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Algal toxins and their impact on human health

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Abstract:

Cyanobacterial blooms have been increasing in frequency and intensity but are often considered an issue restricted to temperate and tropical lakes. Large accumulations of phytoplankton, macroalgae and occasionally, colorless heterotrophic protists are increasingly reported throughout the coastal areas of all continents. Aggregations of these organisms can discolor the water giving rise to red, mahogany, brown or green tides, can float on the surface in scums, cover beaches with biomass or exudates (foam), and deplete oxygen levels through excessive respiration or decomposition. Alternatively, certain species in harmful algal blooms (HABs) can exert their effects through the synthesis of compounds (e.g., toxins) that can alter cellular process of other organisms from plankton to humans. Different species of fresh water Blue Green Algae namely *Anabaena* sp., *Aphanizomenon* sp., *Coleosphaerium* sp., *Gloeotrichia* sp, *Lyngbea* sp., *Microcystis* sp.and *Nodularia* sp. are capable of producing a number of toxins. These cyanobacterial toxins are secondary metabolites which are highly toxic to human beings and other animals.

Keywords:

Blue Green Algae; Cyanobacteria; Toxins; Human Health

1. Introduction:

Eutrophication, is a limnologic term for the process by which a body of water becomes progressively enriched with minerals and nutrients. Water bodies with very low nutrient levels are termed oligotrophic and those with moderate nutrient levels are termed mesotrophic. Eutrophication is characterized by excessive plant and algal growth due to the increased availability of one or more limiting growth factors needed for photosynthesis (Schindler 2006), such as sunlight, carbon dioxide, and nutrient fertilizers.

Blooms of autotrophic algae and some heterotrophic protists are increasingly frequent in coastal waters around the world and are collectively grouped as harmful algal blooms (HABs). Blooms of these organisms are attributed to two primary factors: natural processes such as circulation, upwelling relaxation, and river flow; and, anthropogenic loadings leading to eutrophication. Unfortunately, the latter is commonly assumed to be the primary cause of all blooms, which is not the case in many instances. Moreover, although it is generally acknowledged that occurrences of these phenomena are increasing throughout the world's oceans, the reasons for this apparent increase remain debated and include not only eutrophication but increased observation efforts in coastal zones of the world.

Cyanobacteria blooms and associated cyanotoxins pose significant public health risks during water recreation also. Oral ingestion is the only recognized route of toxin exposure in water recreation guidelines but there are reviews that states human skin is a barrier for the prevention of cyanotoxin absorption and investigates the likelihood of negative health effects through dermal exposure.

Algal toxins are organic molecules produced by a variety of algal species from fresh, brackish and marine waters (Falconer, 1993). Over the past three decades, the occurrence of harmful toxic algal incidents has increased in many parts of the World (Anderson, 1989 and Shum way, 1990). Cyanobacteria produce a wide array of secondary metabolites, a number of which are toxic to shell fish and aquaculture reared fish when exposed to the cells or free toxin in water. Blooms of cyanobacteria result in human and wildlife intoxications due to consumption of or exposure to contaminated water, essentially on a worldwide basis. Over a forty species of freshwater cyanobacteria have been implicated in toxic blooms (Carmichael, 1997). Cyanobacterial toxin rightly called cyanotoxin. Cyanobacterial toxin have long been considered solely of freshwater issue, but the recently microcystin has been identified in marine waters (Anderson, 1993). Cyanobacteria can produce different type of Cyanotoxins which belongs to four major classes namely Neurotoxins, Hepatotoxins, Cytotoxins,

Dermatotoxins and Lipo polysaccharides. Algal toxins are structurally and functionally diverse, and many are derived from unique biosynthetic pathways. In the cyanobacteria, isolated strains within known toxin producing species may be non-toxic. It is not yet clear, whether the toxin producing genes are absent from these strains or if toxin expression is environmentally regulated. Algal toxins that have impact on human health may be functionally categorized as neurotoxins or hepatotoxins.

Cyanobacteria have both beneficial and detrimental properties. When judged from human perspective the extensive growth of Cyanobacteria can create a considerable nuisance for management of inland waters and they may also release various toxic substances in to the water. Many bloom forming species of algae are capable of producing biologically active secondary metabolites which are highly toxic to human health and other animals (Pearson et al., 2010). Cyanobacteria can produce different type of Cyanotoxins which belongs to four major classes namely Neurotoxins, Hepatotoxins, Cytotoxins, Dermatotoxins and Lipo polysaccharides.

2. Toxins produced by blue green algae:

The earliest reports of Cyanobacteria poisoning may have been around 1,000 years ago. First known incidents of Cyanobacteria toxin poisoning was from an Australian lake in 1878 (Chorus and Bartram, 1999, Francis, 1878). More than 50 genera of blue green algae at least 8 have exhibited toxic characteristics of these include *Anabaena sp.*, *Aphanizomenon sp.*, *Coelosphaerium sp.*, *Gleotrichia sp.*, *Lyngbea sp.*, *Nodularia sp.*, and *Nostoc sp.* (Mike Collins, 1978).

