Cyanobacteria, Blooms and Cyanotoxins in East African Lakes

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Cyanobacteria, algal blooms and cyanotoxins have become common environmental enigmas in marine, freshwater and estuarine ecosystems. In East African lakes, mainly *Microcystis, Arthrospira, Dolichospermum*, *Planktolyngbya* and *Anabaenopsis* species of cyanobacteria have been responsible for the production of anatoxin-a, homoanatoxin-a, microcystins, cylindrospermopsin and nodularin. Microcystins and anatoxin-a have been implicated as the proximal cause of indiscriminate fish deaths and epornitic mortality of lesser flamingos

Arthrospira fusiformis | cylindrospermopsin | hepatotoxicity | lesser flamingos | Lake Victoria | crater lakes

1. Introduction

Globally, cyanobacteria (CYB), harmful algal blooms (CYBHAB) and cyanotoxins (phycotoxins) have become a common occurence in marine, freshwater and estuarine ecosystems, attributed to anthropogenic pollution and accelerated climate change [1]. Today, CYBHAB have attracted research interest because of their negative effects on ecosystems and humans. Considered broadly, CYB are photosynthetic prokaryotes that occur naturally in terrestrial as well as aquatic ecosystems [2] and their copious production of phycobilin pigment confers upon them a bluish tint at high concentrations, making them sometimes called blue-green algae [3]. CYB are Gram-negative bacteria, that under certain suitable conditions, are able to proliferate and form CYBHAB or scums. Most cyanobacterial scums and blooms has geosmin and methylisoborneol, which affects the taste of water. While the biology and ecology of CYB has been a subject of intensive research globally, there is a paucity of clearly articulated information regarding factors and processes that regulate toxin production in most cyanobacterial species [4]. Cyanobacterial blooms are *as noticeable, CYBHAB with appreciable effects, including scum formation, marked discoloration of surface waters as well as fish, human, or other invertebrate mortalities* [5]. While many microalgae are present in blooms, CYB are the major algae of toxicological relevance as they can produce toxic metabolites (cyanotoxins) [2].

CYB are usually associated with the production of nocive cyanotoxins. The great diversity and high metabolic potential of CYB implies that there are other unknown or at least little studied cyanotoxins. According to CyanoMetDB (a comprehensive database of cyano-metabolites), at least 2000 molecules, including more than 300 microcystin congeners, are already known [6]. Cyanotoxins are contaminants of emerging concern that are

potentially (eco)toxic. They can adversely impact ecosystem services provided by water resources by depleting oxygen, altering food webs, species assemblages and poisoning animals and humans [7]. Examples of cyanotoxins include cyclic hepatotoxic peptides (microcystins, nodularins), dermatoxic, cytotoxic, genotoxic or neurotoxic alkaloids, polyketides and amino acids (lyngbyatoxin-a, cylindrospermopsins, anatoxins, saxitoxins, aetokthonotoxin, lipopolysaccharides (endotoxins), guanitoxin, beta-*N*-methylamino-L-alanine and aplysiatoxins) [7]. The frequently encountered cyanotoxins are anatoxins, cylindrospermopsin (CYN), nodularins (NODs), saxitoxin, and microcystins (MCs), but the most-studied members are MCs (the -LR variant).

2. Overview of cyanobacteria, harmful algal blooms and cyanotoxins in East African lacustrine ecosystems

The East African Community (EAC), is a regional cooperation constituted by seven sovereign states as of April 2022 namely: Burundi, South Sudan, Rwanda, Democratic Republic of Congo, Tanzania, Uganda and Kenya. The region is blessed with water resources, but the water demands are largely met by eutrophic water bodies [8][9][10]. In this region, MCs and anatoxin-a (ATX) are the main cyanotoxins that garnered early toxicological interest (**Figure 1**). For example, in the DRC, the oligotrophic Lake Tanganyika has CYB (*Anabaenopsis* species, *Dolichospermum flosaquae*, and *Limnococcus limneticus*) [11][12]. Another deep oligotrophic and meromictic water resource with large volumes of exploitable methane in DRC (Lake Kivu) also has been cited to harbour CYB (*Synechococcus* species and *Planktolyngbya limnetica*) [13][14].

