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Reciprocal interactions between anthropogenic stressors and insect microbiota

Pierre Antonelli¹ · Pénélope Duval¹ · Patricia Luis¹ · Guillaume Minard¹ · Claire Valiente Moro¹

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Abstract

Insects play many important roles in nature due to their diversity, ecological role, and impact on agriculture or human health. They are directly influenced by environmental changes and in particular anthropic activities that constitute an important driver of change in the environmental characteristics. Insects face numerous anthropogenic stressors and have evolved various detoxication mechanisms to survive and/or resist to these compounds. Recent studies highlighted the pressure exerted by xenobiotics on insect life-cycle and the important role of insect-associated bacterial microbiota in the insect responses to environmental changes. Stressor exposure can have various impacts on the composition and structure of insect microbiota that in turn may influence insect biology. Moreover, bacterial communities associated with insects can be directly or indirectly involved in detoxification processes with the selection of certain microorganisms capable of degrading xenobiotics. Further studies are needed to assess the role of insect-associated microbiota as key contributor to the xenobiotic metabolism and thus as a driver for insect adaptation to polluted habitats.

Keywords Xenobiotics · Insects · Bacteria · Detoxification · Insect-microbiota interactions

Introduction

Over the past 50 years, humans have significantly impacted their environment (Jacobson et al. 2019) at such magnitude that ecological and biogeochemical shifts are comparable to those described for major geological transitions (Corlett 2015). To illustrate those profound changes, the Anthropocene (derived from the Greek *anthropos* “a human being” and *kainos* “new”), a new geological era has been proposed to succeed the ongoing Holocene (Corlett 2015). Overproduction of greenhouse gases, natural habitat degradation, and massive release of human-made xenobiotics in the

environment are among the most important factors contributing to a sustained and rapid disruption of ecosystems. Xenobiotics (from *xenos* “foreign” and *bios* “life”) refer to a foreign substance within an organism.

Among these living organisms, insects represent 85% of animal biodiversity with about 1 million described species and strongly contribute to biogeochemical cycles (Stork 2018; Goulson 2019). For instance, they contribute to the reproduction of flowering plants (pollination by bees, bumblebees, butterflies), they are a source of food for other species (e.g., locusts, flies), or contribute to soil fertility by bio-conversion of agricultural wastes (e.g., dung beetles, black soldier fly larvae, houseflies). Some species are important for human agricultural activities as they act as pest control (e.g., ladybugs, parasitoid wasps) whereas some others have adverse effects on economy crop pests and public health (pathogen vectors) (Bradshaw et al. 2016). Based on these important ecological roles, insect response to xenobiotics can be a proxy to estimate wider alterations of ecosystem functions as well as economy losses and epidemic risks.

Increasing exposure of insects to many xenobiotics has contributed to the development of resistance mechanisms (i) at the metabolic level by increasing the activity of detoxification and excretion enzymes, (ii) at the cellular level by

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modifying the xenobiotics' targets, and (iii) at the behavioral level by contact avoidance with the xenobiotic or limitation of the contact duration (Palli 2020; Gao et al. 2022). At the same time, biology faces a significant paradigm shift. Higher eukaryotic organisms are no longer considering as isolated individual but also integrate the influence of their associated microbial communities (i.e., their microbiota). This refers to a super-organism called holobiont (from the Greek holo "everything" and bios "life") (Morris 2018). Thus, the intrinsic capacities of insects heavily rely on functions carried by their microbiota, composed of a rich and diverse community of bacteria, viruses, fungi, algae, and protists that mainly colonize the digestive tract. The microbiota influences insect's biological processes such as development, physiology, nutrition (Feldhaar 2011; Guégan et al. 2018), or resistance to biotic (e.g., pathogens) and abiotic (e.g., temperature, xenobiotics) stresses (Dunbar et al. 2007; Douglas 2015; Agamennone et al. 2019; Shukla and Beran 2020). In this context, understanding the effects of xenobiotics on insect holobionts becomes an important asset in the current ecological transition in order to better estimate consequences for ecosystem functioning.

In this review, we synthesize current knowledge on the impact of anthropic xenobiotics on insect-microbiota interactions highlighting their effects on the microbiota composition and structure and its role in detoxification processes. We focus specifically our attention on the bacterial component of the microbiota as it was more intensely studied compared with the rest of the microbiota. Studying the intricate links between insects, their associated microbiota, and the xenobiotics may advance our understanding of insect xenobiotic responses and could have practical applications in the field through the use of biological pest and vector control methods.

Anthropogenic stressors: classification, origin, and impact

Anthropogenic stressors include a wide variety of compounds and particles with heterogenous properties. The effects of xenobiotic compounds are complex since they can affect many organisms and are modulated by multiple factors (host, nature, and concentration of the xenobiotic, intensity of exposure). Therefore, within individuals, effects cannot be easily generalized. Xenobiotics are released in the environment either in their original forms or as by-products after being metabolized by living organisms or transformed by abiotic factors such as chemical or physical agents. Long-term exposure to these compounds is called chronic exposure while acute exposure refers to short contact. Xenobiotic activity, their concentration, their dissemination routes, and frequency as well as the characteristic of the focal ecosystem they affect determine their environmental consequences

(Dinka 2018). Xenobiotics can affect the health of organisms but may also indirectly influence the microorganisms they host (following the concept of holobiont) as well as the organisms with which they interact within the ecosystem (e.g., trophic transmission from prey to predators). Direct effects of xenobiotics on the host are very heterogeneous and can, for example, result in an alteration of the hormonal system (endocrine disruptors) (Williams et al. 2016), a modification of gene expression (Wang et al. 2020) or in some cases lead to the death (Daisley et al. 2018). Deleterious effects are often observed during acute and chronic exposure, the latter taking longer to be detected. Furthermore, intermediate concentrations can also lead to high response of the individuals. This is especially the case when biphasic effects are observed. Hormesis is a model in which intermediate concentrations lead to the highest values of individual responses. Low-dose exposure is therefore as important as high dose, and probably more frequent. This is the case with bisphenol A, which is widely used in plastic products and has been shown to disrupt neural differentiation in human-derived neural progenitor cells, potentially disrupting brain development (Fujiwara et al. 2018).

The pharmaceutical products are a wide range of anthropogenic stressors. The first synthetic drug is acetylsalicylic acid, which was discovered in 1897. This medicine is widely used for more than 120 years because of its remarkable pain relief as well as cardiovascular event prevention properties. The global pharmaceutical markets currently represent 479 products considered essential (WHO 2021). Human and animal medicines used to prevent and/or treat diseases often contaminate the environments through wastewater and animal agriculture manure. It was estimated that between 2010 and 2030, the global consumption of antimicrobials will increase by 67%, from $63,151 \pm 1560$ t to $105,596 \pm 3605$ t (Van Boeckel et al. 2015). Among these pharmaceutical products, there are very diverse molecules such as anti-inflammatory compounds, painkillers, antidepressants, contraceptives, antiparasitics, or antibiotics. Their impact on non-target species is a major environmental concern (Fent et al. 2006). It has been reported that the presence in water of drugs containing promethazine affects the reproduction of planktonic crustaceans of the genus *Daphnia* (Furuhagen et al. 2014). Another study showed that exposure to ibuprofen, diclofenac, and propranolol decreases the metabolic activities of the common mussel *Mytilus edulis* and its ability to adhere to a substrate (Ericson et al. 2010).

