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ORIGINAL PAPER

Effect of abiotic factors on the stability of chosen oligopeptides isolated from the freshwater cyanobacterium *Woronichinia naegeliana*

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Abstract

Cyanobacterial blooms have a significant impact on water quality. Implementing appropriate treatment methods to remove cyanobacterial secondary metabolites requires assessing their stability. In contrast to cyanotoxins, the effect of abiotic factors on cyanopeptides has been poorly studied. The present study analysed the impact of pH, temperature, visible and ultraviolet (UV) radiation on the stability of chosen oligopeptides found in a freshwater cyanobacterium *Woronichinia naegeliana* bloom that frequently appears in drinking water reservoirs worldwide. The tested cyanopeptolin 1081 (CYA-1081) and anabaenopeptin 899 (ANB-899) were relatively stable at room temperature for 12 weeks regardless of pH. However, boiling (100 °C) for one hour affected the partial decomposition of the compounds in a pH-dependent manner; the highest decrease in the initial content of CYA-1081 to 47.0% was recorded at pH 9, while for ANB-899 to 42.4% at pH 3. The tested cyanopeptolin was resistant to visible radiation, but UV radiation in an acidic condition caused its degradation by 32.3%. Treatment of ANB-899 with visible or UV radiation for 3 h caused its partial decomposition with a maximum reduction of 40.4 and 70.8%, respectively, at acidic pH. The presented data provided information on factors affecting the cyanopeptides persistence and may be useful in the search for and development of effective methods of removing cyanobacterial metabolites.

Keywords Anabaenopeptin · Cyanobacteria · Cyanopeptides · Cyanopeptolin · Stability · *Woronichinia naegeliana*

Introduction

Climate change, as well as progressive eutrophication, is responsible for the global expansion and increased frequency of cyanobacterial blooms in aquatic environments (Pearl et al. 2016). This phenomenon has received a lot of attention worldwide, as it is a serious problem for drinking water management. The massive occurrence of cyanobacteria has a significant impact on the physical and chemical properties of water (e.g. reduced transparency of water column, oxygen deficit) and they are well known to produce many bioactive compounds with various chemical structures and mechanisms of action. Among them are compounds that affect taste and odour of water (e.g. geosmin), toxins (e.g. hepatotoxic microcystins, neurotoxic anatoxin-a, cytotoxic cylindrospermopsin) as well as oligopeptides of unclear biological function (e.g. aeruginosins, microginins, anabaenopeptins, cyanopeptolins) (Janssen et al. 2019). The presence of these metabolites in water used for drinking and food production (e.g. through crops irrigation) may have potentially serious ecological and toxicological consequences. Reducing harmful exposure to cyanobacterial secondary metabolites may be achieved either by preventing blooms (e.g. reduction in eutrophication) or by the implementing water treatment methods to remove them (Merel et al. 2013). Much information has been published on the removal of cyanotoxins in drinking water treatment (see references in de la Cruz et al. 2013; Roegner et al. 2013; Vlad et al. 2014). Chemical and biological processes may degrade toxins, thus improving water quality (Bober et al. 2008; Dlugosz et al. 2015; Duchnik et al. 2021). However, the development of appropriate methods was made possible by intensive research on their stability. In contrast, the abundance and persistence