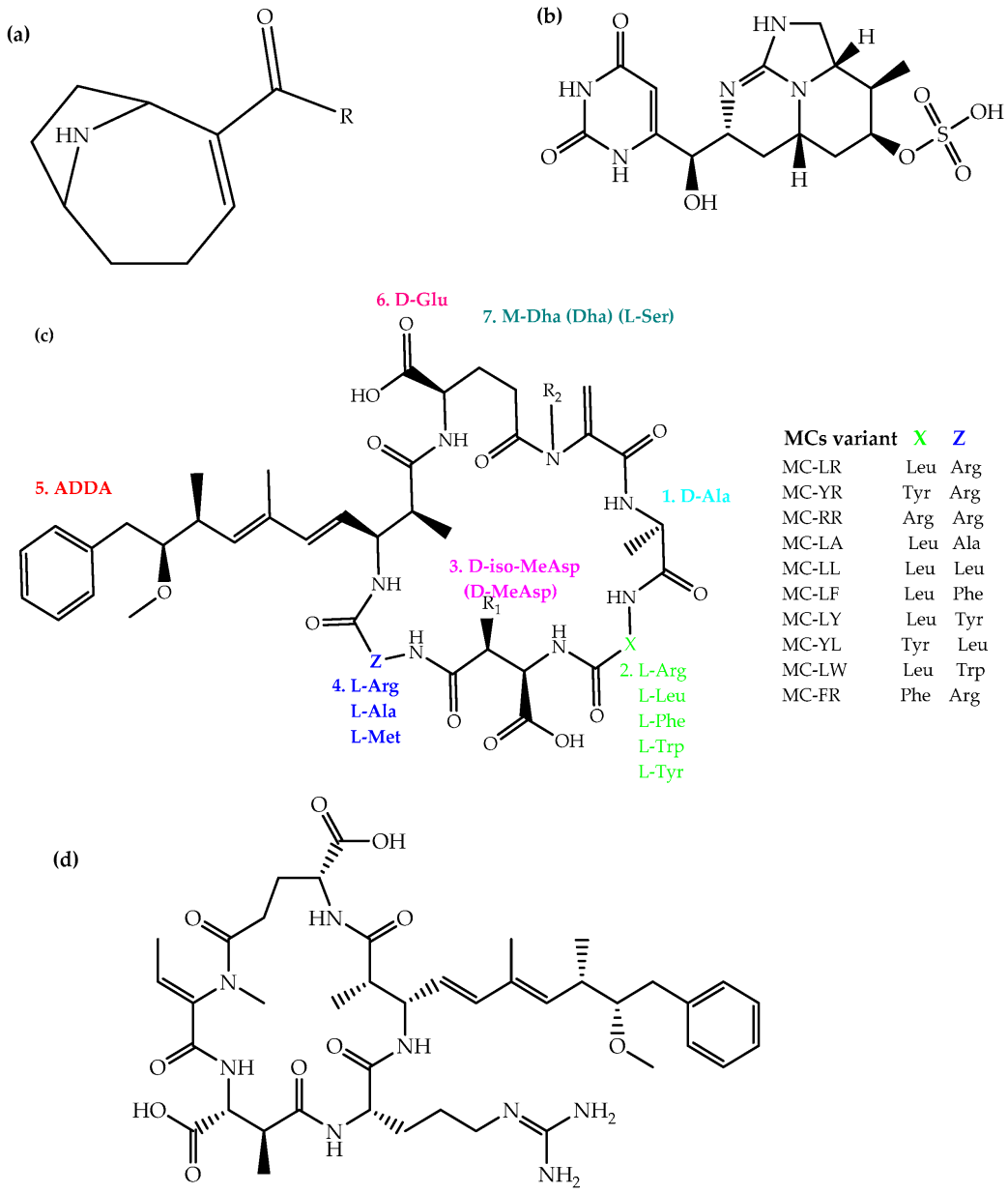

Figure 1. Chemical structure of cyanotoxins reported in EAC lacustrine ecosystems: (**a**) ATX and HATX (R = CH_3 and C_2H_5, respectively); (**b**) cylindrospermopsin; (**c**) microcystins: 1 to 7 are amino acid residues; congeners (variants) with different combinations of amino acids are shown; (**d**) nodularins.