Another important class of anthropogenic stressors comprise pesticides. They include all substances eliminating or preventing damages caused by adverse organisms (i.e., pests). Among them, phytosanitary products are used to increase agricultural production by avoiding pest development. They include many classes of products, such as insecticides (prevent insect damages), fungicides (which

eliminate fungi), herbicides (weeding), nematicides (which kill nematodes and earthworms), rodenticides (used to get rid of various rodents such as rats, field mice...), and are responsible of significant environmental impacts. Sharma et al. (2019) reported that global pesticide usage in 2020 was approximately 3.5 million t, with herbicides accounting for 47.5% of the total amount, followed by insecticides (29.5%), fungicides (17.5%), and others (5.5%). As agricultural intensification is needed to respond to the global population increase (i.e., from 2.3 billion in 1950 to 7.5 billion in 2019 according to the United Nations), the utilization of phytosanitary products increased. The risk assessment constitutes therefore an essential tool for the evaluation of the potential effects of these compounds on organisms (classes of toxicity to human health from 1 to 8) and ecosystems (environmental impact) (Sauer et al. 2015). However, despite the development of technical guidance documents, many side effects due to their massive use disrupted the functioning of ecosystems. A significant example of harmful impacts is the non-selective systemic herbicide glyphosate, the most used (by volume and land area treated) herbicide in the world (Benbrook 2016). It has been shown to induce cardiotoxicity in developing zebrafish *Danio rerio* resulting in heart rate and circulation decrease/absence (Gaur and Bhargava 2019) as well as adverse pregnancy outcomes in many organisms (de Araujo et al. 2016). In addition, the negative impact of pesticides on human, animal, and environmental health or One Health initiative is exemplified through their persistence use in the environment leading to increased human exposure in food that can cause important metabolic disorder (Duarte-Hospital et al. 2019). One of the most striking examples is honey in which more than 19 pesticide residues from organophosphate insecticides have already been detected following their incorporation by bees after pollination of treated fields (El-Nahhal 2020). This can be explained by the fact that many of them, particularly organophosphates, are actually directly applied in the hives against *Varroa* mites.

Compounds of industrial origin are the final class of anthropogenic stressors. The industry has strongly expanded since the early nineteenth century. Although environmental protection is of global concerns of many industries (improvement of treatment and waste recycling), manufactured products and the waste they generate still remain a major issue. This is particularly the case for plastic derivatives as the production of plastics have reached 368 million t worldwide in 2019 (Plastics Europe 2020). Following growing exposure to plastic materials in the environment, some insects like the mealworm *Tenebrio molitor* showed strong ability to degrade these complex polymers (Yang et al. 2021). Given this potential, they are considered as promising candidates in bioremediation in the context of contaminated soils. Other residues such as nanoparticles (compounds < 100 nm) are

also increasingly used in textile, cosmetic, food, electronic, and medicine industries (Nel et al. 2006; Buzea et al. 2007; Ahamed et al. 2010). These compounds are easily disseminated in the environment and can significantly impact the life history traits of many insect species such as their development, reproduction, or survival but also their immunity (Li et al. 2020a).

Although it may be challenging to evaluate the effects of anthropogenic stressors on insect holobionts, this can be critical for understanding their adverse effects since insects provide ecological services such as pollination, pest control, and decomposition.

Xenobiotics on insect microbiota and host consequences

Insects harbor large and diverse microbial communities whose composition and structure vary during their development (Hammer and Moran 2019). While direct impacts of xenobiotics on insect are often studied (Li et al. 2007; Gao et al. 2022), it is increasingly apparent that the insect microbiota can also influence those interactions (Li et al. 2020a, b, c). Some insect models and life cycle stages are particularly studied because of their health, environmental, or agronomic relevance. As an example, in bees, most of studies have concerned adults because it is during this stage that they forage on flowers and enter in contact with the xenobiotic. Conversely, the crop pest butterfly *Helicoverpa* is more particularly studied at the larval stage due to potential application of those investigations for pest control.

Impact of pesticides

Insecticides

Insecticides are widely used to control insect pests and vectors of diseases. According to their source of origin, they can be synthetic and natural (either organic or inorganic). They can impact the insect microbiota through various ways. Among chemical insecticides, methoprene (a growth regulator blocking the development of insects at the larval stage) causes a strong remodeling of bacterial composition in *Ae. stimulans*, resulting in an increase in relative abundance of Enterobacteriaceae and *Staphylococcus* (Li et al. 2011; Receveur et al. 2018; Zhao et al. 2020). Conversely, three chemical insecticides (i.e., permethrin, malathion, and imidacloprid) were tested against the Asian tiger mosquito *Aedes albopictus*, the honeybee *Apis mellifera*, and the fruit fly *Drosophila melanogaster* with poor consequences on their bacterial microbiota composition (Daisley et al. 2017; Raymann et al. 2018; Juma et al. 2020). However, the authors reported that imidacloprid can modify the bacterial

microbiota of *D. melanogaster* at the larval stage, resulting in higher abundances of bacteria belonging to the genera *Acetobacter* and *Lactobacillus* which were previously reported for their probiotic activity (Consuegra et al. 2020). In some cases, specific microorganisms confer higher resistance of insects to insecticides. In *Anopheles albimanus*, the microbiota was suggested to lead to phenotypic resistance toward fenitrothion, a neurotoxic insecticide (Dada et al. 2018). In the fall, armyworm *Spodoptera frugiperda*, bacterial genera *Enterococcus*, and *Leclercia* are able to metabolize certain insecticides (e.g., chlorpyrifos, deltamethrin, spinosad) into assimilable carbon sources (Gomes et al. 2020). Conversely, additive toxic effects of certain members of the microbiota were also reported. For instance, the reintroduction of bacterial species such as *Enterobacter ludwigii*, *Citrobacter freundii*, and *Serratia marcescens* in axenic individuals restored the sensitivity of the beetle to insecticides (Polenogova et al. 2021). Similarly, some bacteria associated with *D. melanogaster* are able to metabolize chlorpyrifos (a chemical insecticide of the family chlorinated organophosphates) into a metabolite that is 10 times more reactive and toxic for the insect (Daisley et al. 2018). Among bioinsecticides, *Bacillus thuringiensis* (commonly called *Bt*) is a bacterial species used for its insecticidal properties (Bravo et al. 2011). It is notably the most widely used bioinsecticide in organic farming. Its activity relies on the production of Cry and Cyt toxins in the insect gut after bacterial ingestion (Bel et al. 2020). The *Bt* effects on the microbiota vary according to the insect host and the conditions of *Bt* exposure (toxin variants, *Bt* formulation, concentrations...). They are ranging from no impact in the mosquito *Aedes stimulans* or the ladybugs *Propylea japonica* to a strong alteration of the bacterial community structure, in the mosquito *Ae. aegypti* (Receveur et al. 2018; Tetreau et al. 2018; Zhao et al. 2020). Such community remodeling were also observed in the Colorado potato beetle *Leptinotarsa decemlineata* after being exposed to *Bt* or avermectin (another bioinsecticide) of (Polenogova et al. 2021). These insecticides led to an increase of Enterobacteriaceae, *Bacillus*, and *Serratia* within the insect microbiota. The authors suggested that these bacteria could play a role in accelerating *Bt* infection and avermectin-induced toxicosis and that the additive effect between both bioinsecticides could be linked with alterations in the bacterial community. In the corn earworm *Helicoverpa zea* and the old-world bollworm *Helicoverpa armigera*, an increase in bacterial diversity was also observed in the presence of *Bt*-producing transgenic plants. More specifically, a proliferation of bacteria of the *Enterococcaceae* family and more particularly of species *Enterococcus casseliflavus* and *Klebsiella oxytoca* was reported (Gracy et al. 2016; Deguegon et al. 2021). Similarly, exposure to *Bt* increased the bacterial density within the gut and hemolymph of *Spodoptera littoralis* larvae and the cabbage moth *Plutella xylostella*

