity
286 (i.e. high number of individuals) of microbes, and most of these microbes are dependent on
287 their host's nutrition (see Engl et al., 2020; Harris et al., 2019 for a recent review; Herren et al.,
288 2014; Mason, 2020; Pernice et al., 2014; Wilkinson et al., 2007; Wong et al., 2015). In wood-
289 feeding termites, changes in diet are accompanied by shifts in the dominance of protist species
290 (Tarayre et al., 2015), and in flies, the gut microbiota composition varies with plant and food
291 type, and diet shifts (see for instance Chandler et al., 2011, Fink et al., 2013; Vacchini et al.,
292 2017). More recently, it has been shown that black soldier fly (*Hermetia illucens*) larvae fed a
293 high-fibre diet harbour a gut microbiota with greater bacterial richness (i.e. total number of
294 bacterial strains/species) and diversity (i.e. amount of bacteria from each of the bacterial
295 strains/species present) compared to individuals fed protein-rich and fat-rich diets (Greenwood
296 et al., 2021). Although there is strong evidence that the nutritional conditions influence the gut
297 microbiota composition at both larval and adult stages, the physiological significance and
298 fitness consequences of this variation remain to be fully understood (see Harris et al., 2019 for
299 discussion).

300 Microbiota diversity correlates with insect immunity and resistance to pathogens. In
301 bumblebees, Mockler et al. (2018) found that individuals with high microbiota diversity have
302 lower infection loads of *Crithidia bombi*, which is a common bumblebee gut parasite. A more
303 diverse insect microbiota could intensify the competition experienced by pathogens when
304 colonising their insect hosts (Engel and Moran, 2013), and this may be the case for insects that
305 acquire most of their microbes from the environment (Boissière et al., 2012; Hammer et al.,

306 2017). Also, in honeybees, the gut bacterium *Snodgrassella alvi* enhances survival after
307 pathogen challenge, through an upregulation of antimicrobial genes (i.e. abaecin, apidecin and
308 hymenoptaecin; Horak et al., 2020). The gut bacteria might also directly produce antimicrobial
309 compounds, such as antimicrobial peptides and antibiotics, involved in protecting the host
310 against infections (Daisley et al., 2020; Horak et al., 2020, see Jang and Kikuchi, 2020 for
311 review; Osborne et al., 2012). Although the microbiome influences immunity across a large
312 number of insect species, its influence in insects that have minimal symbiotic communities,
313 such as lepidoptera (Hammer et al., 2017), needs to be investigated.

314 **Intracellular symbionts**

315 In addition to the gut microbiota, insects harbour specific bacterial symbionts that live
316 intracellularly, mostly within specialised organs known as bacteriocytes (Douglas, 2011). Most
317 intracellular symbionts have limited metabolic functions, with their growth and abundance
318 being dependent on the host's nutrition (see Whittle et al 2021 for review). For instance, high
319 levels of nitrogen in the diet of the pea aphid (*Acyrtosiphon pisum*), increase the density of
320 the obligate bacterial symbiont *Buchnera aphidicola* (Wilkinson et al., 2007), whereas in the
321 tsetse fly, thiamine dietary supplementation results in reduced numbers of the obligate
322 symbiont *Wigglesworthia morsitans* (Snyder et al., 2012). Some insects may indeed reduce the
323 supply of nutrients to their symbionts to provide additional nutrients to host functions (Whittle
324 et al. 2021). However, it remains to be fully explored how the host nutritional conditions
325 regulate intracellular symbiont populations based on how obligative or facultative (see
326 Glossary) their relationship with the host is.

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

338 insect hosts. Indeed, the presence of symbionts at varying densities may involve a trade-off
339 between their impact on host immunity and metabolic resources (Whittle et al., 2021).

