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# The functional relationship between aquatic insects and cyanobacteria: A systematic literature review reveals major knowledge gaps

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## ABSTRACT

Cyanobacteria and aquatic insects are major components of food webs in freshwater ecosystems. However, the functional relationship between cyanobacteria and aquatic insects has been poorly studied. The blooms of cyanobacteria are more likely to intensify with rising temperatures, such that climate warming may influence this relationship. To improve our understanding of this relationship, we performed a systematic literature review (SLR) and analyzed 104 peer-reviewed research articles published between 1985 and 2020. The articles were categorized into three themes: the role of cyanobacteria as food source and habitat for aquatic insects, the impact of cyanotoxins on aquatic insects, and the use of *Bacillus thuringiensis* (Bt) expressing transgenic cyanobacteria to control Diptera, mainly mosquitoes. Major findings on each of these themes were summarized and research gaps and opportunities were highlighted. Major gaps include the lack of ecological modelling studies that describe or model this relation, the absence of studies of cyanotoxins' impact on key aquatic insects like dragonflies (Odonata), the impact of Bt larvicidal engineered cyanobacteria on biological indicators like Chironomidae, the lack of studies on climate change impacts on the functional links between cyanobacteria, aquatic insects and other organisms. These gaps and research opportunities should be addressed in future research to increase the understanding of the relationship between cyanobacteria and aquatic insects and therefore the biology of freshwater ecosystems.

## 1. Introduction

Bodies of freshwater are complex ecosystems involving the coupling of physical, chemical, and biological processes. Understanding how communities, biomass, and species are arranged in these complex aquatic systems is a major goal for contemporary ecologists for maintaining ecosystem functions as our climate is changing. However, while the response of key taxa (e.g., insects) to environmental changes has been relatively well covered (Erwin et al., 2013; Weyl and Hill, 2012), many interactions among different freshwater taxa remain relatively understudied, in particular between bacteria and insects which are two key components (see below). This review focuses more particularly on the relationship between aquatic insects and cyanobacteria.

Aquatic insects are classic targets of environmental monitoring and assessment as well as ecological research. Insects are dominant organisms in aquatic ecosystems since some species are capable of spending part of or all their life cycles in the water (Koroiva and Pepinelli, 2019). Several factors influence their distributions, including substrate heterogeneity (Milesi et al., 2016), land use resulting in hydrological

changes or nutrient influx (Fadel et al., 2021; Gimenez and Higuti, 2017; Song et al., 2009), physical-chemical conditions (e.g. water temperature and thermal stratification, pH, salinity, and oxygen concentration) (Dallas and Ross-Gillespie, 2015), the aquatic vegetation that affects the physical-chemical conditions of water (Briggs et al., 2019; Díaz-Valenzuela et al., 2016), and water current velocity (Fenoglio et al., 2013). In aquatic food webs, insects serve as food for a large range of vertebrate and invertebrate predators (Hershey et al., 2010). At the same time, they predate on zooplankton and phytoplankton, connecting these organisms with superior consumers (like fish and other vertebrates) across the hydrobiological chain and providing a critical link in the aquatic food web. Yet, according to Starr and Wallace, (2021), the ecology and biology of many aquatic insect groups are still poorly understood, leaving gaps in ecological knowledge concerning habitat use or partitioning of larval or adult stages, or even both.

Cyanobacteria, also known as blue-green algae, are one of the most widespread phytoplankton groups throughout bodies of freshwater. They are primary producers in aquatic ecosystems, producing organic matter and oxygen via photosynthesis. They can tolerate extreme

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changes in salinity, water temperature, nutrient availability, and irradiance, which give them an extraordinary competitive advantage on other phytoplankton groups in aquatic ecosystems (Paerl and Otten, 2013; Reynolds, 2006). They are usually promoted by nutrient enrichment of agricultural, urban, and industrial waters. Rising temperatures and thermal stratification can favor cyanobacteria growth allowing them to outcompete other phytoplankton groups (Fadel et al., 2015; Wagner and Adrian, 2009). They often bloom and dominate aquatic ecosystems during dry season when water temperature rises as they outcompete other groups such as diatoms and green algae at higher temperatures (Paerl and Huisman, 2008). Some species use gas vesicles to float upward during stratified conditions and accumulate in dense surface blooms shading nonbuoyant diatoms and green algae and suppressing them through competition for light (Jöhnk et al., 2008).

Cyanobacteria can produce a wide range of toxins known as cyanotoxins (Hammoud et al., 2021). Cyanotoxins are classified based on their toxicological targets (on human) as follows: 1) hepatotoxins (Microcystins and Nodularin) targeting the liver, 2) cytotoxins (Cylindrospermopsin) targeting both the nervous system and liver, 3) neurotoxins (Anatoxins, Saxitoxins, and  $\beta$ -Methylamino-L-Alanine-BMAA-) targeting the nervous system, and 4) dermatotoxins (Lyngbyatoxins, Lypopolysaccharide, and Aplysiatoxin) targeting skin resulting in irritation upon contact. Some cyanotoxins like cylindrospermopsin can be found as extracellular form (Bormans et al., 2004; Fadel et al., 2014) in freshwater bodies because of their slow degradation (Wormer et al., 2008). Others, like microcystins are mostly found inside cyanobacteria cells but can be released outside cyanobacteria during cell lysis (eg, during the decline of blooms). However, microcystins breakdown under sunlight with a half-life period of 10 days in the presence of  $1 \text{ mg} \cdot \text{l}^{-1}$  of cyanobacteria pigments (Schmidt et al., 2014; Tsuji et al., 1995).

The functional link between cyanobacteria and aquatic insects has not been deeply formalized before. On one hand, cyanobacteria can be a food source for aquatic insects. Cyanobacteria were reported among the major categories of food items found in the gut content of stoneflies (Plecoptera), caddisflies (Trichoptera), mosquitoes (Diptera: Cylicidae), chironomids (Diptera: Chironomidae) and mayflies (Ephemeroptera) (Keiper and Harris, 2002; Kornijow et al., 2019; Tierno de Figueroa and Sánchez-Ortega, 2000; Zhou et al., 2020). On the other hand, cyanotoxins may pose a significant risk to freshwater ecosystems (Guzmán-Guillén et al., 2015; Sieroslawska and Rymuska, 2019; Ziková et al., 2013). This risk can directly impact aquatic insects when feeding on cyanobacteria, or indirectly when inhabiting waters that are contaminated by cyanotoxins. High concentrations of cyanotoxins are lethal to various species of mosquitoes (Kiviranta et al., 1993; Mosleh and El-Ela, 2011). This lethal property was used to control mosquito populations that transmit human disease. Cyanobacteria were used as gene delivery systems to make the bacterium *Bacillus thuringiensis* (Bt) expressing their mosquitocidal toxins (Boussiba et al., 2000; Zaritsky et al., 2010). Depending on their feeding mode and physiology, aquatic organisms can bioaccumulate or biodilute cyanotoxins (Kozłowsky-Suzuki et al., 2012). Aquatic organisms (like zooplankton and zooplanktivorous fish) can bioaccumulate these toxins and transfer them throughout the food chain to wildlife and humans (Ferrão-Filho and Kozłowsky-Suzuki, 2011; Hardy et al., 2015; Kozłowsky-Suzuki et al., 2012). Human consumption or skin contact of water containing cyanotoxins can result in skin irritation and symptoms usually ranging from severe headache to fever, respiratory paralysis and in rare case, death (Carmichael et al., 2001; Christensen and Khan, 2020; Koreivienė et al., 2014). The World Health Organization (WHO) has issued a provisional guideline value of  $1 \mu\text{g l}^{-1}$  in drinking water for Microcystin-LR (MC-LR), the most widespread, and common cyanotoxin in water supplies (WHO, 2003, 1999).

Changes in physical-chemical properties of bodies of water may result in changes in the biomass, and diversity of both cyanobacteria and aquatic insects. Those physical-chemical changes have cascading consequences on the entire aquatic food web. Global warming and rising

$\text{CO}_2$  concentrations are likely to stimulate the development of more intense harmful cyanobacterial blooms in eutrophic aquatic ecosystems with negative consequences on the aquatic organisms inhabiting these ecosystems (Slim et al., 2014; Visser et al., 2016). It is unclear, however, if insects that feed on cyanobacteria are more or less sensitive to such increases in cyanotoxin production compared to insects that do not feed on them but live in the same body of water. Several studies determined the dynamics of cyanobacterial biomass and cyanotoxins in the aim to link cyanobacteria to other aquatic organisms like zooplankton (Esterhuizen-Londt et al., 2016; Fadel et al., 2019; Falfushynska et al., 2019; Lance et al., 2007; Marie et al., 2012). These have shown that cyanobacteria are considered a poor-quality food for zooplankton due to nutritional constraints and defensive traits of cyanobacteria (Ger et al., 2016). The production of cyanotoxins and the morphology of cyanobacteria (colonial or filamentous) had direct influence on the fitness of large generalist grazers (i.e., Daphnia). A large variation in species-specific responses of zooplankton to cyanobacteria was found (Tillmanns et al., 2008). However, few studies that comprehensively describe the relationship between cyanobacteria and aquatic insects were published so far. This information is scattered in the literature, as shown in this review (see below). Therefore, our aim is to review, for the first time, the functional relationship between cyanobacteria and aquatic insects. The objective of our review is to identify the gaps in the available knowledge on this relationship to provide recommendations for future research. Classical narrative review has been so far the most used way of conducting a literature review. Nevertheless, this method is often based on the experience and subjectivity of the authors and has shown several disadvantages including use of random unreliable scientific sources and often inadequate number of studies (Cipriani and Geddes, 2003). By contrast, systematic literature review (SLR) is an effective, complete, more rigorous, and transparent methodology that can successfully lead to evidence-based conclusions (Koutsos et al., 2019).