(Caccia et al. 2016; Li et al. 2021). The colonization of the hemocoel by high densities of bacteria also reflects a septicemia leading to higher mortality of individuals exposed to toxins (Caccia et al. 2016). Conversely, in the beet armyworm *Spodoptera exigua* and the red flour beetle *Tribolium castaneum*, a low bacterial density leads to a higher sensitivity of the insect to *Bt* treatment, while a high bacterial density improves its resistance (Hernández-Martínez et al. 2010; Futo et al. 2015). Depending on the insect, *Bt* can thus induce either an increase in the bacterial load that can lead to sepsis or increasing resistance to insecticide.

Herbicides

Plants provide food source for pollinator or pest-control insects and can serve as nesting sites or shelter to many species. Other insect species negatively impact plant fitness either by consuming plant tissues or infecting them with vector-borne pathogens. These interactions promote close contact between insects and herbicides which used to protect crops from weeds and therefore insects are frequently exposed to herbicides. Most studies on the influence of herbicides on insect microbiota concerns glyphosate, the world's most widely used broad-spectrum and non-selective herbicide for control of grass and broad-leaf weeds. It targets the key enzyme of the shikimate pathway, 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), which synthesizes three essential aromatic amino acids (phenylalanine, tyrosine, and tryptophan) in plants but also in certain bacteria (Motta et al. 2018). The effect of glyphosate on the honey bee *Apis mellifera* at different stages has extensively been studied. The core microbiota of bees is dominated by eight bacterial species that play a role in insect growth and immunity (Daisley et al. 2020). Glyphosate has been shown to halve relative abundance of four of these species (i.e., *Snodgrassella alvi*, *Bifidobacterium*, *Lactobacillus* Firm-4, and *Lactobacillus* Firm-5) during the adult stage (Motta et al. 2018). This herbicide also induces an increase in some bacterial-genera abundance including part of the keystone species (i.e., *Bartonella*, *Lactobacillus*, and *Frischella*) (Blot et al. 2019; Motta et al. 2020). Moreover, those studies also highlighted that glyphosate affected the bee physiology (e.g., decrease of brood survival and larval weight, increase mortality of bees from hives) in a dose-dependent way. These modifications of the microbiota are most often dose-dependent (Dai et al. 2018; Motta et al. 2020) and strongly alter bee survival and pollinator activity at high concentrations. In newly emerged adults, exposure to glyphosate affects the gut colonization by beneficial bacteria. When treated with commercial formulation of glyphosate (0.1% Roundup), weakened individuals are thus more vulnerable to opportunistic infections

by entomopathogens belonging to the genus *Serratia*. However, glyphosate would not promote infections by the microsporidian *Nosema ceranae*, an emerging parasite described as the major cause of bee decline in some areas (Burnham 2019). In addition, the acid aminomethylphosphonic (AMPA), a derivative from the degradation of glyphosate often found in treated soils does not induce any significant change in the bee microbiota composition and structure. These results suggest that modifications observed on the microbiota of newly emerged adult bees are due to glyphosate (Blot et al. 2019). The effect of glyphosate on bacterial microbiota has also been studied in the greater wax moth *Galleria melonella* and in the mosquito *Anopheles gambiae*, the major malaria vector, which feed on honeycombs containing significant amount of beeswax and floral nectar, respectively. The results show that glyphosate exposure induces changes in the bacterial microbiota composition and structure in treated individuals in comparison of their untreated counterparts (Smith et al. 2021). This resulted in a significant increase in the relative abundance of the bacterial genus *Asaia* and a decrease of Enterobacteriaceae. Such a dysbiosis has been linked with reduced survival of Lepidoptera following infection with the entomopathogenic fungus *Cryptococcus neoformans* and increased colonization by the protozoan parasite *Plasmodium falciparum* in the mosquito. These observations suggest that Enterobacteriaceae such as *Serratia marcescens* may reduce the probability of infection of *G. melonella* with fungus and that of *A. gambiae* with the protozoan (Smith et al. 2021). A decrease in Enterobacteriaceae in the insect microbiota following glyphosate exposure was also observed in *Leptinotarsa decemlineata* with drastic microbiota modifications at the adult stage (Gómez-Gallego et al. 2020). Interestingly, it was shown that chronic exposure to atrazine, a synthetic herbicide of the triazine class, impacts the bacterial microbiota of the parasitoid wasp *Nasonia vitripennis* and confers an insect higher herbicide resistance. This effect is not only transgenerational but also generalizable to other herbicides such as glyphosate (Wang et al. 2020). In addition to its effect on microbiota, atrazine was also toxic to the insect host at very high doses (LC50 at 45.50 ± 15.73 parts per million). Moreover, transcriptomic analysis showed that the most downregulated genes were involved in immunity and odorant binding. This suggests that atrazine exposure on *N. vitripennis* affects the insect behavior and immune system.

More globally, pesticides may indirectly alter the trajectory of host-microbiota coevolution as revealed in honeybees through modulation of social behaviors and the insect gut-brain axis (Daisley et al. 2022). On top of their direct impacts on insects per se, we should also critically

evaluate the pesticide influence on their microbiota and the functions it ensures.

Impact of pharmaceutical products

Pharmaceuticals are commonly used in human health and breeding. Antibiotics are more particularly used to cure and prevent infections by pathogens but can also serve as growth hormones. Due to the increasing resistance to antibiotics, current research aims to find potential alternatives (Gadde et al. 2017; Lillehoj et al. 2018). Antibiotics are bacterial antagonists and can therefore disrupt the insect bacterial microbiota. Insects enter in contact with drugs either in aquatic and terrestrial environments contaminated by pollution. Occurrence of antibiotic residues in the environment is highly increased by medical and veterinary activities (between 40 and 90% of the administered antibiotic is excreted in the feces and urine) or application of contaminated manure on the agricultural lands as fertilizer as well as irrigation of crops with wastewater (Polianciuc et al. 2020). In some cases, as for honeybee, insects can directly be treated with antibiotics to prevent or treat bacterial infections (e.g., honeybee). The german cockroach *Blattella germanica* remains one of the most difficult indoor insect species to control because of its ability to develop resistance toward many insecticides. Recent studies have assessed the efficiency of integrated management methods based on antibiotic treatments that disrupt insect-associated mutualistic bacteria (Zhang and Zhang 2018). A treatment combining levofloxacin and gentamicin caused a significant decrease in bacterial density and diversity (Li et al. 2020a, b, c). After 14 days, while bacterial density reached similar values to that observed in the initial state, shifts in the microbiota composition were reported and consisted in an increase of Bacteroidetes and Fusobacteria and a decrease of Firmicutes. Such disturbance of *B. germanica* microbiota did not alter the host physiology. Gendrin et al. (2015) are the first to report the influence of high antibiotic usage on the transmission of vector-borne diseases. They showed that antibiotics in ingested blood enhance the susceptibility of *A. gambiae* mosquitoes to malaria infection by disturbing their gut microbiota. The massive proliferation of bacteria seen at 24 h after the blood meal was reduced by 70% in the presence of antibiotic treatment and associated with a near clearance of Enterobacteriaceae and an *Asaia* increase. Antibiotic-induced dysbiosis not only increases mosquito susceptibility to *Plasmodium* infection but also alters their survival and fecundity. The antibiotic tetracycline is widely used in honeybees to cure hives infections. It was shown that antibiotic treatment of *A. mellifera* induced higher mortality rates as well as gut dysbiosis that in turn