Interesting results on CYB and cyanotoxins in EAC stems from Kenya. For example, one of the groundbreaking and pioneering reports was by Ballot et al. [15] who found intracellular ATX (0.3 to 9 and 5 to 223 µg g^{-1} dry weight (dw) and MCs (16 to 155, and 130 to 4593 µg MC-LR eq. g^{-1}) in seston samples from Lake Bogoria and Lake Nakuru. Interestingly, phycotoxins were not detected (NT) in Lake Elmenteita cyanobacterial samples. Later, MCs (2.2 µg MC-YR g^{-1} dw) and ATX (0.3 µg g^{-1} dw) were traced in axenic *Arthrospira fusiformis* (*A. fusiformis*) from Lake Sonachi, though the same species along with *Anabaenopsis* species from Lake Simbi had no detectable phycotoxins [16]. Other reports on CYB in Kenya are available for its L. Victoria part (bays, gulfs and satellite lakes) where CYB (>35%) and diatoms (>30%) of *Microcystis*, *Merismopedia* and *Dolichospermum* genera are the

primary phytoplankton. Sitoki and others [17] also hinted on the cocurence of MCs in L. Victoria water on the Kenyan portion. They concluded that the levels varied greatly between seasons, coming in concordance with later inferences of other researchers [18][19] who investigated MCs contamination of water and fish consumed by fisher communities of Winam Gulf, Homa Bay, Kisumu, Siaya and Busia counties of L. Victoria (Kenya). The latter reports showed that up to 30% of water from the sampled stations surpassed MCs compliance limit (1.0 µg L^{-1}) of WHO [19]. These reports indicate that CYBHAB is a potential year-round health threat to the riparian East African communities [19]. Another study in Lake Naivasha confirmed the dominance of *Microcystis* species in a 2010 CYAHAB in the lake [20]. From a recereational perspective, a 2023 study [21] substantiated that cyanobacterial (*Microcystis* and *Dolichospermum* species) cell counts in water from Winam Gulf of L. Victoria exceeded WHO standards for recreational risk in 84% of water samples. The same samples had MCs (0.02 to 23.31), whcih surpasses the provisional WHO drinking water guideline for MCs.

In the United Republic of Tanzania, studies done on lakes: Big Momela, Embagai and Manyara recorded CYB (>50%) namley: *Anabaenopsis elenkenii*, *A. fusiformis* (Lake Big Momela), *A. fusiformis*, *Oscillatoria*, *Hantzschia* (Lake Embagai), *Oscillatoria jenensis* and *Pseudoanabaena terebriformis* (Lake Manyara) [22][23]. *A. fusiformis* have equally been prevalent in Momela Lakes and Lake Natron with MCs detected in water at concentrations of 0.1–4.5 µg mL^{-1} of scum in the latter [24]. In the lentic waters of L. Victoria, the occurrence of CYB (upto 82%) reported in samples from several parts of the southern portion. A later investigation by Miles et al. [25] indicated the presence of putative MCs analogues in extracts of a bloom sampled from Tanznaia's Mwanza Gulf, but no cyanotoxin quantifications were done. On 27 islands of Ukerewe district, MCs (0.0028 to 0.0102 µg L^{-1}) were reported [26]. Other studies in L. Victoria (several bays, open water and Gulfs) have found MCs (up to 13 µg MC-LR eq L^{-1}). An incidence of multiple cyanotoxins: CYN (0.004 to 0.01 µg L^{-1}), NODs (0.010 µg L^{-1}) and MCs (0.0028 to 0.0118 µg L^{-1}) in water from L. Victoria has been communicated [26]. The report emphasized that multiple and repeated exposure to phycotoxins could amplify their toxicity and/or adverse effects.