We used the systematic literature review method to assess the current challenges and existing research opportunities on the following major topics that emerged from our search (see below): (a) cyanobacteria role as food source and habitat of aquatic insects; (b) the impact of cyanotoxins on the different groups of aquatic insects; and (c) the use of cyanobacteria to control dipterans by means of the introduction of insecticidal *Bacillus thuringiensis* (Bt) toxins.

## 2. Materials and methods

### 2.1. Data sources and search criteria

A systematic search of peer-reviewed articles was conducted on November 11, 2020 using Scopus and Web of Science databases (WoS). The following search string was used to identify studies that report a link between cyanobacteria and/or their toxins and aquatic insects:

("cyanobacteria"OR"cyanophyta"OR"blue-green algae"OR"microcystin"OR"cyanotoxin"OR"microcystis"OR"cylindrospermopsin"OR"anatoxin")

AND

("insect"OR"mosquito"OR"Diptera"OR"Aedes"OR"culex"OR"odonata"OR"dragonfly"OR"damsel"OR"mayfly"OR"Ephemeroptera"OR"Megaloptera"OR"alderflies"OR"fishflies"OR"dobsonflies"OR"Neuroptera"OR"lacewings"OR"Stonefly"OR"Lepidoptera"OR"moth"OR"Mecoptera"OR"scorpionflies"OR"Plecoptera"OR"Caddisfly"OR"Trichoptera"OR"Strider"OR"Gerridae").

No year restriction was applied. However, only articles from a peer-reviewed journal and published with English language were included.

### 2.2. Inclusion and exclusion criteria

After removing the duplicate references, all the records were

screened by the same observer (AF). The titles and abstracts were first reviewed and then the full texts of the potential eligible studies were assessed to identify whether the inclusion criteria were met. As we wanted to limit our study to aquatic insects, we did not explicitly search for studies examining the impact of cyanobacterial blooms and their toxins on cladocerans, rotifers, copepods, and other zooplankton species unless the study linked them to aquatic insects. Moreover, we excluded articles that studied: 1) the relationship between terrestrial cyanobacteria and insects, 2) the impact of cyanotoxins on purely terrestrial insects, 3) the occurrence of cyanobacteria and aquatic insects in the gut of fish or copepods and that report them without any identified link, and 4) the impact of insecticides on aquatic cyanobacteria. As a result, 1437 papers were considered as irrelevant from the first set of 1536 publications retrieved.

We also examined the references for all selected papers to look for any additional papers meeting our inclusion criteria. Six additional papers were identified through this method and included in the analysis (Fig. 1).

### 2.3. Keyword analysis

The aim of this analysis was to objectively show the different specific topics by which aquatic insects and cyanobacteria are associated in the studies we retrieved. The keywords analysis was performed using VOSviewer (van Eck and Waltman, 2010). This screening applies text-mining techniques to the titles, abstracts, and keywords of articles. It identifies multiple keywords that occur together in the same articles and the relationship between these keywords. VOSviewer uses a similarity measure known as the proximity index or the association strength that

estimates the similarity of two items based on the number of their co-occurrences. It then maps the two items in such a way that the graphical distance between them reflects their similarity. Items close to each other in the map have a high similarity, while those far from each other have a low similarity. To perform the keyword analysis, we combined the datasets retrieved from the Scopus and WoS databases in a .csv file and imported them to VOSviewer.

Before the screening process (Fig. 1), 12,758 keywords were extracted from the 1536 publications. However, only 1359 keywords were obtained when the minimum number of occurrences of keywords was set to five. After the screening process, 1682 keywords were extracted from the resulting 104 publications, and 105 keywords met the indicated threshold of five minimum occurrences. The keywords “articles” and “priority journal” were unselected before running the keyword analysis.

## 3. Results and discussion

### 3.1. Keyword analysis

The Fig. 2 visualizes the network of co-occurrence of keywords resulting from the search on SCOPUS and WOS databases before and after screening. Four clusters are emerging (Fig. 2a and b). Before the screening (Fig. 2a), the keyword “cyanobacteria” appears in the middle of a large and dense network of keywords. The link between cyanobacteria and aquatic insects appeared better after the screening analysis. The link differed among insect taxa (Fig. 2b). For instance, Ephemeropteran species appeared in the cluster associated with toxicity studies. By contrast, Diptera and Trichoptera were more strongly associated to

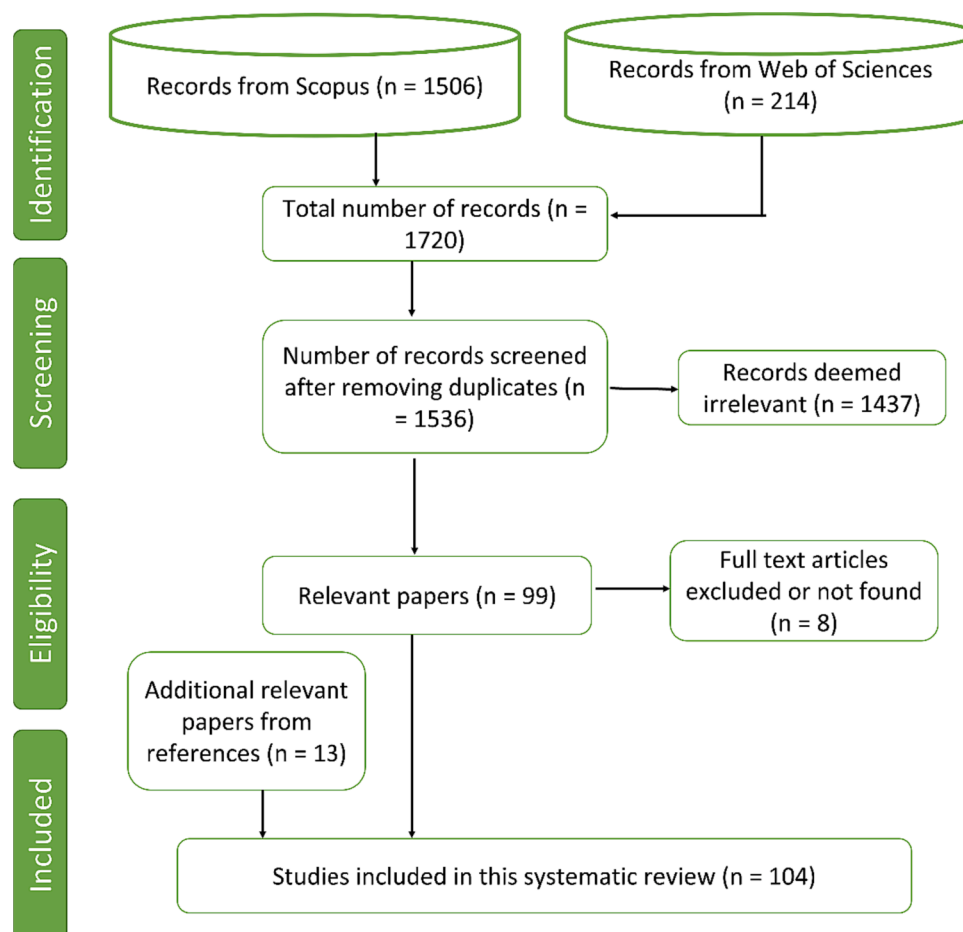
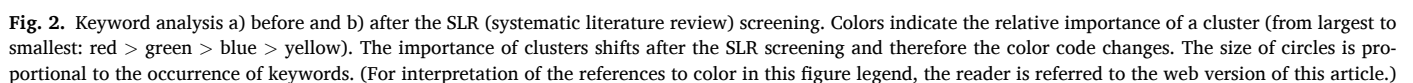


Fig. 1. Screening process of the systematic review, showing the steps from identified studies to final inclusion, using PRISMA methodology (Liberati et al., 2009).





biological control on the other hand. Thus, this analysis illustrated the extent to which the link between aquatic insects, cyanobacteria and their toxins is rather blurred in the literature.