340 **Fungal symbionts**

341 Insects generally also have fungal symbionts, which may reside extra- or intra-cellularly
342 (Gibson and Hunter, 2010). Despite being neglected in many earlier studies on insect
343 symbioses, there has been an emerging interest in the role of insect–fungal symbioses in
344 immunity (Brentassi et al., 2017; Cappelli et al., 2014; Gibson and Hunter, 2010; Meriggi et
345 al., 2019; Tauber et al., 2019). Symbiotic fungi provide some developmental and survival
346 benefits to their hosts (Brentassi et al., 2017), and can produce antimicrobial molecules
347 (Cappelli et al., 2014). In the paper wasp (*Polistes dominula*) infected by *Escherichia coli*
348 bacteria, yeast strains reduced the *E. coli* load in foundresses but not in workers (Meriggi et al.,
349 2019). Associated with their enhanced immunity, wasp foundresses with prior yeast treatment
350 show increased diversity and changes in the composition of their gut bacterial communities,
351 but without changes in their fungal communities (Meriggi et al., 2019). Further, when
352 honeybees are exposed to the pathogenic fungus *Nosema ceranae*, the growth of the bacterial
353 symbiont *Lactobacillus Firm-5* is supported when young individuals are fed *Wickerhamomyces*
354 *anomalus* yeast, which contributes to the honeybee’s immune health (Tauber et al., 2019).
355 Fungi might have caste- and developmental stage-specific direct involvement in immunity, or
356 may be involved indirectly by supporting the growth of other important symbionts.

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

358 Understanding the direct effect of symbionts on immunity and resistance to infection is
359 challenging. The first challenge is to define a healthy composition of the symbiont communities
360 inhabiting the host. Studies usually compare the symbiont composition of treated animals to
361 control ones, and, in parallel, measure some physiological and life history traits to inform on
362 the health status of the individuals. The composition of the symbiont communities also changes
363 with physiological parameters such as age and developmental stage (Wang et al., 2020),
364 implying that parameters need to be well controlled during experiments. Diet can influence the
365 composition of the symbiont communities. 16S rRNA sequencing of *Hermetia illucens* gut
366 microbiota showed, for instance, strong differences between soybean and insect diet groups in
367 both type and relative abundance of microbial species (Zhineng et al., 2021). Some recent
368 studies have attempted to explore the impact of insect diet on their immunity in relation to their

369 microbiota. In greater wax moth (*Galleria mellonella*) larvae, a more diverse diet is associated
370 with a higher number of Enterococci in the microbiota, which may be linked to a greater
371 expression of AMP genes (Krams et al., 2017). A greater expression level of AMPs is also
372 induced when soldier fly larvae have a high inhibition of Gram-negative bacteria linked to
373 high-protein diets (Vogel et al., 2018). In another study, Maes et al. (2016) demonstrated that
374 aged diet (i.e. when hive frames were housed with 500 adult bees at 50% humidity and 35 °C
375 until bees reached an average of 14 and 21 days old) leads to a dysbiosis of the gut microbiota
376 (see Glossary), involving a reduction in the numbers of the core symbiont, *S. alvi*, but an
377 increase in the amount of the pathogenic bacteria *Frischella perrara* and *Parasacharibacter*
378 *apium* (Cariveau et al. 2014; Engel et al. 2015). Gut dysbiosis in honeybees results in decreased
379 survival and colonisation by another pathogenic fungus, *Nosema*; this can be prevented by the
380 core symbiont *S. alvi* taking up residence in the gut in early development (Maes et al., 2016).
381 Castelli et al. (2020) examined whether nutritional stress simultaneously affects honeybee gut
382 microbiota, immunity and infection by *Nosema*. Honeybees fed a nutritionally poor diet (i.e.
383 *Eucalyptus grandis* pollen) showed a lower abundance of *Lactobacillus Firm-4*, *Firm-5* and
384 *Bifidobacterium spp.* in their gut, and a higher abundance of *Bartonella apis* compared to bees
385 fed a polyfloral pollen. They also observed a decrease in the expression levels of vitellogenin
386 and genes associated with immunity (glucose oxidase, hymenoptaecin and lysozyme).