From the available literature, Uganda has the highest number of reports about CYB in the region. Of these, Western Uganda crater lakes (Kyaninga, Saaka, Nyabikere, Nyinambuga, Munyayange, Kikorongo, Maseche, Murumuli, Bunyampaka, Katwe, Bagusa, Nyamunuka, Mwamba, Katanda, Karolero, Kerere, Kacuba, Mwengenyi, Kyerbwato, Katanda, Kanyamukali, Nkugute, Kyanga, Mirambi, Nyanswiga, Kitere, Chibwera, Lugembe, Nyanswiga, Kamweru, Nyahirya, Nyabikere, Kyasanduka, Kifuruka, Wandakara, Nyamusingire, Nyungu and Katinda) were found to contain CYB (35% to 100%), primarily of the genera *Planktolyngbya*, *Microcystis*, *Anabaena* and *Cylindrospermopsis*. No determination of cyanotoxins was performed [27][28]. Other interesting studies are available on the Albertine lakes (Edward and George) [29]. Species from *Raphidiopsis* and *Anabaenopsis* genera are the primary community in Lake Edward, though *Aphanocapsa*, *Merismopedia*, *Microcystis*, *Aphanothece* and *Anathece* genera are also present. According to several authors, shallow Ugandan lakes near Mount Rwenzori (Lake George, Lake Edward and Lake Mburo) are eutrophic, with *Microcystis* species being the most abundant CYB [29][30][31][32][33]. Lake Mburo was earlier reported to have more than 90% of its phytoplanktonic community as CYB [34][35]. In the Ugandan part of L. Victoria, *Microcystis*, *Dolichospermum* and *Cylindrospermopsis* species are the prevalent CYB (>80%). Cyanotoxin analyses have reported concentrations of NT to 93 µg L^{-1} of MCs in water from Murchison Bay, Napoleon gulf and open lake water. Worth citing are

pioneering studies in Murchison Bay where MCs were quantified in *Oreochromis niloticus* (Nile tilapia fish), unveiling that the concentrations in biota and aqueous phase were correlated. The study highlighted that there has been an increase in MCs-producing CYB in the lake which are plausibly ingested by fish, agreeing with previous research findings [33][36][37]. The maximum concentration of total MCs reported for guts, liver and muscles of phytoplanktivorous *Oreochromis niloticus* (Nile tilapia) and *Lates niloticus* (Nile perch) from Murchison Bay of L. Victoria (1.86 to 1479.24 µg kg^{-1}) is slightly higher than those from other Ugandan lakes such as Lake Mburo (73.10 to 1312 µg kg^{-1}) [36].

The remaining report on cyantoxins in the EAC is a single report on CYB from a Rwandese Lake (Lake Muhazi). *Microcystis aeruginosa* occured along with the dinoflagellate *Cerutium hirundinellu* [38] and this was confirmed by a follow up study which substantitated that the CYB were being ingested Nile tilapia fish from the same lake [39]. Overall, volcanic and tectonic lakes in the East African Great Rift Valley possess distinguished extents of hydrological connections. Volcanicity in the region resulted in endorheic basins whose bedrock, groundwater connection and climate have favored schizohaline water formation [40]. These, in turn, have contributed to the dominance of CYB, and occurrence of CYBHAB and cyanotoxins. The present literature reveals that toxigenic microalgae recorded from EAC lakes are *Dolichospermum*, *Microcystis, Arthrospira*, *Planktolyngbya* and *Anabaenopsis* species. The prevalence of CYBHAB and cyanotoxins in EAC lakes is of concern due to potential bioaccumulation and trophic transfer in zooplanktivorous and carnivorous fish species [33][37]. Moreover, the observed levels of MCs in whole fish, gut, liver and muscles (2.4 to 1479.24 µg kg^{-1}) could pose human health risks to a daily consumer, as the WHO daily intake limit of MCs in fish is 0.04 µg kg^{-1} [36].