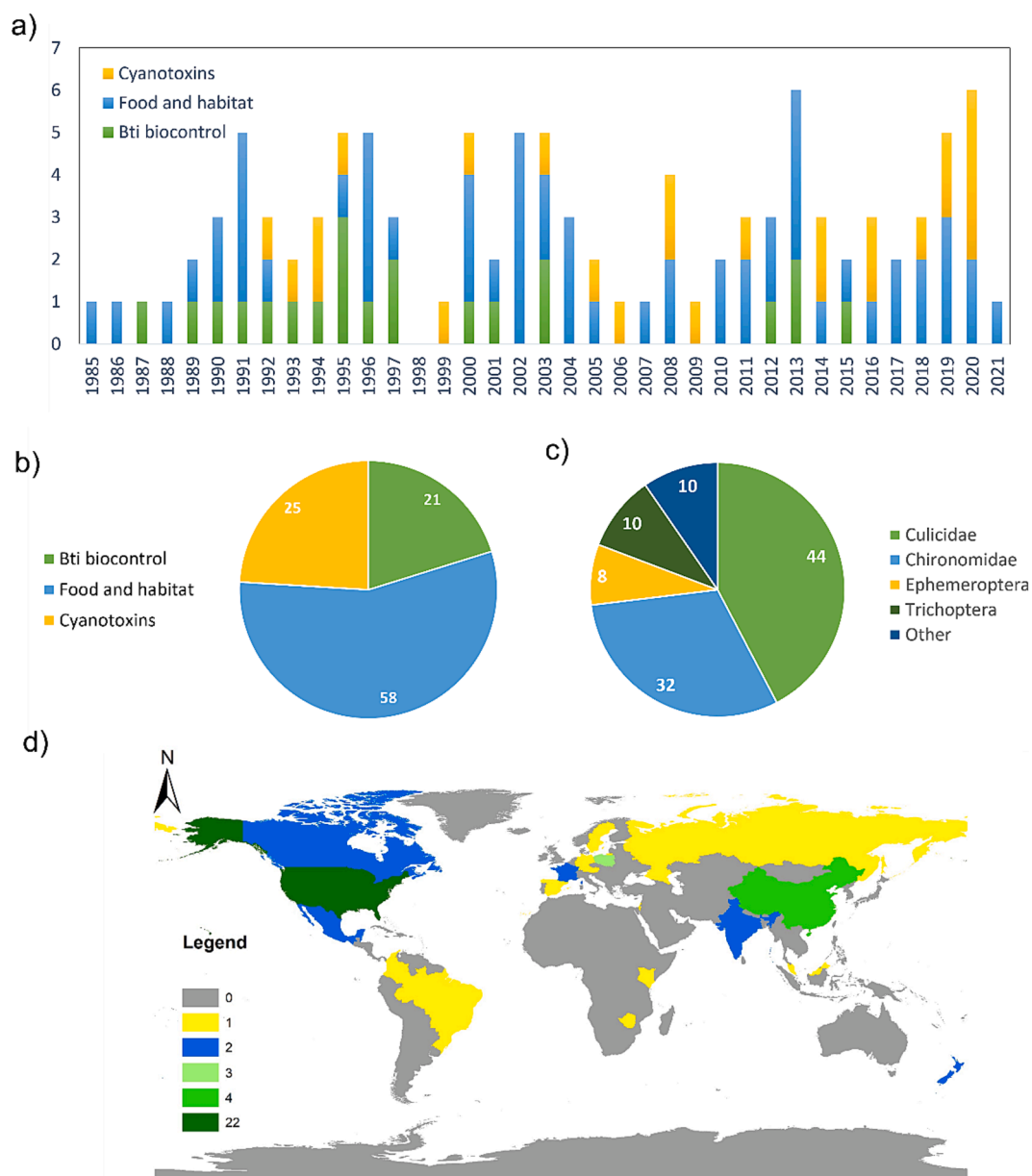
### 3.2. Temporal and spatial distribution of publications

The temporal distribution of the 104 publications selected through the SLR method is shown in Fig. 3a. There is no particular temporal trend of the number of research publications on the topic, although it has been fluctuating across time periods. Nonetheless, only few works were published every year overall since the 80 s (from 0 up to a maximum of 6 publications each year). In general, these studies mostly deal with cyanobacteria as food and habitat for Culicidae and Chironomidae (Fig. 3b, c). The analysis also revealed the absence of important insect taxa that are mostly predatory in aquatic systems, such as Odonata or Coleoptera. In addition, the most recent years seem to indicate a slight increase in the number of publications on the topic of cyanotoxins and aquatic insects, but this needs to be confirmed in the coming years.

The geographical pattern of the number of field studies linking cyanobacteria and aquatic insects is shown in Fig. 3d. Most studies were conducted in the United States followed by China and Poland. Overall,

the South hemisphere is poorly covered. A high heterogeneity was also observed for the North hemisphere. Overall, this distribution somewhat follows the geographical distribution of human and animal poisonings associated with cyanobacteria or cyanotoxins (Svirčev et al., 2019), except that some Southern countries (i.e., Australia and few African countries) with reported poisoning cases do not display studies on the link with aquatic insects.

Our SLR approach revealed that the functional relationship between aquatic insects and cyanobacteria was studied almost exclusively according to 3 topics: (a) cyanobacteria role as food source and habitat of aquatic insects (blue and green clusters in Fig. 2b); (b) the impact of cyanotoxins on the different groups of aquatic insects (red cluster in Fig. 2b); and (c) the use of cyanobacteria to control dipterans by means of the introduction of insecticidal *Bacillus thuringiensis* (Bt) toxins (yellow cluster in Fig. 2b). Below we discuss the knowledge and gaps on those specific topics.



**Fig. 3.** A) time series of the 104 publications categorized into the three main identified categories, b) number of publications per category, c) number of publications per aquatic insect orders ("other" includes plecoptera, odonata, coleoptera, and hemiptera) and d) global distribution of the number of field or laboratory studies (using aquatic insects collected in the field) linking cyanobacteria and aquatic insects..

### 3.3. Role of cyanobacteria as food source and habitat for aquatic insects

#### 3.3.1. Cyanobacteria as food source

Cyanobacteria is an important food source for aquatic insects including Diptera (Krivosheina, 2008; Winterbourn, 1996; Yeh and Chuang, 1996), Ephemeroptera (López-Rodríguez et al., 2009), and Trichoptera (Graca et al., 2018; Holomuzki et al., 2013). This is mainly due to their morphology (unicellular, colonial, and filamentous) and spatial-temporal diversity, with multiple species available at different location and time throughout the year. The consumption of cyanobacteria by aquatic insects is quite variable among insect taxa, and complex (Dudgeon et al., 2010). This consumption is often not differentiated from the larger food web that is often impacted by several factors like eutrophication, habitat destruction (Chen et al., 2021; Yule et al., 2015), invasive species (Kwong et al., 2010), and climate change (Woodward et al., 2012).

Cyanobacteria were reported as the main microorganism in the gut flora of several aquatic insects (Table 1). For instance, *Oscillatoria* spp. composed 39 % of the food items found in the gut of *Chironomus balatonicus* in Vistula lagoon in USA. *Chroococcales* sp. composed 100 % of the food items found in the gut of *Chironomus plumosus* in Curonian lagoon in USA (Kornijow et al., 2019). Moreover, pyrosequencing bacterial 16S rRNA method showed that cyanobacteria represented 40% of the communities found in the gut of *Anopheles gambiae* during the larval and pupal stages (Wang et al., 2011). Although, cyanobacteria have good nutritional values with high amount of protein (between 18 and 70 % of dry weight (Nagarkar et al., 2004)), necessary for primary consumers like insects, some cyanobacteria can kill the insect larvae when ingested in large quantities or due to their toxicity (Frouz et al., 2004a, 2004b).

#### 3.3.2. Cyanobacteria as habitat for aquatic insects

The presence of cyanobacteria was often reported in the larval habitat of mosquitoes (Duguma et al., 2013; Manguin et al., 1996; Ponnusamy et al., 2008; Vázquez-Martínez et al., 2003; Vázquez-Martínez et al., 2002), Chironomidae (Ali et al., 2002; Bourassa and Cattaneo, 2000; Furey et al., 2012; Gingras et al., 2007; Kownacki et al., 1997; Lee et al., 2019a; Majdi et al., 2020; Mantel et al., 2004; Niedrist et al., 2018; Sela and Halpern, 2019; Ståhl-Delbanco and Hansson, 2002; Tarkowska-Kukuryk, 2013), stoneflies (de Figueroa and Sánchez-Ortega, 2000), mayflies (Jacobus and McCafferty, 2004; Salas and

Dudgeon, 2001), and Odonata (Anusa et al., 2012). Most of these studies however only report presence and do not investigate on the functional link between the two. Inferences from these studies can inform us on the ability of particular insect taxa to tolerate the presence of cyanobacteria.

Cyanobacteria are often planktonic. However, they can occur as benthic, epiphytic/epilithic and as mats. Cyanobacterial mats are dense, layered communities of cyanobacteria that form complex structure with other microorganisms like bacteria, algae, and fungi (van Gemerden, 1993). They are often found in shallow water bodies such as lakes, ponds, rivers, and estuaries occur in environments with abundant nutrients, favorable temperatures, and suitable light conditions (Paerl and Huisman, 2009). Depending on environmental factors, they can persist from short (few weeks) to longer periods (several years).