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of cyanopeptides have been poorly studied (Natumi et al. 2021). Cyanopeptides contain unusual amino acids and are structurally classified as linear (aeruginosins, microginins), cyclic (anabaenopeptins, cyanopeptolins, cyclamides) or multicyclic (microviridins) (Welker and von Döhren 2006). Among them, anabaenopeptins and cyanopeptolins are frequently detected in freshwater bodies at concentrations up to 10 µg L^{-1} that may exceed 1000 µg L^{-1} during blooms (Gkelis et al. 2015; Janssen 2019; Zervou et al. 2022). These cyclic nonribosomal oligopeptides have been identified in cyanobacteria of the genera *Anabaena*, *Microcystis*, *Planktothrix*, *Lyngbya*, *Nodularia*, *Schizotrix*, *Nostoc Planktothrix*, *Scytonema*, *Symploca* and *Woronichinia* (Le Manach et al. 2019; Bober et al. 2021). Anabaenopeptins (ANBs) are cyclic hexapeptides consisting of a ring formed by five amino acids, including a conserved lysine, which both closes the ring and forms a ureido bond with one amino acid of the side chain. In contrast, cyanopeptolins (CYAs) contain the characteristic 3-amino-6-hydroxy-2-piperidone amino acid (Ahp) within the ring structure and a side chain of variable length. The high structural variability of cyanopeptides representing more than 75 variants of ANBs and 170 variants of CYAs is also reflected in the wide range of masses between 590 and 1200 Da (Le Manach et al. 2019). Although these compounds are not currently considered toxins, their potential toxicological effects on aquatic ecosystems are unknown (Beversdorf et al. 2017; Lenz et al. 2019). One of the cyanobacteria that has been identified as a rich source of cyanopeptides is *Woronichinia naegeliana* (Unger) Elenkin (Bober et al. 2011). This cyanobacterium is frequently found in freshwater around the world (Willén and Mattsson 1997; Bucka and Wilk-Woźniak 2002; Willame et al. 2005; Oberholster et al. 2006; Santos et al. 2012). The results demonstrated that its cell extract caused biological activity against zooplankton (Bober and Bialczyk 2017). Oligopeptides found in the natural population of *W. naegeliana* belong to microginins, cyanopeptolins and anabaenopeptins. Some of them such as cyanopeptolin 1081 (CYA-1081) and anabaenopeptin 899 (ANB-899) were first described in the literature by Bober et al. (2021). CYA-1081 has leucine, isoleucine, N-methylated phenylalanine, tyrosine, glutamine, threonine, a highly unusual amino acid 3-amino-6-hydroxy-2-piperidone amino acid and glyceric acid in its structure, while ANB-899 consists of isoleucine, valine, lysine, phenylalanine and homotyrosine (Fig. 1). Preliminary evaluation of the biological activity of CYA-1081 and ANB-899 against the zooplankton *T. platyurus* did not yield conclusive results. However, the observed deterioration of the physiological state of crustacean larvae exposed to both peptides indicates their possible negative effects on the aquatic organism (Bober et al. 2021).

While there is a substantial amount of information on factors affecting the persistence of cyanotoxins in water, data concerning cyanopeptides stability are scarce. Given that CYA-1081 and ANB-899 are found in a *W. naegeliana* bloom that may frequently appear in drinking water reservoirs, the main objective of the presented study was to determine the effect of selected abiotic factors including pH, temperature, visible and ultraviolet radiation on their stability. A better understanding of the effects of external factors on cyanopeptides is essential to develop an appropriate procedure of their reduction (Munir et al. 2019, 2022).

Materials and methods

Preparation of samples

CYA-1081 and ANB-899 were extracted and purified from lyophilized *Woronichinia naegeliana* (Unger) Elenkin cells according to the procedure described by Bober et al. (2021). Cyanopeptides solutions (100 µg mL^{-1}) were prepared in Britton-Robinson buffer with respective pH: 3, 5, 7 and 9. pH was controlled using a glass pH microelectrode (InLab423, Mettler Toledo, Switzerland). Afterwards, the prepared samples were immediately used in the experiments.

Experimental procedures

Effects of time and temperature

CYA-1081 and ANB-899 solutions were kept in darkness at room temperature (23 ± 1 °C), shaken regularly and analysed after 2, 8 or 12 weeks. Samples not subjected to this condition were incubated at 40 °C or 100 °C for 1 h to determine the effect of temperature.