increased susceptibility to opportunistic pathogens (Raymann et al. 2017). A recent study showed that the impact of tetracycline on honeybee microbiota is dose-dependent (Jia et al. 2022). While the residue of tetracycline treatment does not exert lethal effects on gut bacterial communities, high dose of antibiotics induced a microbiota dysbiosis (Jia et al. 2022). Tetracyclines were found to be the most abundant antibiotic groups found in pig manure with about to 376,210 µg/kg (Frey et al. 2022). Tetracycline is also used to treat infections in cattles and can enter in contact with insects such as the dung beetle *Aphodius fossor* which feeds on the animal's excrement. Antibiotic-induced restructuring of dung beetle microbiota was not associated with significant differences in the insect development, survival, or reproduction (Hammer et al. 2016). Nevertheless, long-lasting transgenerational effects on insect microbiome after tetracycline treatment at subinhibitory concentrations were suggested in the cabbage root fly *Delia radicum* with potentially tetracycline resistant and heritable bacterial genera (Ourry et al. 2020). Although water treatment is a health priority, many chemicals may be carried out through water. The impact of different contaminants (hormones, antibiotics, paracetamol) has been evaluated on the bacterial microbiota of *Culex quiquefasciatus* mosquito larvae (Pennington et al. 2016). Each treatment individually leads to an overall decrease in the bacterial diversity while the mix of hormonal and antibiomatic treatments leads to the selection of bacteria that were absent under control conditions or antibiotics alone. These results suggest that the bacteria could use hormones as substrates to grow.

Impact of nanoparticles

Silver nanoparticles (Np-Ag) have a drastic effect on the bacterial microbiota of *D. melanogaster* larvae and act as powerful antimicrobials by targeting in particular gram-negative bacteria. After Np-Ag treatment of larvae, 91% of the sequences obtained with metabarcoding were assigned to the *Lactobacillus* (Gram-positive bacteria) genus and in particular the species *Lactobacillus brevis*. Elimination of Gram-negative bacteria was correlated with a lower larval viability (83% vs. 4% in the absence and presence of nanoparticles, respectively) (Han et al. 2014). Their impact has also been extensively studied on the silkworm *Bombyx mori* since they are commonly used in sericulture in order to prevent silkworm from getting infected with pathogens. A dose-dependent effect was thus demonstrated on the microbiota. A treatment at 20 mg/L of Np-Ag leads to an increase in bacterial diversity and the abundance of certain bacterial taxa (Firmicutes, Bacilli, and Enterococcus). On the other hand, these taxa were completely replaced by others (e.g., *Blautia*, *Terrisporobacter*...) after the larvae were exposed

to 100 mg/L of Np-Ag. While high doses of titanium dioxide (TiO₂) are toxic to the silkworm, intermediate ones (5 mg/L) enhance the immunity and insect growth rate. This treatment does not alter the dominant bacterial species but increases the abundance of subdominant species involved in nutrition and metabolism (*Staphylococcus* and *Lachnospiraceae*), or detoxification (*Pseudomonas* and *Sphingomonas*) and decreases that of *Serratia marcescens*, an opportunistic entomopathogen (Han et al. 2014). Similarly, copper and zinc oxide nanoparticles were shown to decrease abundance of probiotics (e.g., *Acetobacter*) and increase pathobionts (e.g., *Pseudomonas*, *Bacillus*, *Escherichia*, *Enterococcus*, and *Ralstonia*) in the silkworm gut bacterial microbiota following diet exposure (Muhammad et al. 2022). Another recent study demonstrates that nano-La₂O₃ can cause detrimental effects on honeybee health, potentially by causing dysbiosis of gut bacterial communities leading to the enrichment of bacterial pathogens *Serratia* and *Frischella* and the alteration of digestion-related taxa *Bombella* (Liu et al. 2021). Studies on the impact of nanoparticles on insects are still few. It is unknown how exposure to nanoparticles affect insect microbiota and its metabolic activity or which specific microbes are involved in their detoxification.

All these examples clearly demonstrate a direct impact of anthropogenic stressors on the insect bacterial microbiota and their deleterious consequences for the host (summarized in Table 1). However, the microbiota can also modulate the insect's response to xenobiotic compounds and contribute to its resistance or sensitivity.

Stressor exposure favors insect performance through beneficial impact on microbiota

Despite deleterious effects, anthropogenic stressors may also favor insect performance through positive impacts on their microbiota. However, to date, these examples are still scarce. For instance, in the silkworm *Bombyx mori*, insecticide resistance develops faster, thanks to the selection of microbial symbionts. This beneficial impact results from an increase in host fitness following essential amino acids provisioning by bacteria allowing larvae to resist more efficiently the deleterious effects of insecticides. Similarly, exposure of *B. mori* to TiO₂ NPs alters the composition of its gut microbiota, such an impact results in higher insect growth and development rates, and immune response (Li et al. 2020a, b, c). It also enhances the insect resistance to insecticide. *D. melanogaster* flies treated with the carrageenan-oligosaccharide prebiotic showed higher gut microbiota diversity and increased abundance of the genus *Commensalibacter* (Ma et al. 2021). This modification in their microbiota was positively correlated with an extension of the individuals' lifespan. Most of these examples highlight indirect effects without demonstrating any clear causation.

Table 1 Anthropogenic xenobiotic impacts on bacterial microbiota and consequences for the insect host

Xenobiotic Group	Class	Name	Insect		Species	Impact on bacterial microbiota		Bacterial taxa affected	Impact on insect host	References
			Common name			General impact				
Pesticides	Insecticides	Bacillus thuringiensis (Bt)	Mosquito	<i>Aedes aegypti</i>	<i>Aedes aegypti</i>	Decreased diversity	UND	More insecticide tolerance	Tetreau et al. 2018	
						No impact	-	No impact	Receveur et al. 2018	
						No impact	-	No impact	Li et al. 2011	
						No impact	-	No impact	Zhao et al. 2020	
						Increased bacterial load and decreased diversity	UND	Lower insecticide tolerance	Li et al. 2021	
						Modifications in the hemocoel microbiota composition	Augmentation of <i>Clostridium</i> and <i>Serratia</i>	Sepsis and death	Caccia et al. 2016	
						Increased bacterial load and diversity	Augmentation of <i>Enterococcus</i>	UND	Deguenon et al. 2021	
						Increased diversity	UND	Multiple insecticide resistance	R. Gandhi Gracy et al. 2016	
						Increased bacterial load	Augmentation of <i>Enterococcus</i>	More insecticide tolerance	Hernández-Martínez et al. 2010	
						Microbiota composition modification	Augmentation of Enterobacteriaceae Diminution of <i>Spiroplasma leptinotarsae</i>	Lower insecticide tolerance	Polenogova et al. 2021	
Mosquito			<i>Leptinotarsa decemlineata</i>	<i>Aedes aegypti</i>	Decreased diversity	Augmentation of Enterobacteriaceae	UND	Kryukov et al. 2021		
					Increased bacterial load and diversity	Augmentation of Flavobacteria and <i>Pseudomonas</i> / Diminution of <i>Microbacterium</i>	UND	Noskov et al. 2021		
					No impact		No impact	Juma et al. 2020		
Organophosphate	Fenitrothion	Malathion		<i>Aedes albopictus</i>	Decreased diversity	Diminution of Actinomycetes and Firmicutes	More insecticide tolerance	Dada et al. 2018		
					Increased bacterial load and diversity	Augmentation of Proteobacteria				