3. Toxicity, Human and Ecological Health Implications of Cyanotoxins in EAC Lakes

3.1. MCs

MCs are hepatotoxins, majorly produced as secondary metabolites of planktonic cyanobacterial species from genera such as *Microcystis*, *Cylindrospermopsis*, *Anabaena*, *Oscillatoria (Planktothrix)*, *Anabaenopsis*, *Nostoc*, *Arthrospira*, *Hapalosiphon*, *Limnothrix*, *Lyngbya*, *Phormidium*, *Rivularia*, *Synechocystis* and *Synechococcus* [41]. Acute effects such as nausea, diarrhea, dermal, eye and throat irritations have been associated with their ingestion. Chronic exposure to MCs culminates in hepatic necrosis, retarded growth, reduced reproduction potential and, ultimately, death in fish and humans. The neurotoxicity of MCs is also known, but this applies specifically to invertebrates without livers [42]. In addition, exposure to MCs is associated with colorectal and primary liver cancer, with MC-LR receiving classification as a possible human carcinogen (group 2B) [43]. For humans, exposure to MCs occurs principally through the ingestion of contaminated aquatic organisms (e.g., fish) or water, as well as through the recreational use of water. Upon ingestion and absorption into the liver by organic anion transport proteins, MCs inhibit protein phosphatases, thereby selectively distorting cytoskeleton formation, degrading hepatic ultrastructure in eukaryotic cells, resulting in hepatic failure, intrahepatic hemorrhage and shock [44][45]. In EAC, MCs and ATX were implicated in the death of *Phoeniconaias minor* Geoffroy Saint-Hilaire 1798 (lesser flamingos) [46]. The pink birds feed on *A. fusiformis* [47], which confers upon them the pink plumage following

the accumulation of ingested cyanobacterial pigments [48]. While this phenomenon is not new (e.g., in the Greater flamingos and Western Tanager [49][50]), it should be anticipated that other nutrition-based compounds may become bioaccumulated in lesser flamingos, e.g., potentially toxic metals. Event-driven reports of lesser flamingo die-offs are available for soda lakes such as Bogoria and Nakuru of Kenya [51][52], Momela, Natron, Rishateni, Manyara and Empakai Crater of Tanzania [8][23][53][54]. While it is still debated that MCs may be a potential initiator of avian botulism, other probable causes of the unnatural mass death of wild birds include avian tuberculosis [55], cholera, botulism, heavy metals [56][57], pesticide residues, or combinations of these [51][58][59][60][61]. Indeed, mycobacteriosis was reported in lesser flamingos from Lake Nakuru, Kenya [62]. Nevertheless, anatoxins and MCs (at concentrations higher than reported in EAC flamingos) have been associated with avian mortalities [58][63][64][65][66].

3.2. Anatoxin-a

ATX is toxicologically known as Very Fast Death Factor for its fast lethal effect in animals, which could be related to its high rate of absorption into the gastrointestinal tract [67]. ATX is a secondary bicyclic amine alkaloid with peracute neurotoxic effects. Its discovery and identification in the 1960s and 1972 from CYB (*Anabaena flos-aquae*) followed the mortality of cattle herds that ingested contaminated water from Saskatchewan Lake in Ontario [67]. It is known to be biosynthesized by CYB from *Arthrospira, Anabaena*, *Microcystis*, *Planktothrix*, *Oscillatoria*, *Aphanizomenon* and *Cylindrospermum* genus [67]. Exposure to ATX (through ingestion of contaminated water or dried algal crusts, accidental swallowing/inhalation) has been associated with burning, tingling, respiratory paralysis and dysrhythmias, which are fatal. ATX antagonizes the activity of neuronal α4β2 and α4 nicotinic acetylcholine receptors (nAchRs) of the central nervous system and (α1)2βγδ muscle-type nAchRs of the neuromuscular junction [68]. With an affinity >20 times that of acetylcholine, ATX has the same effect as the former when it binds with nAchRs, i.e., it induces a conformational effect on the receptor, opening the channel pore to permit the passage of ions (Ca^{2+} and Na^{+}) into the neuron. This culminates into cell depolarization, the generation of action potentials and thus muscle contraction. During ATX-mediated toxicity, the acetylcholine neurotransmitter does not dissociate from the nAchRs, resulting into irreversible inhibition and blockage of neuromuscular transmission [69].