The adverse effects on human health of harmful algal blooms (HABs) occur primarily through the impacts of natural phycotoxins via various exposure routes including the ingestion of contaminated sea-food, inhalation or direct skin contact (Berdalet et al., 2016). Numerous species of microalgae are known to produce these toxins, with well recognised acute patterns of illness. Human fatalities are not in-frequent, e.g. with outbreaks of Amnesic Shellfish Poisoning (ASP) (Perl et al., 1990), CP (Hamilton et al., 2010), Palytoxicosis (Wu et al., 2014) and Paralytic Shellfish Poisoning (Suleiman et al., 2017). However, precise estimates of the human health impacts of HABs on population health, and associated trends, are lacking in the absence of robust surveillance systems. Poisoning by water blooms of cyanobacteria is virtually worldwide in occurrence. They have been frequently reported in central North America, especially from the states of North Dakota, South Dakota, Minnesota,

Lowa Wisconsin, Michigan and the provinces of Alberta saskatchewan, Monitoba and ontario. Algal poisonings have also been reported from Australia (Francis; 1878). Cyanobacterial toxins can be categorized into two general groups based on their mode of action are the neurotoxin and hepatotoxin.

3. Neurotoxins:

Neurotoxins produced by cyanobacteria include the saxitoxins (STX) and anatoxins (AnTx). STX and neoSTX have been identified in *Aphanizomenon flos-aquae* in New Hampshire, U. S. A. (Ikawa, 1982).NSP (Neurotoxic Shellfish Poisoning) by *Gymnodinium breve*, a dinoflagellate. Neurotoxins are produced by different genera of Cyanobacteria. The species which are included in the neurotoxin production are *Anabaena* sp, *Aphanizomenon* sp, *Microcystis* sp, *Planktothrix* sp, *Raphidopsis* sp, Saxitoxins (STXs) are natural alkaloids also known as Paralytic Shellfish Poisoning (PSP) toxins (PST). They were originally found in molluscs after poisonings of humans following consumption of seafood. Clinical manifestations of oral numbness, gastrointestinal distress, vertigo, tachycardia, and headache occur within approximately 30 minutes of saxitoxin ingestion. Symptoms may include incoordination, dysarthria, and respiratory distress. Death secondary to respiratory failure can occur within 1 to 24 hours. In marine environments, including brackish waters, STXs generally are produced by eukaryotic dinoflagellates of the genera *Alexandrium*, *Gymnodinium* and *Pyrodinium* while in freshwater, producers are cyanobacteria.

Cyanobacterial taxa for which STX production has been demonstrated belong to Nostocales (*Anabaena circinalis* (*Dolichospermum cicinale*), *Dolichospermum lemmermannii*, *Cylindrospermopsis raciborskii*, *Aphanizomenon gracile*, *Aph. issatschenkoi*, *Aphanizomenon* sp., *Scytonema* sp.), Oscillatoriales (*Lyngbya wollei*, *Planktothrix* sp., *Oxynema* sp.), and possibly Chroococcales (*Cyanobium* sp.). In mild cases of PSP clinical symptoms include a tingling sensation or numbness around lips, which usually appear within 30 minutes, gradually spreading to the face and neck. These effects are probably due to local absorption of the PST through the mucous membranes of the mouth.

Later, a prickly sensation in the fingertips and toes, headaches, dizziness, nausea, vomiting and diarrhea usually occur. Sometimes, temporary blindness is also observed. Most symptoms have a quick onset (hours) which may last for days. Paralytic shell fish poisoning

symptoms generally onset within 30 minutes of ingestion and invariably begin with a tingling or burning of lips, tongue and throat increase to total numbness of face (Lewellyn, 2006).

Anatoxin-a is one of the neurotoxic alkaloids that have been produced from cyanobacteria include *Anabaena*, *Planktothrix*, *Oscillatoria*, *Aphanizomenon*, *Cylindrospermum*, *Microcystis spp.* It is a bi cyclic secondary amine that mimics the neurotransmitter acetyl choline and binds to the nicotinic acetyl choline receptor at the axon terminal at the neuromuscular interface (Botana, 2007, Huisman *et al.*, 2005). Binding of anatoxin-a is irreversible, the sodium channel is locked open, becomes over stimulate, fatigued and eventually paralyzed (Carmichael, 1975). The exposure results in a lack of oxygen to the brain, subsequent convulsions and death by suffocation.