Table 1 (continued)

Group	Class	Name	Insect		Impact on bacterial microbiota	Impact on insect host	References		
			Common name	Species					
Xenobiotic	Pyrethroid	Permethrin			General impact	Bacterial taxa affected			
									<i>Aedes albopictus</i>
			<i>Anopheles albimanus</i>		Microbiota composition modification	Augmentation of <i>Pantoea agglomerans</i> and <i>Pseudomonas fragi</i>		Supposedly more insecticide tolerance	Dada et al. 2019
		Flumethrin	Honeybee	<i>Apis mellifera</i>	Decreased abundance and diversity at low doses / Increased abundance and diversity at high doses	UND		More insecticide tolerance (at high doses)	Yu et al. 2021
	Neonicotinoids	Imidaclopride			No impact	-		Increased mortality and susceptibility to bacterial infections	Raymann et al. 2018
			Drosophila	<i>Drosophila melanogaster</i>	Decreased diversity in the long term	Alteration of <i>Frischella, lactobacilli and bifidobacteria</i>		Reduced related nutritional and defense functions	Alberoni et al. 2021
					Microbiota composition modification	Augmentation of <i>Acetobacter</i> and <i>Lactobacillus</i>		Increased susceptibility to bacterial infections and tolerance to heat stress	Daisley et al. 2017
		Thiaclopride	Honeybee	<i>Apis mellifera</i>	Decreased abundance and diversity	Diminution of <i>Lactobacillus Firm-5</i> and <i>Bombella apis</i>		UND	Liu et al. 2020
					Decreased diversity in the short term	Alteration of <i>Frischella, lactobacilli and bifidobacteria</i>		Reduced related nutritional and defense functions	Alberoni et al. 2021
		Clothianidin			Increased diversity	UND		Decreased survival	El Khoury et al. 2021

Table 1 (continued)

Xenobiotic Group	Class	Name	Insect		Impact on bacterial microbiota	Impact on insect host	References
			Common name	Species			
Nitenpyrame							
					Microbiota composition modification	Higher mortality	Zhu et al. 2020
					Augmentation of <i>Bar- tonella</i> , <i>Bifidobacterium</i> and <i>Frischella</i> . Diminution of <i>Gilliamella</i>		
		Guadipyr	Silkworm	<i>Bombyx mori</i>	Microbiota composition modification with increased diversity	Higher mortality	Hou et al. 2021
					Augmentation of <i>Pseudomonas</i> Diminution of <i>Curvibacter</i>		
	Carbamate	Carbaryl	Honeybee	<i>Apis mellifera</i>	Microbiota composition modification with decreased bacterial load	Modification of bee's behaviour	Nogradio et al. 2019
					Diminution of <i>Alphaproteobacteria</i> and augmentation of <i>Snodgrassella alvi</i> and <i>L.kullabergensis</i>		
Herbicides	Glyphosate	Glyphosate	Buterfly	<i>Galleria mellonella</i>	Microbiota composition modification	Increased host sensibility to fungal infections	Smith et al. 2021
					Augmentation of <i>Asaita</i> and diminution of Enterobacteriaceae		
			Mosquito	<i>Anopheles gambiae</i>	Microbiota composition modification	Enhance the susceptibility of mosquitoes to malaria infection	Smith et al. 2021
					Augmentation of <i>Asaita</i> and diminution of Enterobacteriaceae		
			Honeybee	<i>Apis mellifera (adults)</i>	Microbiota composition modification	Alteration of health and pol- lination activity, increased susceptibility to bacterial infec- tions	Motta et al. 2018, 2020; Blot et al. 2019
					Diminution of core microbial species : <i>Snodgrassella alvi</i> , <i>Lactobacillus Firm-4</i> et 5 and <i>Bifidobacterium</i>		
				<i>Apis mellifera (larvae)</i>	Microbiota composition modification with decreased diversity / Microbiota changes in emerged adults	Reduced survival	Dai et al. 2018
					Augmentation of Gammaprotéobacteria, Lachno- spiraceae		

Table 1 (continued)

Group	Class	Name	Insect		Impact on bacterial microbiota	Bacterial taxa affected	Impact on insect host	References
			Common name	Species				
Xenobiotic			Colorado potato beetle	<i>Leptinotarsa decemlineata</i>	Microbiota composition modification (higher in adults than in larvae)	Augmentation of <i>Agrobacterium</i> and diminution of Enterobacteriaceae	UND	Gómez-Gallego et al. 2020
		AMPA	Honeybee	<i>Apis mellifera</i> (adults)	No impact	-	No impact	Blot et al. 2019
	Triazine	Atrazine	Wasp	<i>Nasonia vitripennis</i>	Microbiota composition modification with increased abundance and diversity	Augmentation of <i>Serratia marcescens</i> and <i>Pseudomonas protegens</i>	More insecticide tolerance to herbicides	Wang et al. 2020
			Drosophila	<i>Drosophila melanogaster</i>	Microbiota composition modification	Augmentation of Lactobacilliales / diminution of <i>Acetobacter</i> and Rhodospirillales	UND	Brown et al. 2021
			Mosquito	<i>Aedes albopictus</i>	No impact	-	No impact	Juma et al. 2020
	Quaternary ammonium	Paraquat	Drosophila	<i>Drosophila melanogaster</i>	Microbiota composition modification	Augmentation of Lactobacilliales / diminution of <i>Acetobacter</i> and Rhodospirillales	UND	Brown et al. 2021
	Fungicides	Carboxamide and Quinone outside inhibitors	Honeybee	<i>Apis mellifera</i>	Microbiota composition modification	Diminution of <i>Gilliamella</i> at low doses / Augmentation of <i>Lactobacillus</i> at high doses	Reduced nutritional function	DeGrandi-Hoffman et al. 2016
	Organochlorine	Chlorothalonil			Microbiota composition modification	Diminution of Lactobacillales	UND	Kakumanu et al. 2016
	Antibiotic	Levofloxacin / Gentamicin	Fly	<i>Musca domestica</i>	Microbiota composition modification and increased diversity	Augmentation of <i>Providencia</i> , <i>Halomonas</i> and <i>Morganella</i>	Lack of development	Li et al. 2021
Pharmaceutical compounds			Cockroach	<i>Blattella germanica</i>	Decreased of bacterial load and diversity. Microbiota composition modification after 14 days	Augmentation of Bacteroidetes and <i>Fusobacteria</i>	UND	Li et al. 2020

Table 1 (continued)