Cyanobacterial mats can be used as habitat for aquatic insects. For instance, the larvae of the mosquito *Anopheles albimanus* Wiedemann in Northern Belize were found to inhabit cyanobacteria floating mats (Manguin et al., 1996). In contrast to fast current underneath the floating cyanobacterial mats, water current within cyanobacterial mats is negligible forming a favorable and attractive environment for *Anopheles albimanus* females to lay their eggs (Manguin et al., 1996). In Ecuador as well, a positive association was found between *Anopheles albimanus* (W.) and floating cyanobacterial mats in their habitats (Pinault and Hunter, 2012). Those floating mats can serve as refuge against predators for mosquito larvae, although a direct demonstration of this function seems to be missing.

Like mosquitoes, Chironomidae can inhabit cyanobacteria colonies and mats and their relationship can become symbiotic. For instance, stream-inhabiting cyanobacterium colonies of *Nostoc parmelioides* often contain a single chironomid species (*Cricotopus nostocicola*), which induces a morphological change of colonies from small spherical to larger ear-shaped ones, increased rates of nitrogenase activity, and CO<sub>2</sub> uptake (Dodds and Marra, 1989). Sabater and Muñoz, (2000) also reported that chironomid larvae (*Cricotopus* sp.) colonizing *Nostoc verrucosum* made them globose and changed the structure of the pads to become slightly compressed and positioned in parallel to the stream flow (Sabater and Muñoz, 2000).

#### 3.3.3. The trophic relationship between cyanobacteria and aquatic insects

Eutrophication is a serious problem in lakes, as it can result in severe environmental deterioration and promotes the occurrence of cyanobacterial blooms. Depending on their genera and ability to produce cyanotoxins, cyanobacterial blooms can have varied impacts on aquatic insects' community and vice versa. For instance, Tubificidae and Chironomidae were reported the only benthic community capable to tolerate eutrophication, harmful algal blooms, microcystins and associated habitat deterioration in Lakes Chaohu and Taihu, China (Cai et al., 2012). Mundie et al., (1991) reported that an increase in phosphorus concentration increased the biomass of chlorophyll by 3.5 times favoring Cyanophyta over other phytoplankton groups and increased the emerging aquatic insects by 2.2 times with 77% or more of emerging insects as Chironomidae. On the other hand, a drop by 50% in both total nitrogen (TN) and total phosphorus (TP) influxes in Lake Müggelsee (Berlin, Germany) resulted in the reduction and disappearance of dominant cyanobacteria *Planktothrix agardhii* and *Limnithrix redekei*. This change decreased Chironomids by 80% (Köhler et al., 2005).

On the other hand, grazing by aquatic insects larvae can reduce the biomass of the algal community, shifting it from one dominant group to another (Feminella and Resh, 1991; Graca et al., 2018). In a tropical forest stream in Brazil, grazing by the caddisflies *Helicopsyche* caused 50% reduction in algal biomass and appeared to favor the cyanobacteria *Dolichospermum* sp. over diatoms (Graca et al., 2018). Walton et al., (1995) also found that after three weeks of grazing by *Dicosmoecus gilvipes*, the cyanobacteria *Phormidium* composed over 61% of the community in grazed treatments compared to only 35% in ungrazed ones (Walton et al., 1995). The food preference of caddisfly therefore directly sets the direction of the interaction. Both cyanobacteria and chironomid

**Table 1**

List of cyanobacteria species consumed by aquatic insects or reported in their guts.

Trichoptera	Culicidae	Chironomidae
<i>Phormidium</i> sp. <sup>1, 2</sup>	<i>Microcystis</i> <sup>9</sup>	<i>Aphanizomenon</i> spp. <sup>14</sup>
<i>Anabana</i> <sup>2</sup>	<i>Phormidium</i> <sup>10,12</sup>	<i>Chroococcales</i> spp. <sup>14</sup>
<i>Chroococcus</i> <sup>2,7</sup>	<i>Oscillatoria prolifera</i> <sup>11,12</sup>	<i>Oscillatoria</i> spp. <sup>14, 17, 24</sup>
<i>Pseudanabaena</i> <sup>2</sup>	<i>Arthrospira</i> <sup>12</sup>	<i>Snowella</i> spp. <sup>14</sup>
<i>Dolichospermum</i> sp. <sup>3</sup>	<i>Merismopedia</i> <sup>12</sup>	<i>Woronichinia</i> sp. <sup>14</sup>
<i>Oscillatoria</i> <sup>4,8</sup>	<i>Anabaena</i> <sup>12</sup>	<i>Anabaena</i> spp. <sup>14, 15, 19, 21, 22</sup>
<i>Nostoc</i> <sup>5</sup>	Unidentified by the author	<i>Microcystis</i> spp. <sup>14,16</sup>
<i>Dicosmoecus</i> <sup>6</sup>	<sup>13</sup>	<i>Nostoc</i> sp. <sup>18</sup>
<i>Rivularia</i> sp. <sup>6</sup>		<i>Anacystis</i> <sup>20</sup>
		<i>Gloeocapsa</i> , <sup>20</sup>
		<i>Merismopedia</i> <sup>20</sup>
		<i>Lyngbya</i> <sup>20, 21, 22</sup>
		<i>Phormidium</i> <sup>23</sup>

Source: 1 (Walton et al., 1995), 2 (Keiper and Harris, 2002), 3 (Graca et al., 2018), 4 (Fuller and Fry, 1991), 5 (Dudley and D'Antonio, 1991), 6 (Holomuzki et al., 2013), 7 (Poff and Ward, 1992), 8 (Vaughn, 1986), 9 (Zhou et al., 2020), 10 (Vázquez-Martínez et al., 2003), 11 (Beasley and Walton, 2016), 12 (Charles et al., 2011), 13 (Duguma et al., 2017; Sharma et al., 2014; Wang et al., 2011), 14 (Kornijow et al., 2019), 15 (Stanković et al., 2020), 16 (Yu et al., 2013), 17 (Beasley and Walton, 2016), 18 (Poinar and Poinar, 2003), 19 (Forsyth and James, 1988), 20 (Ali, 1990), 21 (Frouz et al., 2004a), 22 (Frouz et al., 2004b), 23 (Kohshima, 1985).



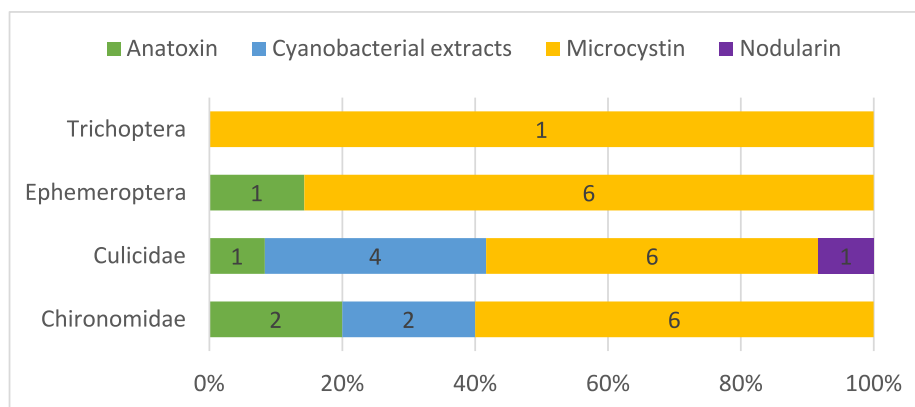


Fig. 4. Number of studies reporting the impact of cyanotoxins on aquatic insects.

larvae can be affected by the presence and abundance of fish that can have large effects on predators, herbivores, and the food webs. In a fish manipulation experiment, Power (1990) found that in the presence of fish, filamentous green algae were reduced to low, prostrate webs, infested with chironomids. However, in the absence of large fish, smaller predators are released, thereby suppressing chironomids and resulting in higher algal biomass (Power, 1990). These changes in algal biomass can induce variations in cyanobacterial populations.

A direct and positive link between cyanobacteria and Culicidae was found in few occasions. Cyanobacteria density had a positive correlation with the number of pre-imaginal stages of *Aedes aegypti* mosquitoes in water tanks in Colombia (Garcia-Sanchez et al., 2017). In rice fields, cyanobacteria were found to favour the abundance of multiple *Culex* species and the intake rate of cyanobacteria by late instars was 58% (Sunish and Reuben, 2002).

### 3.4. Impact of cyanotoxins on aquatic insects

Twenty-five articles discussing the impact of cyanotoxins on aquatic insects were found in the database. Some of these studies report the impact of more than one cyanotoxins on a given aquatic insect and sometimes the use of one cyanotoxin on multiple families of aquatic insects. The distribution of these studies is summarized in Fig. 4. Microcystin was the most studied cyanotoxin followed by unidentified cyanobacterial extracts, anatoxins and nodularin. Anatoxin impact was studied on Ephemeroptera and Diptera while nodularin was only applied to Diptera. Unidentified cyanobacterial extracts were used in the early 90s to study the impact of toxic cyanobacteria on aquatic insects when it was still hard to identify cyanotoxins. Nothing was published on the impact of other cyanotoxins like cylindrospermopsins, Saxitoxins, and  $\beta$ -Methylamino-L-Alanine (BMAA). Studies only covered three insect orders: Trichoptera, Ephemeroptera, and Diptera (Culicidae and Chironomidae). Trichoptera were the least studied aquatic insect taxa with only one study applying microcystin, while Culicidae represents the main group investigated so far (Table 2, Fig. 4). Overall, both lethal and sublethal effects were reported.