Irradiation conditions

CYA-1081 and ANB-899 samples were placed in quartz vials with a screw cap and irradiated with visible light (VIS) or ultraviolet (UV-B) radiation, stirring at regular intervals. The VIS source was a Sylvania F58W/865 lamp (500 µmolm^{-2} s^{-1} flux). For UV-B radiation, two Philips TL 40 W/12 fluorescent tubes with a flux of 36 µmolm^{-2} s^{-1} were used. Irradiance was measured using a Li-1800 spectroradiometer (Li-COR, USA). The control was CYA-1081 and ANB-899 solutions kept in darkness. Experiments were run at room temperature (23 ± 1 °C). Samples were collected and analysed after 3 h irradiation.

Analytical procedure

Changes in cyanopeptides concentration under the tested abiotic conditions were measured by using high performance liquid chromatography (HPLC) with a photodiode array

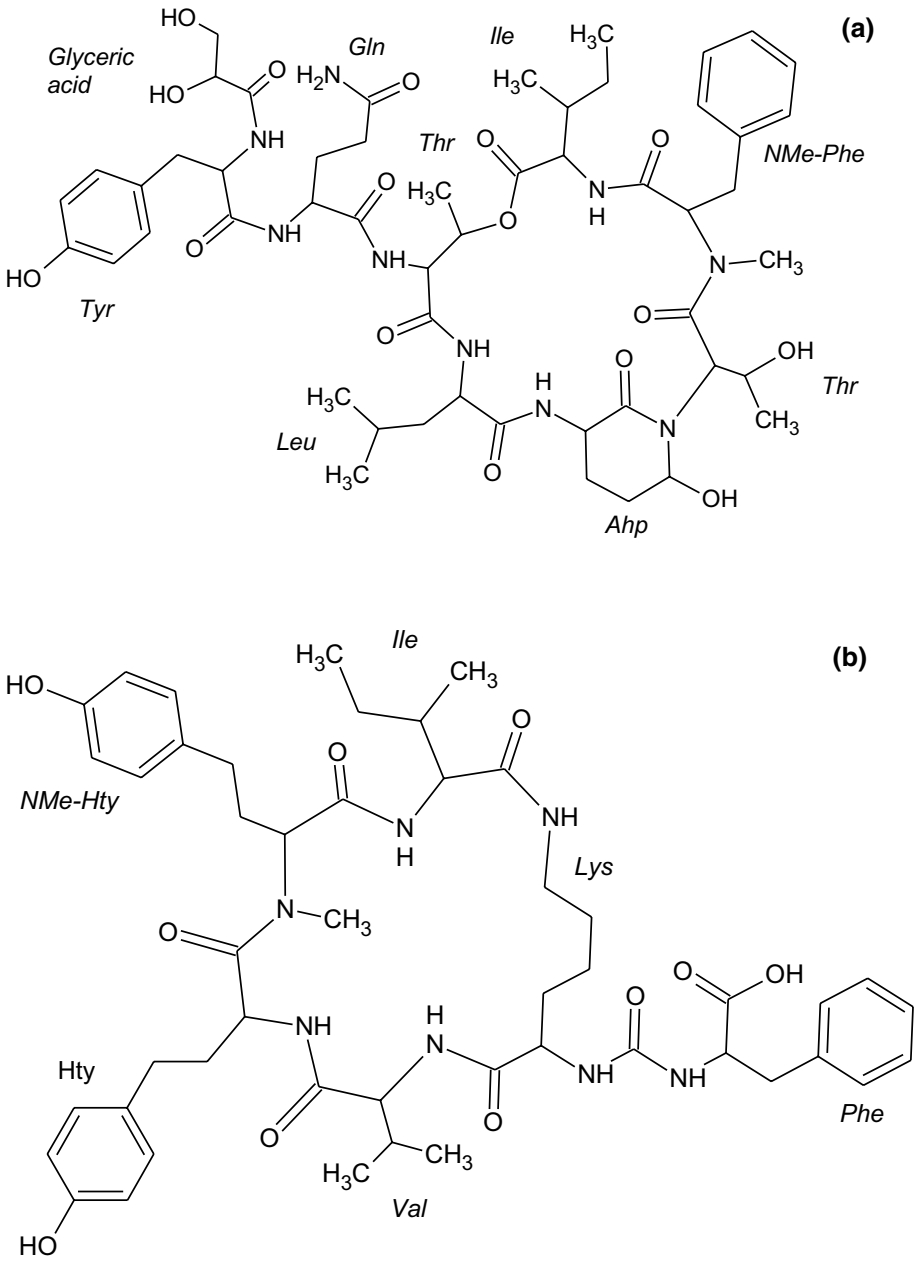

Fig. 1 Chemical structure of cyanopeptolin 1081 (**a**) and anabaenopeptin 899 (**b**)

(PDA) detector (Waters, Milford, MA, USA). The HPLC system consisted of a 600E gradient pump, 717 plus autosampler, a 996 PDA detector, Millenium^{32}SS software with PDA option, and a Jetstream 2 plus column thermostat. A gradient mobile phase consisting of water (A) and acetonitrile (B), both acidified with trifluoroacetic acid (0.05%, v/v), was applied at a flow rate of 1.0 mL min^{-1}. The Symmetry C_{18} column (4.6 × 250 mm; 5 µm; Waters) was maintained at 23 °C. CYA-1081 was analysed using a gradient mobile phase changing from 70 to 60% of A in 12 min, while ANB-899 using a gradient varying from 60 to 35% of A in 15 min. Concentration of both compounds was quantified by absorbance monitored at 220 nm using appropriate standard curves. Sample contents were additionally analysed by ultra-performance liquid chromatography–mass