Xenobiotic Group	Class	Name	Insect		Impact on bacterial microbiota	Bacterial taxa affected	Impact on insect host	References
			Common name	Species				
		Tetracyclin	Honeybee	<i>Apis mellifera</i>	Decreased bacterial abundance including core microbiota species	Diminution of <i>Snodgrassella alvi</i> , <i>Lactobacillus Firm-4</i> and 5 et <i>Bifidobacterium / Serratia</i> and <i>Halo-monadaceae</i>	Higher mortality	Raymann et al. 2017
			Fly	<i>Delia racidum</i>	Microbiota composition modification and decreased diversity	Augmentation of Enterobacteriaceae and Pseudomonaceae / diminution of <i>Acinetobacter</i> , <i>Providencia</i> , <i>Comamonas</i>	UND	Ourry et al. 2020
			Dung beetle	<i>Aphodius fossor</i>	Microbiota composition modification	UND	UND	Hammer et al. 2016
		Doxycyclin	Cockroach	<i>Blattella germanica</i>	Decreased diversity	Augmentation of Gammaprotéobacteria	Lower insecticide tolerance	Pietri et al. 2018
		Lincomycin	Fly	<i>Hermetia illucens</i>	Decreased bacterial load and increased diversity	Augmentation of Firmicutes	No impact	Luo et al. 2022
		Penicillin, Streptomycin	Mosquito	<i>Anopheles gambiae</i>	Decreased diversity and reduced bacterial proliferation after blood meal	Augmentation of <i>Asaia</i> and diminution of Enterobacteriaceae	Increased survival and fecundity rates	Gendrin et al. 2015
	Hormones	Estrones, Norethisterone, Estradiol		<i>Culex quinquefasciatus</i>	Increased diversity	UND	UND	Pennington et al. 2016
	Prebiotic	Carrageenan, Oligosaccharide	Drosophila	<i>Drosophila melanogaster</i>	Increased diversity	Augmentation of <i>Commensalibacter</i>	Increased lifespan and fecundity	Ma et al. 2021

Table 1 (continued)

Group	Xenobiotic	Insect		Impact on bacterial microbiota	Impact on insect host	References
		Class	Name			
				General impact	Bacterial taxa affected	
Industrial compounds		Nanoparticles	Titanium dioxide	Modification of the abundance of certain taxa without modifying the dominant taxa	Augmentation of Lachnospiraceae, <i>Pseudomonas</i> and <i>Sphingomonas</i> / Diminution of <i>Serratia</i>	Increased weight and number of cocoons M. Li et al. 2020
			Silver	Increased abundance and diversity at low doses / Decreased abundance and diversity at high doses	Augmentation of Firmicutes, Bacilli and <i>Enterococcus</i> at low doses but diminution at high doses	Increased weight at low doses Lin et al. 2020
			Drosophila	<i>Drosophila melanogaster</i>	Decreased diversity and dominance of Lactobacilli	Augmentation of <i>Lactobacillus brevis</i> and Gram positive bacteria / Diminution of Gram negative bacteria

It points out the importance for future research prospect dedicated to mechanistic interactions between xenobiotic exposure, microbiota, and insect health.

Anthropogenic stressors as human activities become more and more prevalent across the globe. However, due to different factors, such as life histories, previous exposition, and additive effects, the insect stress response is extremely context-dependent and difficult to predict or generalize. In order to cope with these stressors, insects evolved adaptive strategies that partly depend on their microbiota.

Microbiota-mediated physiological insect response to xenobiotics

Direct microbiota-mediated detoxification pathways

Insects evolved adaptive strategies to minimize the effects of xenobiotics that occur at different levels: behavioral, cellular, and metabolic (Haubruge and Amichot 1998). Cellular and metabolic adaptations can result in (i) modification of the xenobiotic target, (ii) stimulation of the excretory activity, and (iii) sequestration of the compound (Clark et al. 1995; Davies et al. 2008). Detoxification-based resistance mechanisms, such as enzyme overproduction and modification, were fully described in different insect models (Li et al. 2007; Misra et al. 2011; Gao et al. 2022). Among them are isoenzymes called cytochromes P450 monooxygenases can oxidize exogenous molecules (Feyereisen 1999, 2006, 2015). Other enzymes such as glutathione S-transferases, UDP glucuronosyltransferases, carboxylesterases, and ABC transporters (ATP-binding cassette) are able to modify some functional groups of xenobiotics (Pan et al. 2019; Yang et al. 2020; Mao et al. 2021). Such modifications reduce the compounds toxicity or increase their solubility so they can get excreted or degraded (Fig. 1). However, the insect microbiota can also be influenced by exposure to anthropogenic stressors and enhance enzyme activity through a wide range of metabolic pathways able to break down and/or modify xenobiotics (Itoh et al. 2018; Gangola et al. 2022). The role of bacterial microbiota in the detoxification of xenobiotics in insects was first described in 1967, in the apple maggot *Rhagoletis pomonella* (Boush and Matsumura 1967). It was shown that the bacterial symbiont *Pseudomonas melophthora* degrades up to six different insecticides.

The microbial enzymatic repertoire in the insect gut is very diverse and implies many enzymatic functions among which are microbial hydrolytic enzymes such as glycosidases, proteases, and sulfatases (Banerjee et al. 2022). Bacterial communities associated with insects can be directly involved in detoxification processes through (i) secretion of enzymes that

enable direct xenobiotic metabolization (acetylcholinesterase, carboxylesterase, glutathione S-transferase, and cytochrome P450) in the insect gut, (ii) xenobiotic reduction, (iii) through addition of acetyl and methyl groups, (iv) xenobiotic sequestration in bacterial cells, (v) bacterial efflux pumps capable of moving toxic compounds out of cells, or (vi) the formation of a protective biofilm to prevent xenobiotic to access host cells (Fig. 2). Comparative genomics analysis allowed identifying detoxifying genes in some bacterial symbiont isolates even though the degradation routes have not been yet fully identified (Siddiqui et al. 2022). For instance, nitro-reduction and oxidation are the main ways that some bacterial symbionts such as *Arsenophonus*, *Pseudomonas*, *Ensifer*, *Stenotrophomonas*, and *Variovorax* use to degrade the insecticide imidacloprid (Lu et al. 2016; Fusetto et al. 2017). *Pseudomonas* spp. and *Ensifer adhaerens* are able to metabolize the thiamethoxam pesticide by changing its N-nitroimino group to N-nitrosimine/nitrosoguanidine and urea (Hussain et al. 2016). *Citrobacter* and *Burkholderia* possess respectively phosphatase genes as well as methyl parathion-degrading enzyme, and an organophosphorus hydrolase able to degrade the trichlorophon and fenitrothion insecticides in the oriental fruit fly *B. dorsalis* and stinkbugs (Tago et al. 2005, 2006; Singh 2009; Cheng et al. 2017). An isolate of the genus *Burkholderia* was showed to be able to use fenitrothion as the sole carbon source for its growth (Kikuchi et al. 2012). Interestingly, *B. dorsalis* inoculated with this symbiont showed higher trichlorophon resistance compared to antibiotic-treated flies (Cheng et al. 2017). Most studies that describe the involvement of bacterial symbionts in detoxication activity were not examined *in insecta*. As biotic (presence of other microorganisms, multipartite interactions) and abiotic (pH, presence of nutrients, oxygen concentration, ...) factors strongly influence the within environment of insects, the outcome of detoxication success may be different in comparison to studies performed *in vitro* on bacterial isolates cultivated on artificial media. The resistance of the fruit fly *D. melanogaster* to chlorpyrifos insecticide depends on the bacteria present in the fly. While *Lactobacillus plantarum* degrades this compound into a more toxic metabolite (oxon chlorpyrifos), *Lactobacillus rhamnosus* is capable of sequestering the compound thus allowing enhanced insect survival (Daisley et al. 2018). Atrazine-degrading *atzA*, *atzB*, and *atzC* genes were identified in the *Acinetobacter tropicalis* symbionts associated with atrazine-resistant *D. melanogaster* (Brown et al. 2021). Those genes have been shown to be widespread and associated with plasmids from multiple atrazine-degrading isolates (Martinez et al. 2001). The gut microbiota of the mealworm *T. molitor* contribute to accelerate polystyrene biodegradation, and potential strategies for cultivation of plastic-degrading bacteria are currently investigated (Yang et al. 2021; Pivato et al. 2022). Finally, it was suggested that the gut bacterial microbiota of black soldier fly larvae *Hermetia illucens*