It is one of the major toxins produced sporadically and unpredictably by the blue green algae *Anabaena flos-aquae*. Over the past hundred years, the number of domestic and wild animal deaths from *Anabaena flos-aquae* poisoning has sometimes numbered in the thousands (Gorham, 1964). No human deaths have been attributed to anatoxin-a poisoning; however, cases of acute gastrointestinal disease, allergic dermatitis and general malaise have been documented and attributed to *Anabaena flos-aquae* (Schwimmer and Schwimmer, 1968). This leads to concern that possible ingestion of sub – acute doses of anatoxin-a might because delayed toxicological symptoms in human beings and animals, a likely possibility based on the common occurrence of *Anabaena flos-aquae* in reservoirs and other water supplies. Toxin produced by toxic strains of cyanobacteria includes alkaloids, polypeptides and pteridines. Most of the toxins have been designated as anatoxins (Carmichael and Gorham, 1978) because they are produced by strains of *Anabaena flos aquae*. Only one, anatoxin-a, has been chemically identified and it is an alkaloid, 2-acetyl-9, azabicyclo (4-2-1) non-2-ene, having a molecular weight of 165 (Devlin *et. al.*, 1977).

4. Hepatotoxins:

Hepatotoxins are the most commonly encountered in cyanobacterial blooms. Recently, cyanobacteria have become one of the important sources for bioactive substances and their importance has increased considerably. Since 1970's, many types of compounds have been isolated and they show characteristic biological activities, cytotoxic, immuno-suppressive, antifungal, cardioactive and enzyme inhibitory.

Organisms responsible including about 40 genera but the main ones are *Anabaena sp*, *Aphanizomenon sp*, *Cylindro-spermopsis sp*, *Microcystis sp*, *Nostoc sp* and *Oscillatoria planktonica*. The cyclic pentapeptide Nodularin is most commonly produced from the filamentous, planktonic, Cyanobacterium, *Nodularia spumigena*. Nodularin is a potent hepatotoxin for humans and other animal. It induces liver hemorrhage in mice, when it injected in artificial way. The consumption of *N.spumigena* may cause massive liver hemorrhage in animals (Nehring., 1993; Carmichael and Eshedor., 1988; Carmichel., 1994; Francis, 1878).

5. Cylindrospermopsin:

Cylindrospermopsin is a polyketide derived alkaloid which was first discovered in 1979. It is produced by eight fresh water Cyanobacterial members which includes *Cylindrospermopsis raciborskii*, *Aphanizomenon ovalisporum*, *Aphanizomenon flos-aquae*, *Anabaena bergi*, *Anabaena lapponica*, *Lyngbya wollei*, *Rhaphidiopsis carvata* and *Umezakia natans*.

Generally it is a cytotoxin that blocks glutathione, protein synthesis, and cytochrome p450. (Runnegar *et al.*, 1995; Runnegar *et al.*, 1994; Froscio *et al.*, 2003). It also interferes with systems of liver, nerves, thymus and heart. It is considered a potential carcinogen. (Runnegar *et al.*, 1995; Runnegar *et al.*, 1994; Runneagr *et al.*, 2002; Kiss *et al.*, 2002).

Based on available studies, the liver, kidneys and erythrocytes may be important targets of cylindrospermopsin toxicity; however, the mode of action (MOA) for cylindrospermopsin - mediated toxicity is not fully elucidated.

6. Microcystins:

Microcystins are produced by *Microcystis aeruginos*, *Microcystis viridis.*, *Aphanizomeno flos-aquae*, *Oscillatoria haplosporium* and *Anabaena* species are associated with Microcystins. The known toxins of *Microcystis aeruginosa* are peptides. These peptides were of low molecular weight compounds ranging in size from 500-1700 dalton. They are termed as microcystin, anatoxin-c and Microcystis type C. (Gorham and Carmichael, 1980).

M.aeruginosa are most frequently associated with the algal blooms and associated with hepatotoxicity. (Chorus & Bartram *et al.*, 1999; Hitzfeld and Hoger, 2000). Microcystins are

cyclic hepta peptides with variable aminoacids at seven different positions. The microcystins are generally associated with Hepato toxicity (Chorus and Bartram, 1999.) The first laboratory culture of toxic strains were obtained from the colonial species *Microcystis aeruginosa* by (Hughes et. al., 1958) using a modified Fitzgerald medium (Fitzgerald et al., 1952) the known toxins of *Microcystis aeruginosa* were peptides. These peptides were of low molecular weight compounds of 500-1700 dalton. They were termed as Microcystin type-C. (Gorham and Carmichael, 1980).

7. Lipopolysacchrides (LPS):

Lipopolysaccharides are known as irritant toxins and are generally found in the outer membrane of the cell wall of Gram-negative bacteria, including Cyanobacteria, where they form complexes with proteins and phospholipids. Another source of potential environmental toxicants was the species of *Schizothrix* producing lipopolysaccharide endotoxins. These toxin may cause outbreaks of gastroenteritis (Keleti et.al., 1979). Cyanobacterial LPS are considerably less potent than LPS from pathogenic Gram-negative bacteria such as *Salmonella* (Chorus and Bartram, 1999 and Masango, 2007).

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