spectrometry (UPLC-MS/MS) of a Waters ACQUITY system coupled to a Waters TQD Electrospray Ionization–tandem quadrupole mass spectrometer. Chromatographic separations were done on an Acquity UPLC BEH (bridged ethyl hybrid) C_{18} column (2.1 × 100 mm; 1.7 µm; Waters) equipped with an Acquity UPLC BEH C_{18} VanGuard pre-column (2.1 × 5 mm; 1.7 µm; Waters) maintained at 40 °C. The gradient mobile phase consisting of water (A) and acetonitrile (B), both acidified with formic acid (0.1%, v/v), was varied from 95 to 0% of A in 10 min at a flow rate 0.3 mL min^{-1}. The following operating conditions of the Waters TQD mass spectrometer were

used: source temperature 150 °C, desolvation temperature 350 °C, desolvation gas flow rate 600 L h^{-1} and cone gas flow 100 L h^{-1}. Capillary and cone potentials were set at 3.00 kV and 20 V, respectively. Nitrogen was used as both nebulizing and drying gas. A scan mode from 50 to 2000 m/z at 1.0 s intervals was applied; eight scans were summed up to obtain the final spectrum. Collision activated dissociations (CAD) analyses were carried out 40 eV energy, and all fragmentations were observed in the source. Ion spectra were obtained by scanning from 50 to 1100 m/z range. Values of 1082 m/z and 900 m/z in positive mode were used to qualify CYA-1081 and ANB-899, respectively. MassLynx V 4.1 (Waters) software was used to evaluate the data.

Chemicals

All the reagents were HPLC or analytical grade and all were purchased from LabScan (POCh, Poland) except trifluoroacetic acid (Sigma-Aldrich, St. Louis, MO, USA).

Statistical analysis

Data reported were expressed as mean ± SD of five replicates. All results were subjected to one-way ANOVA, and all means were tested for significant differences ($p < 0.05$) by Tukey's test.