387 Work on the African armyworm, *Spodoptera exempta*, also shows the importance of the
388 microbiota in immunity. When larvae of this species were brought into the laboratory and fed
389 a semi-synthetic diet (i.e. a wheatgerm-based diet including a broad-spectrum antibiotic), their
390 gut microbial diversity was reduced and this led to a reduction in their capacity to resist
391 infection with the baculovirus *Spodoptera exempta* nucleopolyhedrovirus (Donkersley et al.,
392 2023). The capacity to resist the virus was greatly improved when the gut microbiota was
393 restored following a shift onto a diet supplemented with field-collected armyworm faeces.

394 Overall, studies on the interplay between nutrition, symbionts and infection in insects
395 convincingly show that a healthy microbiota corresponds to effective immune responses, which
396 in turn depends on host dietary conditions. Immune responses of insects are affected by their
397 nutrition, with the microbiota modulating this interaction. Although high microbiota diversity
398 seems to have immunological benefits generally, this is not always the case (Yoon et al., 2019).
399 Within the symbionts inhabiting the insect body, multiple taxa may interact to either
400 compromise insect host immunity (Fast et al., 2020) or synergistically enhance the capability

401 of individuals to fight infections (Consuegra et al., 2020; Oliver et al., 2014; Xie et al., 2014),
402 making the combined transient and resident symbionts important. Apart from bacterial
403 communities and yeasts, other kingdoms such as viruses, archaea and protozoa might also be
404 important (Gurung et al., 2019) and may be influenced by nutrition. Only a small number of
405 studies in insects have investigated the combined effects of food quality on symbiont
406 communities, immunity and resistance. Hence, the functional relationships between symbionts,
407 diet and infection remain to be fully explored.

408

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

410 There is extensive evidence across taxa that diet quality and access to specific nutrients, both
411 during early development and in the parental generation, affects the development and
412 performance of the immune system. Nutrition in early development plays a key role in the
413 maturation of the immune system (Calder et al., 2006). If nutritional needs are not met during
414 the critical period of early development, the immune system may be ineffective upon infection
415 or even over-sensitised against innocuous and beneficial antigens (Calder et al., 2006; Nwaru
416 et al., 2010; Vassallo and Camargo Jr, 2010).

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

432 immunity through development and across generations. This section also proposes methods to
433 further test alternative hypotheses explaining the immunological impact of insect nutrition.

434 **Nutrition impacts insect immunity during development**

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

442 Priming effects have also been observed, whereby larvae experience low nutritional conditions
443 but, as a result, develop into adults with enhanced immune responses in anticipation of
444 suboptimal conditions (Wang et al., 2016). For example, when mosquito larvae are reared with
445 nutrient limitation caused by higher food competition, the resulting adults show reduced
446 immune responses (i.e. melanisation and antibacterial responses) when exposed to the
447 insecticide permethrin (Hauser and Koella, 2020). Such priming effects may be more prevalent
448 in holometabolous insects in comparison to hemimetabolous species, given that the larval stage
449 requires greater adaptive plasticity compared to the later adult stage, as larvae tend to show a
450 reduced ecological range relative to the adults. This means that they have less opportunity to
451 alter their nutritional state through their diet and modulate their immune system in this manner
452 (English and Barreaux, 2020). Further, predicting the effect of larval diet in adults is likely
453 dependent on reproductive strategies (e.g. some adults do not feed, live for only a few days and
454 then die); further investigation is needed to explore this.

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

456 The experimental studies cited above highlight how nutrition in development is important for
457 later immunity at adulthood. However, these effects can also occur across generations in the
458 form of a carry-over or priming effect (Uller et al., 2013). Parental nutrition in insects affects
459 offspring immunity: poor nutrition has been shown to have negative effects across generations.
460 For example, in a study on Indian meal moths (*Plodia interpunctella*), offspring immune
461 reactivity is reduced when either parent received poor nutrition, with further reduction in
462 immunity when both parents receive poor nutrition (Triggs and Knell, 2012). By contrast,