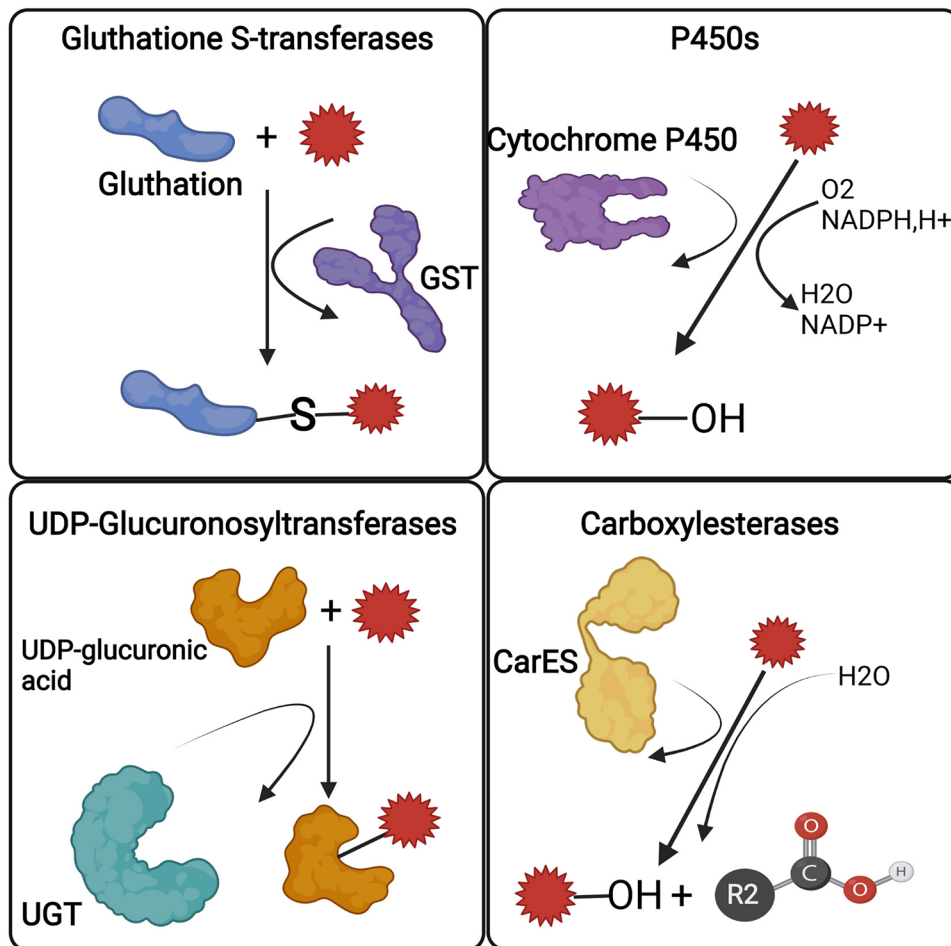
would be involved in tetracycline degradation. Those insects were often in contact with such antibiotic when feeding on organic animal waste (manure, corpses). Different *tet* genes involved in antibiotic tolerance and/or effective degradation were identified in the insect microbiota (97% in 12 days). A role of Bacteroidetes was suspected since their relative abundance strongly increases in the presence of tetracycline (46.2% when tetracycline is present vs. 1% when absent) (Cai et al. 2018). However, their formal intervention in this detoxification pathway has not yet been demonstrated. More recently, it was reported that gut bacterial microbiota of the black soldier fly larvae contributes to lincomycin degradation after isolating lincomycin-degrading strains from larval guts and composts (Luo et al. 2022).

Anthropogenic stressors can impact insect hosts and their microbiota independently but insect-microbiota interactions can, in turn, expand or constrain insect adaptation to stressor exposure. As previously mentioned, some insects have acquired bacterial symbionts to overcome the deleterious effects of stressor exposure allowing insects to adapt in polluted environments (Lemoine et al. 2020). This was the case for *Burkholderia* spp and *Pseudomonas* spp found in *Riptortus pedestris* and

Spodoptera frugiperda respectively that confer insecticide resistance to their hosts (Kikuchi et al. 2012; de Almeida et al. 2017). In most insect models for which bacterial detoxification were observed, the route of detoxifying bacteria acquisition still needs to be determined. Those can be seeded from the environment (mostly through nutrition) and/or transmitted among individuals through horizontal or vertical transfer.

Surprisingly, few results support the role of microorganisms in the shielding or efflux of anthropogenic stressors. Further studies are still needed to provide empirical evidence of microbial-assisted degradation of xenobiotic compounds and decipher the underlying mechanisms. Microbial enzymes sequence and activity differ from one species to another, and inter-individual variations occur in the composition and structure of insect-associated microbiota. Therefore, the diversity of chemical reactions catalyzed by the insect microbiota is difficult to predict. The high diversity of insect bacterial microbiota and intricate interactions among microbial communities suggest that this xenobiotic-degrading potential is currently underestimated and merit further investigation. Moreover, detoxication enzymes are often encoded in plasmids that can be horizontally transferred from species to species.

Fig. 1 Main families of detoxication enzymes in insects. The xenobiotic metabolizing enzymes have a primary role in the metabolism and elimination of xenobiotics. They include (i) cytochromes P450 and carboxylesterase that facilitate the solubilization of the xenobiotic in water and its storage in less sensitive tissues or its excretion and (ii) glutathione S-transferases and UDP-glucuronosyltransferases that add hydrophilic groups to the xenobiotic allowing better mobilization and then its excretion. Once the xenobiotic has been modified by one of the enzymes, it can be degraded or excreted via specific transporters or ABC-type transporters. Created by BioRender.com