3.3. Homoanatoxin-a

HATX being structurally a higher homologue of ATX has the same toxic effects as ATX. In addition to its nicotinic agonistic effects, HATX also upregulates acetylcholine release from cholinergic nerves [70]. This may explain why the potency of HATX is greater than that of ATX. Mortalities from CYBHAB with HATX are rare, but a report of dog neurotoxicosis from New Zealand (where the animals ingested CYB from Hutt River, lower North Island with 4400 μg kg^{-1} wet weight of HATX) has been published [71].

3.4. Cylindrospermopsin

CYN is a hydrophilic potentially hepatotoxic and immunotoxic cyclic guanidinium alkaloid, with characteristic tricyclic hydroxymethyl uracil [42]. It has some analogues such as deoxy-CYN (lacking an oxygen atom), demethoxy-CYN and 7-epiCYN (difference in the orientation of hydroxyl group) isolated in CYB

Cylindrospermopsis raciborskii. The discovery of CYN toxicity happened when more than 100 children from Palm Island in Queensland, Australia suffered from unprecedented gastroenteritis and hepatomegaly. The ordeal was finally found to be due to the ingestion of CYN in contaminated water with CYBHAB of *C. raciborskii* [72]. However, CYN is also produced by other CYB, including *Aphanizomenon flos-aquae*, *Anabaena* species (*bergii*, and *lapponica*), *Aphanizomenon ovalisporum*, *Lyngbya wollei*, *Raphidiopsis curvata Oscillatoria (Planktothrix)* species and *Umezakia natans* [41]. With guideline values of 0.5 to 3 µg L^{-1} in drinking water across continents, CYN is the second-most-studied cyanotoxin known to target the liver, kidneys, heart, spleen, ovary, eye, lung, T lymphocytes, neutrophils and vascular endothelium [73]. CYN elicit toxicity through inhibition of protein synthesis, which can also occur at subtoxic concentrations [74]. Other toxicologists stated that CYN (with its inherent reactive guanidine) could be largely toxic through the induction of DNA wreckage and disruption of the kinetochore spindle. This could possibly result in chromosome loss, aneugenic and clastogenic effects [75]. Chichova et al. [73] found that CYN elicited moderate toxicity in human intestinal epithelial cells with suppression of cellular regeneration of the epithelial layer. CYN shows hepatotoxic, nephrotoxic, and cytotoxic effects, suggesting potential carcinogenicity. The neurotoxic potential of CYN has also been cited, though this could be a direct consequence of its cytotoxicity. To this end, the full underlying mechanisms of CYN toxicity needs to be elucidated [42]. In the EAC, there are no toxicity reports on CYN, which may be due to the absence of robust data on this cyanotoxin. There are, however, episodes of human and animal CYN-related poisoning from other countries. The most notable human poisoning is the 1979 Solomon dam gastroenteritis and hepatomegaly incidence in children from Palm Island [72]. The mortality of a cow and three calves after drinking water from McKinley Shire dam, Northern Queensland (Australia) was also reported. The animals had severe abdominal and thoracic haemorrhagic effusion, hyperaemic mesentery, pale and swollen liver, extremely distended gall bladder with dark yellow bile and epicardial haemorrhages [76]. In the subsequent 21 days, another eight animals (two cows and six calves) died, and analyses implicated CYN in *C. raciborskii* as the cause [76]. In Lake Aleksandrovac (Serbia), indiscriminate fish deaths due to the ingestion of CYN (range: 1.91 and 24.28 µg L^{-1}) were reported [77]. This report may point to the need to establish CYN levels in EAC lakes where indiscriminate fish deaths have been reported, as CYN may be a contributing factor in addition to MCs.