#### 3.4.1. Mortality and toxicity due to cyanotoxins

Several studies reported the toxicity of cyanobacterial extracts in Culicidae (Ayala et al., 2019; Harada et al., 2000; Kiviranta and Abdelhameed, 1994; Rao et al., 1999). Kiviranta et al., (1993) found that toxicity was associated with hepatotoxins and neurotoxins and that *Microcystis aeruginosa* cyanobacterium was the most lethal to the larvae of *Aedes aegypti* mosquito. Ayala et al., (2019) also found that extracts from the benthic cyanobacteria *Moorea producens* exhibited high toxicity against *A. aegypti* larvae.

Relatively high concentrations seem to be required to achieve toxicity. The larvae of *Aedes aegypti* had a lethal concentration ( $LC_{50}$ ) of

$14,900 \mu\text{g l}^{-1}$  when exposed for 48 h to microcystin isolated from the *Microcystis aeruginosa* (Kiviranta et al., 1992). Microcystin causes lesions in the epithelial cells of larvae's midgut resulting in their death (Saario et al., 1994). Microcystin impact on other Culicidae species was also investigated, with a toxin concentration of  $20,000 \mu\text{g l}^{-1}$  resulting in 98.2 and 88.1% mortality in the second instar larvae of *Culex* and *Anopheles* sp., respectively (Singh et al., 2003). These concentrations are 3–4 times below the maximum concentration of microcystin that can be found in nature. For instance, Herrera et al., (2018) reported a microcystin concentration of  $57290 \mu\text{g l}^{-1}$  in Porc II reservoir (Columbia).

In ecotoxicology, toxicity can also be achieved during the process of bioaccumulation (Lee et al., 2019b); but see below). Few studies investigated this process with cyanotoxins. Among cyanotoxins and in addition to unidentified cyanobacterial extracts (Becher and Jüttner, 2006; Becher and Jüttner, 2005), only studies on the impact of microcystin and anatoxins on *Chironomus* spp. were reported. Stanković et al. (2020) revealed that *Chironomus riparius* larvae population suffered oxidative stress and DNA damage fed by *Anabaena* sp. (microcystin-LR producing cyanobacterium) (Stanković et al., 2020). Alterations in the tracheal system and severe histological damage due to microcystin bioaccumulation were also reported in the mayfly *Ecdyonurus angelieri* larvae exposed to  $5 \mu\text{g l}^{-1}$  of microcystins (Liarte et al., 2014). Overall, similar studies are crucially missing to allow comparisons among taxa and concentrations.

#### 3.4.2. Delayed hatching and development

Cyanotoxins can induce sublethal effects on insects. These toxins can impact egg hatching and development of aquatic insects. Rey et al., (2009) found that Mosquito larvae of *Aedes aegypti* exposed to the *Microcystis aeruginosa* strain-producing microcystin developed slower than controls or those grown with the strain that does not produce microcystin. In addition, Smith et al., (2008) examined the effect of microcystin on eggs, hatchling nymph, and pre-emergence nymph of mayflies. They found that a  $100 \mu\text{g l}^{-1}$  of MC-LR microcystin delayed hatching of mayflies' eggs. Large nymphs showed 100% survival rates over seven days exposure to  $10,000 \mu\text{g l}^{-1}$  of MC-LR (Smith et al., 2008).

#### 3.4.3. Cyanotoxins bioaccumulation and propagation to terrestrial food webs

Although low cyanotoxin concentrations might not have severe impacts on some aquatic insects, they can still bioaccumulate in aquatic insects to cross the aquatic/terrestrial boundary and propagate into riparian food webs (Xue et al., 2016). Chen and Xie, (2008) detected up to  $11.54 \mu\text{g g}^{-1}$  (based on dry weight) of microcystin in *Chironomus* sp. larvae taken from the large, shallow eutrophic Lake Chaohu (China) that displays cyanobacterial blooms. Xue et al., (2016) also studied the bioaccumulation of three MC congeners (-LR, -RR and -YR) in the chironomid larvae of *Tanytus chinensis* in Lake Taihu, China. They found that



**Table 2**

Summary of types of cyanotoxins, their concentrations and effects when applied to aquatic insects.

Toxin	Order	Studied species	Size (mm)/ life stage	Mode of exposure and applied concentration	Result or effect	Reference	Method used
Microcystin <sup>i</sup>	Diptera	<i>Aedes aegypti</i>	3rd and 4th instar	6 larvae placed in a 3 ml tube exposed to 14900 µg l <sup>-1</sup> of <i>Microcystin aeruginosa</i> extracts	LC50 in 48 h	(Kiviranta et al., 1992)	Crude toxin was extracted using high-performance liquid chromatography (HPLC) on an ODS (octadecylsilanated silica gel)
		<i>Culex</i> sp.,	2nd instar	Exposed to 20000 µg l <sup>-1</sup> of crude aqueous extract of <i>Microcystis aeruginosa</i>	98.2 % mortality	(Singh et al., 2003)	From <i>Microcystis aeruginosa</i> using thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC)
		<i>Anopheles</i> sp.,	2nd instar	Exposed to 20000 µg l <sup>-1</sup> of crude aqueous extract of <i>Microcystis aeruginosa</i>	88.1% mortality	(Singh et al., 2003)	From <i>Microcystis aeruginosa</i> using thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC)
		<i>Anopheles</i> sp.,	1st instar	Exposed to 7450 µg l <sup>-1</sup> of extracted microcystin**	LC90	(Mosleh and El-Ela, 2011)	According to the method of Abou-El-Ela (2006)*
		<i>Chironomus</i> sp.	Not reported	Exposed to 41 µg l <sup>-1</sup> of microcystin in a dam reservoir	Chironomidae did not disappear	(Gerard and Lance, 2019)	High-pressure liquid chromatography (HPLC) with MC detection limit (DL) of 0.04 µg l <sup>-1</sup>
	Ephemeroptera	<i>Ecdyonurus angelieri</i>	Not reported	Exposed for 3 h to 5 µg l <sup>-1</sup> of microcystin in Petri dish with artificial substrate	toxin bioaccumulation, severe histological damage and alterations in the tracheal system were evident	(Liarte et al., 2014)	Commercial MC-LR and MC-LW (ALEXIS Biochemicals)
		Not reported	Not reported	Exposed to 41 µg l <sup>-1</sup> of microcystin in a dam reservoir	Ephemeroptera did not disappear	(Gerard and Lance, 2019)	High-pressure liquid chromatography (HPLC) with MC detection limit (DL) of 0.04 µg l <sup>-1</sup>
		<i>Hexagenia</i> spp.	3 to 7 mg	Exposed to 300 µg l <sup>-1</sup> of cell-bound microcystins produced by <i>M. aeruginosa</i> ,	no lethality or growth impairments	(Shahmohammadloo et al., 2020)	On-line solid phase extraction coupled to liquid chromatography quadrupole time-of-flight high resolution mass spectrometry detection limit (DL) of 0.05 µg l <sup>-1</sup>
		<i>Hexagenia limbata</i>	22.15 – 34.28 mm	<i>Hexagenia</i> captured from a lake with <i>Microcystis</i> sp. blooms	0.64 µg g <sup>-1</sup> dry weight measured microcystin concentrations in <i>Hexagenia</i>	(Woller-Skar et al., 2020)	Microcystin extracted from samples and detected using HPLC-MS/MS. ELISA was also used to achieve lower detection limits.
	Trichoptera	Not reported	Not reported	Exposed to 41 µg l <sup>-1</sup> of microcystin in a dam reservoir	Trichoptera did not disappear	(Gerard and Lance, 2019)	High-pressure liquid chromatography (HPLC) with MC detection limit (DL) of 0.04 µg l <sup>-1</sup>
Anatoxin <sup>ii</sup>	Diptera	<i>Chironomus</i> spp.	> 20 mm	Exposed to 200 µg l <sup>-1</sup> of anatoxin extracts	No significant mortality	(Toporowska et al., 2014)	Crude extract of <i>D. lemmermannii</i> determined using liquid chromatography (HPLC, Beckman)
		<i>Chironomus</i> spp.	7 days old	12 larvae of <i>C. dilutus</i> placed in 200 ml exposed to of 2 µg l <sup>-1</sup> <i>Phormidium</i> extracts	Species reduced	(Anderson et al., 2018)	Extracts from <i>Phormidium</i> cyanobacteria using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with a detection limit (DL) of 0.28 µg l <sup>-1</sup>
		<i>Aedes aegypti</i>	3rd and 4th instar	6 larvae placed in a 3 ml tube exposed to 27000 µg l <sup>-1</sup> <i>Anabaena circinalis</i> extracts	LC50 in 24 h	(Kiviranta et al., 1993)	Extracted from <i>Anabaena circinalis</i> using high performance liquid chromatography (HPLC)
	Ephemeroptera	<i>Deleatidium</i> spp.	4 to 6 mm	Exposed to 40 ml of 300 µg l <sup>-1</sup> commercially purified anatoxin	No significant mortality	(Kelly et al., 2020)	Commercially available anatoxin fumarate (Abcam) determined by liquid chromatography tandem mass spectrometry (LC-MS/MS) with a detection limit (DL) of 0.05 µg l <sup>-1</sup>

(continued on next page)

Table 2 (continued)

Toxin	Order	Studied species	Size (mm)/ life stage	Mode of exposure and applied concentration	Result or effect	Reference	Method used
<b>Nodularin</b> <sup>iii</sup>	Diptera	<i>Anopheles</i> sp.,	1st instar	Exposed to 14390 $\mu\text{g l}^{-1}$ of nodularin**	LC90	(Mosleh and El-Ela, 2011)	Extracted from <i>Nodularia harveyana</i> (without additional details)
<b>Cylindrospermopsin</b> <b>Saxitoxins</b> <b>BMAA</b>		Not studied					

i: can reach up to MC-LR reached up to 57290  $\mu\text{g l}^{-1}$  in nature (Herrera et al., 2018).

ii: can reach up to 25  $\mu\text{g l}^{-1}$  in nature (Wood et al., 2017).

iii: can reach up to 2  $\mu\text{g l}^{-1}$  in nature (Heresztyn and Nicholson, 1997).