Results and discussion

Studies on the abundance and persistence of cyanobacterial secondary metabolites play a key role in assessing their risk to humans and implementation of possible water treatment procedures. Given the poor knowledge of the physicochemical characteristic of cyanopeptides, the effect of several abiotic factors on CYA-1081 and ANB-899 was investigated. Both tested cyanopeptides were relatively stable at room temperature, however, the results obtained for cyanopeptolin were pH-dependent. As can be seen in Fig. 2a, the content of CYA-1081 after 12 weeks decreased from the initial value by 15.4% at pH 3, whereas at pH 9, the change was approximately twice as large (37.7%). These observations were convergent with those reported for many cyanobacterial metabolites, including cyanotoxins and linear protease inhibitors. Some of the hepatotoxic cyclic penta- or heptapeptides (e.g. nodularin, microcystin-LR), neurotoxic or cytotoxic alkaloids (e.g. anatoxin-a, anatoxin-a(s), cylindrospermopsin), as well as linear microginins (e.g. microginin-757), showed higher stability under acidic conditions than at alkaline pH (Matsunaga et al. 1989; Harada et al. 1996; Kaminski et al. 2013; Bober et al. 2014; Adamski et al. 2016a). In contrast, acidification and alkalization of ANB-899 samples had a non-significant effect on the change in its content, which was determined to be about 30% after 12 weeks (Fig. 2b). Interestingly, the studied compounds stored at room temperature in darkness with a half-life of more than 12 weeks proved to be relatively very stable with a similar persistence as cyclic microcystin-LR (Harada et al. 1996). However, treating cyanopeptides with higher temperature might accelerate their degradation, while treating the samples with 40 °C had slight effect, applying 100 °C caused gradual degradation. After 1 h of boiling, the initial content of CYA-1081 declined to 68.0 and 65.6% under acidic and neutral pH, respectively, whereas it decreased to 47.0% under alkaline condition (Fig. 3a). Moreover, the temperature of 100 °C combined with pH also accelerated the degradation of ANB-899. Its content fell by 57.6% at pH 3 and by 33.4% at pH 9 compared to the initial value (Fig. 3b). In the case of cyanopeptolin, acidification stabilized the sample, while alkalization accelerated its decomposition. A similar observation was made for the cyanobacterial alkaloids anatoxin-a or cylindrospermopsin (Kaminski et al. 2013; Adamski et al. 2016a). Data for other cyanopeptides, such as microcystin-LR or microginin FR3, indicate that they are relatively more resistance to boiling compared to the studied compounds (Harada et al. 1996; Bober et al. 2014).

Like many cyanobacterial secondary metabolites, CYA-1081 proved to be resistant to visible radiation (Fig. 4a) (Tsuji et al. 1994; Kaminski et al. 2013; Adamski et al. 2016b). Interestingly, ANB-899 degraded under visible irradiation and its initial content slightly reduced by about 10% at alkaline and neutral pH, while at pH 3, it was decreased by 40.4% (Fig. 4b). A similar effect of pH on anabaenopeptin stability was observed under UV irradiation. The ANB-899 content at acidic pH was significantly reduced by 70.8%, while at the other tested pH conditions, it was approximately 50% of the initial value (Fig. 4b). UV irradiation caused less degradation of cyanopeptolin compared to anabaenopeptin, although the greatest impact on peptide content was also detected at pH 3. The maximum reduction in CYA-1081 by 32.3% was slightly higher than the values detected at the other pH conditions studied (Fig. 4a). These results have practical implications, as UV is used in water purification procedures. However, its radiation is limited in deeper or turbid waters. Therefore, the combination of UV with oxidizing agents is more important in water treatment. Detailed examination of the chromatographic and mass spectra obtained showed a decreasing content of cyanopeptides exposed to abiotic conditions, but no degradation products were identified (Supplementary Information Figs. S1 – S12). These