463 parental nutrition effects can also influence offspring responses in potentially adaptive ways.
464 In the greater wax moth, a maternal low-nutrition diet increases the survival of offspring when
465 exposed to the pathogenic fungus *Beauveria bassiana* (Kangassalo et al., 2015). The results
466 from Kangassalo et al. (2015) support the hypothesis that poor parental nutrition is being used
467 as an indication of the resources that are likely to be available to the offspring. If the offspring
468 have fewer resources to fuel their immune systems, then selection may favour parents that give
469 their offspring an immunological ‘helping hand’. This mechanism may also provide the
470 offspring with a predictive cue to allow them to adapt and maximise their fitness in a poor
471 environment (Uller et al., 2013).

472 When the parental diet also includes pathogenic agents, this can affect offspring immunity
473 through a phenomenon known as ‘transgenerational immune priming’ (TGIP), which is likely
474 to be an adaptive effect whereby parents prepare their offspring’s immune system for
475 encounters with common pathogens (e.g. Futo et al., 2017; Little et al., 2003; Moret, 2006).
476 For example, when female larvae of the greater wax moth are provided diets containing
477 pathogenic bacteria, the eggs deposited by the developed females show an induced expression
478 of various immunity-related genes (Freitak et al., 2014). The transmission of dietary bacteria
479 was detected from the gut of mothers to their haemocoel, followed by the ovary and lastly in
480 the outer membrane of the laid eggs (Freitak et al., 2014).

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

495 nutritional stress tolerance (Shikano et al., 2015). Taken together, these results emphasise the
496 potential trade-offs between TGIP and the transfer of nutritional stress tolerance. This trade-
497 off may be environment dependent as, for example, TGIP would confer greater fitness
498 advantages in an environment where disease risk is high compared to a resource-depleted
499 environment.

500 The effects of parental diet and nutrition can be sex-specific, although the results from some
501 studies can be complex. In some cases, the diet of one parent but not the other has an effect. In
502 the greater wax moth example discussed above (Kangassalo et al., 2015), the effects on
503 offspring survival during pathogen exposure are evident only when the maternal diet is
504 manipulated, but there was no effect of paternal diet. In a study by Zirbel and Alto (2018) on
505 mosquitoes, both maternal and paternal effects were shown to interact and significantly
506 enhance the survival of their larval offspring when infected by the dengue virus. Specifically,
507 there was a greater positive effect on offspring immunity when diets differed between fathers
508 and mothers (which received a low and high quantity of food, respectively), compared to
509 offspring from parents that were both fed a high quantity of food (Zirbel and Alto, 2018). In
510 the cabbage looper moth, TGIP has been shown to be provided by not just mothers, but also by
511 fathers (Freitak et al., 2009). When both parents are reared on diets containing bacteria,
512 offspring upregulate their immune enzymatic activities, immune protein expression and
513 immune gene transcription when immune-challenged by a bacterial injection (Freitak et al.,
514 2009). Most insects provide relatively little paternal care and resources to their offspring;
515 fathers may compensate for this by priming their sperm following bacterial exposure, to
516 transmit epigenetic factors that enhance the offspring's resistance to diseases and parasitism
517 (Ashe and Whitelaw, 2007).

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

527 parental diet on insect immunity across several generations, focusing on a broad range of
528 immune-related measurements.

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

542 **Nutritional immunology and sociality**

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

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

554 Parasite transmission is typically density dependent (McCallum et al., 2001); therefore,
555 sociality can influence the level of individual exposure to parasites. In solitary individuals, the
556 risk of parasite exposure is usually stochastic, but it is likely to be lower than that experienced
557 by social individuals due to less frequent interactions with conspecifics (except for ‘solitary’

558 species that occur at very high densities, as commonly it occurs in many lepidoptera (e.g.
559 viruses in African armyworm; Rose et al., 2000). Beyond parasites, an organism's sociality can
560 also impact the microbiota they are exposed to at various life stages. The exchange and
561 maintenance of symbionts through sociality facilitates the sharing of characteristic and
562 beneficial microbiota, including those required for nutrition and pathogen defense (Engel et al.,
563 2012). Although solitary individuals still have some methods and opportunities to transfer
564 microbial symbionts (discussed in Engel and Moran, 2013; Voulgari-Kokota et al., 2019), they
565 are comparatively limited.