\*: article not available online.

\*\*: without further details.

the MC that accumulated in *T. chinensis* resulted from the ingestion of MC-producing cyanobacteria.

Cyanotoxin bioaccumulation was also documented in insects at adult (terrestrial) stage. Microcystin concentrations reached up to 0.64  $\mu\text{g g}^{-1}$  dry weight in multiple terrestrial life stages of *Hexagenia limbata* providing evidence of the transfer of microcystins from aquatic to terrestrial food webs (Woller-Skar et al., 2020). Kelly et al. 2020 also detected a bioaccumulation of dihydroanatoxin-a in the tissues of *Deleatidium* spp. Larvae (Kelly et al., 2020). Moy et al., (2016) detected MC in both mayflies (*Hexagenia*) and their consumers (*Tetragnathidae* spiders, *Protonotaria citrea* and *Prothonotary* Warblers). Brown bats collected near Little Traverse Lake (Leelanau County, Michigan, USA) was also found to bioaccumulate cyanotoxins (Woller-Skar et al., 2015). Fecal DNA analysis of these bats accumulating microcystins suggested that emerging aquatic insects (including mayflies) were a primary component of their diet (Jones, 2016). Nevertheless, the ecophysiological impacts of this bioaccumulation of cyanotoxins in terrestrial organisms remain to be determined.

#### 3.4.4. Heterogeneity of methods and cyanotoxin concentrations: cohesive protocols are needed

There is an enormous variation in the methods used for cyanotoxins extraction and quantification in the available literature (Table 2). For instance, using high-pressure liquid chromatography (HPLC) analysis, Laurén-Määttä et al., (1995) found that bioaccumulation of microcystin was undetectable when *Chironomus* sp. does not feed directly on toxic cyanobacteria. This does not mean necessarily that there are no cyanotoxins in *Chironomus* larvae. However, the HPLC method often has a high limit of detection (LOD) (Easterling et al., 2020) preventing the detecting of microcystin in small size insects like *Chironomus*. To achieve lower limit of detection (LOD), Woller-Skar et al., (2020) used ELISA with a LOD between 0.0008 and 0.0125  $\mu\text{g/g}$  dry weight (DW) rather than HPLC with a LOD between 0.4081 and 0.7709  $\mu\text{g/g}$  DW. Depending on the question addressed, the ELISA technique may be more appropriate to detect sublethal concentrations.

Moreover, the cyanotoxin concentrations applied in bioassays are quite variable across studies, making the comparisons difficult. The toxin concentrations used in ecotoxicological studies range from 5 to 20,000  $\mu\text{g l}^{-1}$  for microcystin (Table 2). The methodology used to assess toxicity further makes more difficult to compare studies since the metric used to assess lethal threshold varies in either the time of exposure (24 h or 48 h) or the method used to infer mortality (Table 2). Another crucial methodological factor relies on the importance of providing the size and/or stage of the insect larva. A laboratory experiment by conducted Mosleh and El-Ela, (2011) to determine the efficacy of microcystin and nodularin against the different larval instars, pupal and adult stages of *Anopheles multicolor* (Culicidae) showed that the fourth larval instar was the most resistant instar while the 1st instar was the most sensitive. This

has a huge impact on the obtained results and prevents possible comparison and further meta-analysis. Although underestimated and often not detailed in most studies, exposure scenario greatly impacts the results of ecotoxicological experiments (Table 2). For instance, the toxicity to microcystin varies depending on the mode of exposure. The lethal concentration of microcystin depends on whether the toxin is cell-bound or extracellular (Shahmohamadloo et al., 2020), but overall existing knowledge makes it difficult to quantify and clearly conclude on this effects of mode of exposure.

Finally, the source of cyanotoxin matters to identify and compare the results of bioassays. In the literature authors either use a commercially available cyanotoxin or extract cyanotoxins from cyanobacterial cultures. Toporowska et al., (2014) found that Cyanobacterial extracts were more toxic to riverine larvae of *Chironomus* spp. than pure cyanotoxins (Toporowska et al., 2014). Therefore, not only the identity of the toxin is important but also its origin.

#### 3.5. Transgenic cyanobacterial strains for Diptera control

##### 3.5.1. *Bacillus thuringiensis* as an effective biological control

Traditional pest management methods, which target all stages of the insect life cycle using pesticides are increasingly problematic, especially when these chemicals kill non-target insects that are useful for some ecosystem services, like dragonflies or honeybees. Biological control is a sustainable method to target specific insects. *Bacillus thuringiensis* is regarded as a good biological way to control insects (Zaritsky et al., 2010). It is considered safe, highly specific, and easily mass produced. The subspecies *Bacillus thuringiensis* subsp. *israelensis* (Bti) is used as an effective biological control agent against larvae of many insect species. When the larvae ingest these products, their gut membrane is damaged through ion leakage. The subspecies *israelensis* of *Bacillus thuringiensis* (Bti) was the first to be used as an agent to control aquatic insects like Blackflies (*Simulium* spp.) (Pereira et al., 2013), chironomid midges (Kondo et al., 1995) and mainly mosquito-borne diseases.

However, due to short half-life in many environments, the Bti toxin has limitations. Its efficacy is diminished in polluted or organic-rich waters, requiring much higher amounts. For instance, its toxicity can decrease by about 70% when mixed with leaf litter (Facciponte et al., 2018). One of the best approaches to overcome its short half-life in nature is by expressing the toxin genes in recombinant cyanobacteria as a continuous delivery system to aquatic insects (Boussiba et al., 2000). Cyanobacteria are exceptional candidates to control mosquito larvae. Due to their floating capacity, they can stay in the same microhabitat of larvae. Moreover, cyanobacterial pigments can act as UV-B photoprotectors, preventing Bti toxin deterioration due to sunlight exposure (Manasherob et al., 2003).

### 3.5.2. *Bacillus* toxins-expressing cyanobacteria

First attempts to express *Bti* toxin in cyanobacteria were carried out in 1987. It was then followed by a significant progress during the 90's (Murphy and Stevens Junior, 1995; Murphy and Stevens, 1992; Tandeau de Marsac et al., 1987). Table 3 summarizes the different reported mosquito larvicidal activities of transgenic cyanobacterial strains. The efficiency of transgenic mosquito larvicidal cyanobacteria was mostly tested on *Anopheles* sp., *Aedes* sp., and *Culex* sp. mosquitoes. Significant differences exist in toxicity among the clones expressing genes of mosquitocidal toxins in cyanobacteria. However, these differences are hard to compare due to the use of different instars, various metric to measure mortality, *Bacillus* sp. genes and cyanobacteria species.

The main cyanobacterial strains used in this context are *Anabaena* PCC 7120, *Anacystis nidulans* R2, *Synechococcus* PCC6301, *Synechocystis* PCC6803, *Synechococcus* PCC7002, and *Synechococcus* PCC7942. The capability of other strains needs to be further investigated. For instance, *Phormidium animalis* was successfully ingested and assimilated by larval *Anopheles albimanus*, making it a good candidate to introduce mosquitocidal toxins for malaria control in Mexico region (Vázquez-Martínez et al., 2003).

### 3.5.3. Distribution of study cases among insect taxa

Among the 21 articles classified in this section, only two articles discussed the effect of transgenic *Bacillus* toxin expressing cyanobacteria on Blackflies and chironomid midges. The remaining articles focus on the use of these transgenic cyanobacteria to control mosquito-borne diseases. Details of the distribution of these studies based on the used cyanobacteria strain to control Culicidae genera is presented in Fig. 5. *Anabaena* strain PCC 7120 were the most studied with 8 study cases on the 3 Culicidae genera while *Synechocystis* PCC6803 were least studied with one study case only on *Aedes*. *Anacystis nidulans* R2 and *Synechococcus* PCC6301 were only studied on *Culex* and *Synechococcus* strain PCC7942 were never used on *Aedes*. It remains unclear if this heterogeneity is linked to differences in the ability of mosquito species to ingest

some strains and not others.