3.5. Nodularins

Nodularins, a class of hepatotoxic non-ribosomal cyclic pentapeptides, possess toxicity mechanisms similar to those of MCs [78]. They are structurally analogous to MCs, but differentiable from MCs in their amino acid components. To date, ten naturally occurring variants (isoforms) of NODs have been discovered, but nodularin-R (with Z amino acid = arginine) is the most common, most commercially available and most studied variant. The toxicity of NODs mainly targets the liver, but they also accumulate in the intestines, blood and kidneys [79]. Upon ingestion, NODs diffuse from the proximal and distal ileum into the liver [80], where they inhibit active sites of serine/threonine protein phosphatases (PP) namely: 1 (PP-1), 2A (PP-2A) and 3 (PP-3). A non-covalent interaction occurs at first with the side chain (ADDA part) and a free D-glutamyl carboxyl group in the cyclic structure of the PP, followed by the inhibition of the phosphatase activities. NODs–phosphatase complexes (NODs-PP-1 and NODs-PP-2A) are formed with exceptionally stable bonds. Thus, the key difference between NODs and MCs in their toxicity via protein phosphatases inhibition is that the former binds non-covalently to phosphatases, while the

latter forms a covalent bond [79]. Also, NODs also elicit toxicity through formation of superoxide and hydroxyl radicals (reactive oxygen species) according to a yet incompletely elucidated pathway [79]. Their tumor-promoting activity is, on the other hand, mediated through the induced gene expression of TNF-alpha and proto-oncogenes, the exact mechanism of which is yet to be unraveled. In addition, the deactivation of the resultant tumor suppressor gene products (retinoblastoma and p53) progresses via phosphorylation, and this inevitably promotes tumorigenesis [81]. Overall, the cascade of reactions following NOD ingestion causes cellular disorganizations and damages, apoptosis, necrosis, loss of cell integrity, DNA fragmentation and strand breaks, intrahepatic bleeding and rapid blistering of hepatocytes which results in blood pooling and doubling of the liver weight [82]. Thus, mortalities associated with NOD poisoning is mediated through hemorrhagic shocks, which occurs in a few hours when ingested at high concentrations [83]. There are no toxicity events involving NODs in the EAC. Nevertheless, animal (cattle, dog, sheep, horse, pig and guinea pig) NOD-poisoning-related mortalities have been reported in other parts of the world. For example, hepatotoxicosis of a South African dog following the ingestion of NODs (0.00000347 µg kg^{-1} DW) was reported [84]. This emphasizes that more studies on this cyanotoxin is warranted in EAC aquatic ecosystems

In conclusion, CYB, algal blooms and cyanotoxins have increased in East African lacustrine ecosystems. *Dolichospermum*, *Microcystis, Arthrospira*, *Planktolyngbya* and *Anabaenopsis* species are the major groups of CYB prevalent in EAC lakes. The only direct ecological effects of cyanotoxins in EAC lakes is indiscriminate fish deaths and mass die-offs of lesser flamingos. With the unequivocal increase in climate change and variability, it is inferred that CYBHAB and cyanotoxins will increase in frequency and severity. This calls for urgent action to mitigate nutrient-rich pollutants loading into water resources and the expansion of CYBHAB from eutrophic lakes to the surrounding marine environments. The (eco)toxicological relevance of co-production of phycotoxins should be assessed in the EAC because such exposure may amplify the toxicological outcomes in aquatic biota and humans. As some CYB encountered in EAC lakes produce other cyanotoxins (such as β-*N*-methylamino-L-alanine and saxitoxins), studies targeting these cyanobacterial metabolites should be initiated. While there are no reports of cyanotoxin poisoning of humans in the EAC, future studies should examine the risk of hepatocellular cancer, the ingestion of CYB and mycotoxin-contaminated water and foods, and hepatitis virus, which were earlier linked to increased primary liver cancer cases in Asia. Another potential relationship with microplastics should be assessed because they are known to accumulate toxins and amplify their toxicity.

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