566 The social environment in which an individual lives and grows will also influence how it
567 forages, and the type of food it consumes. In solitary species, individuals may be entirely
568 independent in their choice of food (e.g. Auerbach and Simberloff, 1989), or constrained in
569 their dietary choices (Austin and Gilbert, 2021). Social species will always control offspring
570 diet to some degree but offspring can signal their needs (Hendriksma et al., 2019; Lihoreau et
571 al., 2015; Royle et al., 2012; Dussutour and Simpson, 2008; Kraus et al., 2019; Pernal and
572 Currie, 2002). These differing levels of nutritional control mean that the ability of an individual
573 to adjust its intake in response to infection may be dependent on changing the foraging
574 behaviour of others (but see Simpson and Raubenheimer, 2012 for ingestional mechanisms to
575 modify the nutrients digested, absorbed and assimilated).

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

583 As discussed above, solitary species have been shown to alter their intake of nutrients to fight
584 infections, but how would such a response be achievable on a collective scale? We know that
585 within social insect systems there is often some form of feedback between the larvae and the
586 adults in terms of nutritional requirements (especially in progressively provisioning systems
587 where adults feed larvae directly after hatching until complete development). Honeybee
588 individuals, for example, show the ability to forage differentially to make up for nutrient
589 deficiencies (Hendriksma and Shafir, 2016). Adult social bees also show different foraging

590 behaviours when infected by certain parasites (e.g. Ferguson et al., 2018; Table 1), and both
591 honeybees and bumblebees can adapt at the colony level to changes in nutrient requirements
592 (Hendriksma et al., 2019, see also in ants: Dussutour and Simpson, 2009). It stands to reason,
593 then, that social insects could also alter their colony-level foraging behaviour in response to
594 infection, because an individual's nutrition has a direct impact on its ability to respond
595 immunologically (Daniluk et al., 2018). Furthermore, nutrition can affect group-level defenses
596 (Kay et al., 2014). Thus, there is scope for colonies to self-medicate, not simply altering
597 individual-level immune responses, but social immune responses too. More research is needed
598 to understand how sociality may interact with the interplay between immunity and nutrition in
599 invertebrates.

600

601 **Conclusion and perspectives**

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

618 In terms of the bigger picture, understanding how changes in the environment influence the
619 fitness costs associated with infections is essential when deploying conservation measures for
620 insect populations that have been steeply declining in the last few years (Seibold et al., 2019).

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

635

636 **Funding**

637 Tan Y.X. PhD scholarship is supported by the Australian Department of Agriculture, Fisheries
638 and Forestry and Macquarie University. Forster C. PhD scholarship is supported by Macquarie
639 University.

640

641 **Table and Figure legend**

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

644 **Figure 1: Framework of some of the proximate mechanisms modulating innate**
645 **immunity through the diet.** Akt, Protein kinase B; Dif, Dorsal-related immunity factor;
646 FOXO, Forkhead box; ILS, Insulin-like signaling; Imd, Immune deficiency signaling; InR,
647 Insulin-like receptor; MEF2, Myocyte enhancer factor-2; TOR, Target of rapamycin; S6K, S6
648 kinase; Toll, Toll signaling pathway. Not all connections between molecules and pathways
649 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 anabasin (a nectar alkaloid)	High-anabasin 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 elektroscirra</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>Photobacterium 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

652

653

654 **Box 1**

655 **The Geometric Framework for Nutritional Immunology**

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

668

669 **Glossary**

670 Cellular immunity: Immune responses mediated by cell responses, including nodulation,
671 encapsulation and phagocytosis.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

712 Tolerance to infection: A defence strategy that does have a direct negative effect on the host
713 pathogen load, but relies on the control of the mechanisms involved on tissue damage during
714 an infection.

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