### 3.5.4. Use of genes expressed by other *Bacillus* species

Genes encoding the mosquito larvicidal toxins from *Bacillus sphaericus* were also introduced into cyanobacterial strains to control mosquitoes. Genes of *Bacillus sphaericus* 2297 were expressed in *Anabaena* sp. 7120 (nitrogen-fixing filamentous cyanobacterium) and showed high toxicity against *Culex pipiens*, but lower toxicity against *Anopheles sinensis* larvae (Xu et al., 1993). A 3.6 kb *HindIII* DNA fragment from *Bacillus sphaericus* 1593 M was expressed in the cyanobacterium *Anacystis nidulans* R2 and showed similar toxicity levels as *Escherichia coli* against *Culex* mosquito larvae (Tandeau de Marsac et al., 1987). Genes encoding the mosquitocidal binary toxin of *Bacillus sphaericus* 2362 were introduced into *Synechococcus* PCC6301 and exhibited significant toxicity against 2-day-old and 6-day-old *Culex quinquefasciatus* larvae with LC50 of  $2.1 \times 10^5$  and  $1.3 \times 10^5$  cells ml<sup>-1</sup>, respectively. However, after 20 generations of non-selective growth (without plasmid selection), mosquitocidal activity decreased tenfold (Sangthongpitag et al., 1997).

### 3.5.5. Risk to other aquatic organisms

Although the use of commercial formulations of *Bacillus thuringiensis* subsp. *israelensis* (Bti) remains much better than traditional pest management methods, its effects on non-target organisms are still a matter of debate. Studies were conducted to analyze the effect of Bti-based mosquito control on non-target aquatic organism like invertebrates (Caquet et al., 2011; Lagadic et al., 2014), and phytoplankton (Fayolle et al., 2016). They showed that the dynamics of aquatic organisms in terms of abundance, richness and diversity was driven by environmental factors, rather than by Bti-treatment. However, high doses of Bti-AS were shown to induce genotoxicity, intestine damage, and mortality in *Leptodactylus latrans* tadpoles (Lajmanovich et al., 2015). Intensive application of Bti above the recommended rates can also affect the microbial communities, primary production, nutrient cycling and thus the functioning of

**Table 3**  
Reported mosquito larvicidal activities of transgenic cyanobacterial strains.

Cyanobacteria strain	Expressed genes	Targeted insect	Mortality		References
			Applied concentration	% after 12 h, 24 h or 48 h	
<i>Anabaena</i> strain PCC 7120	<i>Bacillus thuringiensis</i> subsp. <i>israelensis</i> cry genes: cryIVA (cry4A), cryIVD (cry11A), and p20	<i>Aedes</i> sp. 4th instar	$0.35 \times 10^5$ cells ml <sup>-1</sup>	50% mortality after 24 h	(Khasdan et al., 2003)
		<i>Anopheles</i> sp. 3rd instar	between 3.92 and $15.7 \times 10^5$ cells ml <sup>-1</sup> *	50% mortality after 24 h	(Ketseoglou and Bouwer, 2012)
		<i>Anopheles</i> sp. 3rd instar	$9.24 \times 10^5$ cells ml <sup>-1</sup>	50% mortality after 24 h	(Ketseoglou and Bouwer, 2013)
		<i>Aedes</i> sp. 3rd instar	$7.5 \times 10^5$ ng chl-a ml <sup>-1</sup>	50% mortality after 24 h	(Lluisma et al., 2001)
			$1.42 \times 10^5$ cells ml <sup>-1</sup>	50% mortality after 24 h	(Ketseoglou and Bouwer, 2012)
			Not reported $5 \times 10^5$ cells ml <sup>-1</sup>	Not reported 100% mortality after 24 h	(Manasherob et al., 2003) (Wu et al., 1997)
	<i>Bacillus sphaericus</i> 2297 genes (p42 and p51)	<i>Culex</i> sp.	$4.1 \times 10^5$ cells ml <sup>-1</sup>	92% mortality after 24 h	(Xu et al., 1993)
<i>Anacystis nidulans</i> R2	<i>Bacillus sphaericus</i> 1593 M	<i>Culex</i> sp. 2nd instar	1 µg ml <sup>-1</sup>	100% mortality after 48 h	(Tandeau de Marsac et al., 1987)
<i>Anacystis nidulans</i> R2	<i>Bacillus thuringiensis</i> subsp. <i>israelensis</i> cry4Ba gene	<i>Culex</i> sp. 1st instar	$7.5 \times 10^7$ cells ml <sup>-1</sup>	90% mortality after 48 h	(Soltesrak et al., 1995)
<i>Synechococcus</i> PCC6301	<i>Bacillus sphaericus</i> 2362 genes	<i>Culex</i> sp. (2 to 6 days old)	$2.1 \times 10^5$ cells ml <sup>-1</sup>	50% mortality after 48 h	(Sangthongpitag et al., 1997)
<i>Synechococcus</i> strain PCC7002	<i>Bacillus thuringiensis</i> subsp. <i>israelensis</i> cryIVD gene	<i>Culex</i> sp. 1st instar	$2 \times 10^7$ cells ml <sup>-1</sup>	0% mortality after 12 h	(Murphy and Stevens, 1992)
		<i>Aedes</i> sp. 1st instar	$2 \times 10^7$ cells ml <sup>-1</sup>	75% mortality after 12 h	(Stevens et al., 1994)
	<i>Bacillus thuringiensis</i> subsp. <i>israelensis</i> cry4Ba gene	<i>Aedes</i> sp. 2nd instar	10 mg protein ml <sup>-1</sup>	45% mortality after 48 h	(Angsuthanasombat and Panyim, 1989)
<i>Synechocystis</i> strain PCC6803	<i>Bacillus thuringiensis</i> subsp. <i>israelensis</i> cry4Ba gene or cyt1Aa	<i>Aedes</i> sp. 3rd instar	1 mg soluble protein ml <sup>-1</sup>	30% mortality after 48 h	(Chungiatupornchai, 1990)

\*Depending on species.

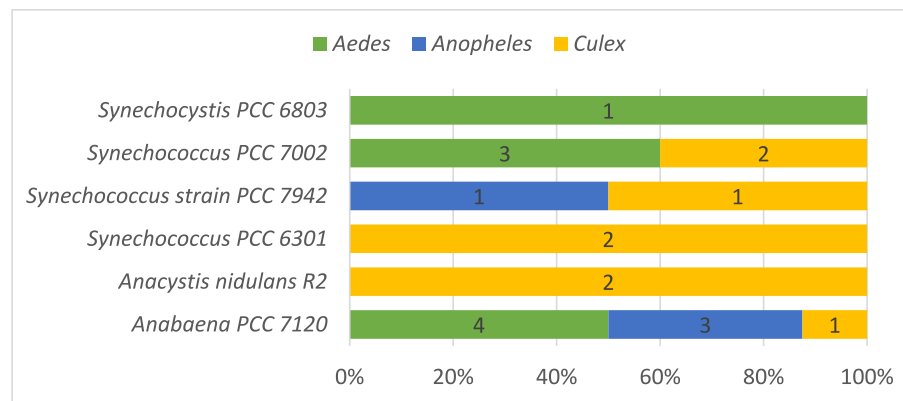


Fig. 5. Distribution of studies according to the use of transgenic cyanobacteria to control mosquitoes (N = 20).

aquatic food webs (Duguma et al., 2015). Bti also has the drawback of being toxic to other species of Diptera such as chironomids that play a significant role in the functioning of freshwater ecosystems (Hughes et al., 2005). However, species belonging to different chironomid sub-families were found to be relatively tolerant until high concentrations of Bti. Yiallourous et al., (1999) reported that Chironomids species are susceptible to high Bti. concentrations, with LC<sub>50</sub> values (24 h) at concentrations 40 to 60-fold higher than those used for LC<sub>50</sub> of *Aedes aegypti* (LC<sub>50</sub> 24 h). The use of transgenic cyanobacterial strains expressing Bti toxins may be an efficient way to target Diptera without affecting non-target organisms like tadpoles through the direct application of commercial Bti in nature. However, further research is needed to investigate the candidate transgenic cyanobacterial strains that would be ideal food source for mosquitoes but not for the other dipteran species.

### 3.6. Climate change impacts on the functional link between cyanobacteria and insects

Over the last decades, many studies have demonstrated that cyanobacterial blooms are promoted by higher temperatures and nutrient loadings (Burford et al., 2020; Davis et al., 2009; Fadel et al., 2019; Jöhnk et al., 2008; Paerl and Huisman, 2008; Slim et al., 2014). Changing climatic conditions are predicted to increase the frequency and toxicity of cyanobacterial blooms (O'Neil et al., 2012). Current climate trajectories (increase in temperature, drought, intense precipitation, and reduced wind speed) will promote seasonal cyanobacterial blooms as they will grow more efficiently at higher temperatures and persist longer under extreme wet/dry cycles with stable thermoclines (IPCC, 2007; Paerl et al., 2016).