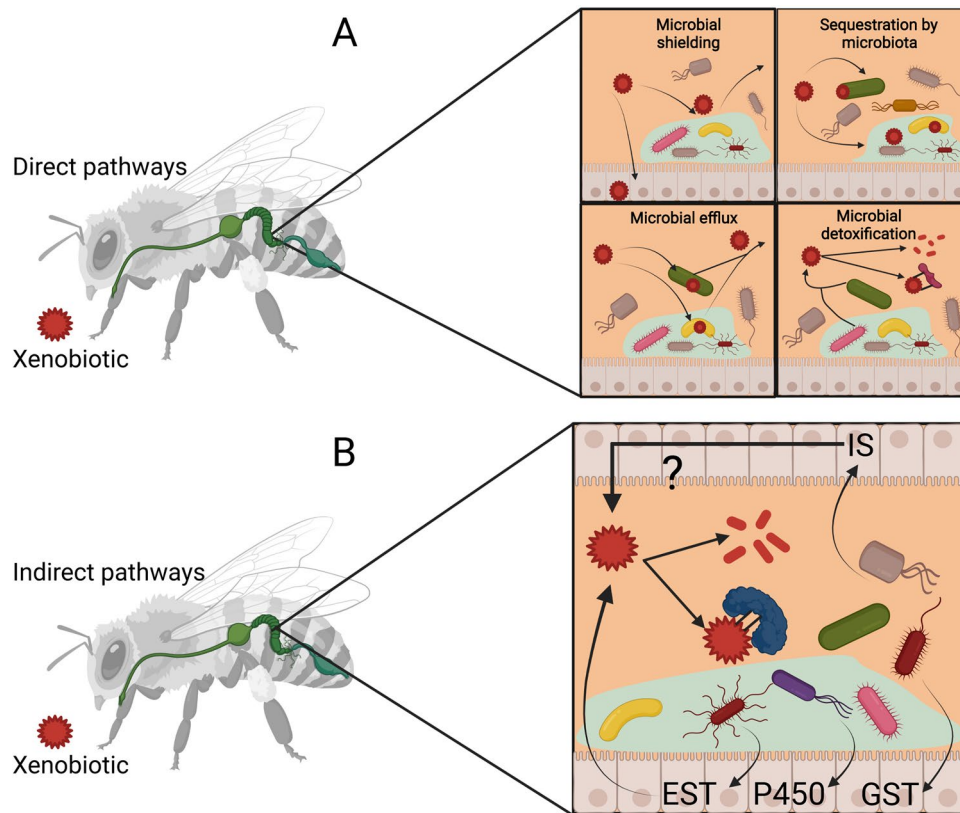


Fig. 2 Direct and indirect insect microbiota-mediated detoxification pathways. The xenobiotic is acquired by ingestion of food. Once in the insect body, the xenobiotic interacts with the microbiota through different pathways. **A** Direct pathways would be involved: (i) biofilm growing on insect cells form a shield that blocks access of the xenobiotic to host cells and prevents contact with the host, (ii) the xenobiotic is sequestered in bacterial cells or in the biofilm matrix preventing its access to the host cells and then excreted via faeces, (iii) the xenobiotic enters the bacterial cells and then is released downstream into the gut via bacterial efflux systems (e.g., efflux pumps), (iv) bacteria in

contact with the xenobiotic produce enzymes capable of modifying or degrading the xenobiotic, limiting its toxicity and facilitating its excretion. **B** Indirect pathways involve the activation of insect microbiota-mediated-host detoxification pathways like the enzymes P450s, Glutathione-S-Transferase (GST), or Esterase (EST). In addition, the microbiota can also induce the activation of the host immune system (IS). This stimulation could amplify detoxification process through pleiotropic effects of immunity genes or interactions between immunity and detoxification pathways. Created by BioRender.com

Indirect microbiota-mediated detoxification pathways

Indirect microbiota-mediated xenobiotic detoxification relies on regulation of host defenses. This means that bacteria alone are not involved in xenobiotic resistance and detoxification but are rather able to promote the host response following stressor exposure. Honeybees treated with antibiotics are less able to degrade thiaclopride and tau-fluvalinate insecticides, which results in a lower survival rate, compared to untreated individuals (Wu et al. 2020). This phenotype is explained by increased expression of insect detoxification genes encoding in particular cytochromes P450 in the midgut colonized by bacteria. This interaction between the microbiota and the insect detoxification enzymes is supported by the fact that individuals harboring a microbiota and treated with a P450 enzyme inhibitor were unable to eliminate insecticides. Similarly, in the German cockroach,

Blattella germanica, resident bacterial microbiota increases resistance to indoxacarb, an insecticide from the carbamate family. It was suggested that bacteria would stimulate the Glutathione-S-Transferase (GST) detoxification enzyme of the host (Pietri et al. 2018). Similar microbiome-related enhancement of the GST activity was reported in multiple insect species such as in the mosquito *A. stephensis*, the leafhopper *Amplipcephalus curtulus* and the honeybee *A. mellifera* (Arismendi et al. 2015; Soltani et al. 2017; Yu et al. 2021). Finally, other studies highlighted that bacterial microbiota triggers out the overexpression of esterases and catalases detoxification genes when *A. curtulus* and *A. stephensis* individuals were exposed to xenobiotics (Arismendi et al. 2015; Soltani et al. 2017).

Gut bacteria play an important role in insecticide resistance of the diamondback moth *Plutella xylostella* (Xia et al. 2018). Although *Enterococcus* sp. isolated from the insect gut was able to degrade chlorpyrifos in vitro, its

enhancement of insect resistance toward the insecticide was not associated to degradative enzymes but rather to vitamin C and acetylsalicylic acid produced by the bacteria. Indeed, other bacteria with similar *in vitro* ability to degrade the compounds did not increase the insect resistance. Vitamin C and acetylsalicylic acid produced by *Enterococcus* sp. were correlated with a specific modulation of insect antimicrobial peptides. It was therefore suggested that the influence of gut bacteria on insecticide resistance could depend on effects on the insect immune system in *P. xylostella* (Xia et al. 2018). These results suggest an indirect process mediated by the microbiota on the immune system for xenobiotic resistance. Interestingly, metatranscriptome sequencing in cockroaches revealed that a large part of downregulated differentially expressed genes were from microbial and viral origins, suggesting that selection for resistance could also be associated with elimination of microorganisms (Scharf et al. 2022). Similar results were observed regarding immune and detoxification of insect-associated microbiota in honeybee larvae (Yu et al. 2021). It was shown that bacterial microbiota served as a barrier in the insect gut and reduce the stress of flumethrin on honeybee larvae. Interestingly, as the concentration of flumethrin increases, larvae stimulate their immune system then detoxification system to protect against the potential detrimental effect of flumethrin. This could be explained either by (i) pleiotropic effects of insect immunity and insecticide resistance or (ii) the effects of some genes that participate in immunity that may be exploited in insecticide resistance (Xia et al. 2018). A crosstalk between microbiota and insect host genes can result from a shared stress response mechanisms that involve both xenobiotic resistance and immunity. Although the direct and indirect pathways involved in the microbiota-mediated xenobiotics degradation are described (Fig. 2), the molecular factors and pathways that lead to the expression and activity regulation of hosts detoxification genes are still unknown. Further studies are needed to investigate the insect-microbiome metabolism relationship and whether insect-associated microbiota metabolic interactions contribute to detoxification processes. Such advances will be essential and dependent upon studies using metabolomics to identify and differentiate metabolites from microbial and host origins.

Conclusion

Numerous studies testify to a deleterious effect of xenobiotics in insects, and some of them testify the strong influence of the microbiota in insect response. Most of the studies are focused on bacteria while the microbiota is more complex and harbors a diversity of organisms (protists, viruses, archaea, eukaryotes) that should be included in future

investigations. Different types of responses were observed depending on the insect species, the bacterial microbiota composition, the xenobiotic, and the dose exposure that may lead to an alteration of key biological functions in insects. In addition, most of the studies are biased toward economic or health importance insect models (pollinators, vectors of pathogens, crop pests...) and most widely used xenobiotics (insecticides, herbicides, antibiotics...), which only partially reflects the complexity of these interactions. To date, other xenobiotics (e.g., anti-inflammatories such as ibuprofen) have not yet investigated. Given the limited literature on this topic and the complexity of those interactions, their effects on ecosystems properties and functioning remain difficult to predict.

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