Changing climate conditions will directly impact aquatic insects. Over the past decades, warming decreased the number of emergent aquatic insects (Jonsson et al., 2015), reduced richness (Timoner et al., 2021), emergence and peak biomass timing (Shipley et al., 2022), modified their body size (Jonsson et al., 2015), and disrupted physiological processes (Deutsch et al., 2008). Such climate change impacts on aquatic insects may have top-down effects on the cyanobacterial biomass through grazing for instance, but such a link has never been investigated so far.

Climate change alters freshwater ecosystems. The more frequent and toxic cyanobacterial blooms during summer seasons under future climatic scenarios will directly impact aquatic insects. As shown in subsection 3.4, such increase in toxic cyanobacterial blooms and cyanotoxin concentrations can result in the decline of aquatic insects' population and biodiversity. A cyanobacteria bloom can result in the elimination of other primary producers, offering only poor-quality food source for aquatic insects.

More work should be done in the future on this link. In parallel,

cyanotoxins may alter aquatic insects' size and development and may be lethal at high concentrations. Moreover, an indirect consequence of cyanobacterial blooms is oxygen depletion through the decay of their biomass (Anderson, 2009). More importantly future blooms will result in more intense hypoxia in freshwater ecosystems (Jane et al., 2021). This can kill aquatic insects of certain taxa and promote anoxia-tolerant insects like *Chironomus*. Such impact on development and population of aquatic insects will have serious consequences on terrestrial ecosystems, as the emergence of aquatic insects represents an important resource flow from aquatic to terrestrial environments (Previšić et al., 2021). Several terrestrial organisms (like birds, bats, lizards, frogs, etc.) consume emergent aquatic insects.

In addition to the direct impact of higher cyanotoxin concentrations expected because of climate change on insects, an interactive effect of cyanotoxins and higher temperature on aquatic insects is expected. Although such combination effect was not investigated yet on aquatic insects, studies on the combination of warming and contaminants showed possible additive or non-additive interactive effects on freshwater invertebrates (Dinh et al., 2022). Another issue is the focus of many studies on the impact of single or multiple environmental variable (temperature, nutrients, precipitation, etc.) on cyanobacteria or aquatic separately without establishing a link between them and/or different components of the aquatic ecosystem. Although such linking can be more complex and challenging, it needs to be done because the impacts of climatic conditions on water temperature, thermal stratification, and nutrient loadings can simultaneously impact the ecology of harmful cyanobacteria as well as the freshwater inhabitants, in particular their consumers (zooplanktons and aquatic insects).

## 4. Gaps and research priorities

Significant gaps in the relationship between cyanobacteria and aquatic insects have also been demonstrated in this review. Below, we address some major issues to be considered in future studies on this topic:

1. The effect of cyanotoxins was never studied on several aquatic insect taxa. For instance, the impact of microcystin, the most studied cyanotoxin, was never studied on dragonflies and damselflies (Odonata) that spend most of their life in freshwater before moving to land. Odonata are directly exposed to cyanotoxins present in the water, and indirectly by consuming mosquito larvae that have bio-accumulated cyanotoxins. Odonata are given as an example here to show research opportunities on investigating the impact of cyanotoxins across trophic levels. These research opportunities can be extended to include other aquatic insects like those living at the water-air interface (e.g., water striders, gerris). Although they can be in contact with the toxin through walking or breathing, these insects



may not be directly exposed to the toxin as much as Odonata larvae that are present at different water depths rather than the water–air interface, depending on the side of the interface they colonize. These biological models would enable to separate the direct and indirect effects of cyanotoxins on aquatic insects: directly by being exposed to cyanotoxin in water during their larval stage, and indirectly by developing in clean water and then feeding on aquatic insects that have bioaccumulated cyanotoxin.

2. More than 80% of the published studies are on the larval stage of aquatic insects. More studies should be conducted on egg hatching and the bioaccumulation of cyanotoxins in adult stages. Studies on egg hatching will help to follow up the possible impact of the toxin on larval size/development. A delayed hatching and development to adult stage can impact other organisms feeding on these adult insects. Studies on bioaccumulation of cyanotoxins in adult stage is also needed to document the transfer of cyanotoxins to terrestrial food web.
3. Only few cyanotoxins were studied so far for their impact on aquatic insects (eg, microcystin, nodularins, and anatoxins). Other cyanotoxins (eg, cylindrospermopsin, BMAA) should be investigated to rank them according to the level of their toxicity for each aquatic insect taxa. In addition, the impact of mixing two or more different cyanobacteria was never tested so far (so-called cocktail effect). Cyanobacteria often appear in communities, and aquatic insects are likely to be routinely exposed simultaneously to several toxins in various relative concentrations. The effects of varying the relative concentrations of different toxins should be determined.
4. While the efficiency of *Bti* expressing cyanobacteria to control mosquitos was relatively well covered, there is a lack of research on the impact of larvicidal engineered cyanobacteria on other families of Diptera, particularly Chironomidae that are considered less problematic for humans and the environment compared to mosquitoes but susceptible to high *Bti* concentrations.
5. The effects of cyanotoxins at the population level were never studied. These toxins may not result in a drastic acute effect on populations of aquatic species when used as food sources. However, the oxidative stress and DNA damage caused by the toxins may pose a danger later to the successive generations that are exposed intermittently or continuously. The effects of cyanotoxins on insects should be studied beyond the tolerance thresholds to include life history traits. Common approaches used in ecotoxicological studies should be applied to score the impact of cyanotoxins on developmental time, reproduction rate, fertility, longevity etc. Such holistic approaches at the population level will certainly help to understand the consequences of cyanotoxins on the dynamics of community structures – but this topic remains unexplored.
6. Aquatic insects live in a multifactorial world. Other stressors like high temperature, low dissolved oxygen or water acidity can occur and often interact with each other to generate unanticipated effects on aquatic organisms (Koussoroplis et al., 2017). The interactive effects of cyanotoxins combined with such environmental stressors was never studied. Coincidentally, larger amount of cyanotoxins may be released during warm seasons/periods when aquatic insects are already experiencing high temperatures and frequent hypoxia. Additive effects may be anticipated. Cyanotoxin may increase the sensitivity of aquatic insects to other stressors in a similar way than the interactive effects of high water temperature and hypoxia (Harrison et al., 2018).
7. Numerous hydrodynamic ecological models like PCLake, Dyresm-CAEDYM, GLM-AED, and others were developed to simulate the impact of zooplankton grazing on the phytoplankton communities and cyanobacterial biomass (Bucak et al., 2018; Fadel et al., 2019, 2017; Gal et al., 2009). These approaches remain to be applied to simulate the impact of grazing by aquatic insects on cyanobacterial biomass. This understudied functional link is critical to better understand ecosystem functioning and to improve water quality for

humans by testing different management scenarios that can reduce cyanobacterial blooms.

8. Spatial-temporal distribution of cyanotoxins and cyanobacteria has been assessed using field sampling and satellite images that can map cyanobacteria biomass through their unique pigment, phycocyanin (Sharaf et al., 2019). However, a study that links their distribution and that of aquatic insects is lacking and therefore recommended to increase the understanding of their relationship.

## 5. Conclusions

Our extensive systematic literature review (SLR) provided an objective and systematic presentation of data from 104 research articles linking cyanobacteria and aquatic insects. The review highlights the tight functional relationship between these two important components of aquatic systems. Cyanobacteria were widely reported in the habitat of numerous aquatic insects. They can be considered as an important food source for them. In some cases, they were the main microorganism in the gut flora of several insects. This made some genetically engineered cyanobacterial strains good candidates to control mosquito larvae. When ingested, these engineered cyanobacterial strains express *Bti* mosquitocidal toxins, lethal to several species of mosquito larvae that are vectors of dangerous parasites like malaria.

Some cyanobacterial species can produce a wide variety of cyanotoxins that can be lethal to aquatic insects. But we noticed large variations in the concentration thresholds among insect taxa and species. When not lethal, cyanotoxins can bioaccumulate in these insects and persist in their terrestrial life stages providing a mode of transfer of these toxins from aquatic to terrestrial food webs, yet this aspect remains understudied. The role and the quantity of cyanotoxins in terrestrial food webs remains underexplored.

Aquatic ecosystems are vital for humans due to the different services they provide including potable water, hydropower, fishing, recreational activities, irrigation, etc. Anthropogenic activities, rising water temperature and CO<sub>2</sub> concentrations are future challenges that will impact the aquatic ecosystems and their inhabitants which may increase or decline. Future climate projection models indicate that blooms of cyanobacteria are more likely to intensify with rising temperatures (Fadel et al., 2019), preventing the use of water for humans in these ecosystems due to the production of cyanotoxins. As shown in the reviewed studies, cyanotoxins pose a serious threat to aquatic insects and can be transferred to terrestrial food webs as well. Climate change will also impact the aquatic insect communities, but the observed effects may be better comprehended and anticipated by considering the interactive effects between these environmental drivers and cyanotoxins. These responses to changing environmental patterns associated with climate change are key topics for future entomological research.

## CRedit authorship contribution statement

**Ali Fadel:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Fernando Guerrieri:** Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Sylvain Pincebourde:** Conceptualization, Writing – review & editing, Supervision.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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