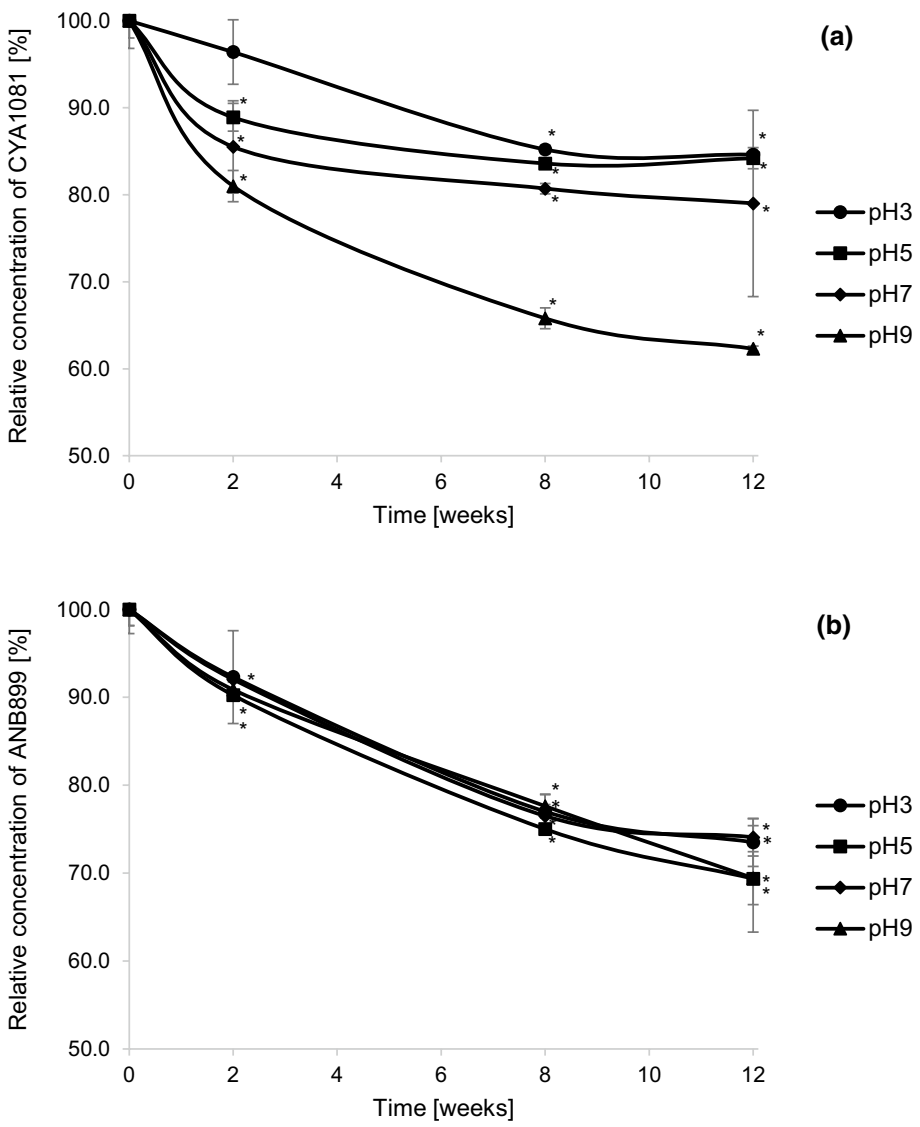

Fig. 2 Change in content of cyanopeptolin 1081 (**a**) and anabaenopeptin 899 (**b**) at various pH and room temperature (23 ± 1 °C) kept in darkness. Data are expressed as means ± SD ($n = 5$), *significant difference from control at $p < 0.05$

results might be influenced by the limited sensitivity of the analytical methods used, particularly related to the presence of buffer solutions.

Most of the experiments reported in the literature concern the degradation of cyanotoxins, whereas cyanopeptides have not been studied in detail yet. Assessing the effect of external factors on their persistence is essential to evaluate risks to humans and implement appropriate abatement methods. Like microcystins, cyanopeptolins and anabaenopeptins belong to cyclic oligopeptides. Microcystins are known for their stability (Rastogi et al. 2014), therefore, the comparable persistence of CYA-1081 and ANB-899 to abiotic factors might be a consequence of their similar chemical structure. The relatively long half-life of microcystins in surface waters, as well as their high stability, makes them a priority for risk assessment (Janssen 2019). Given the analogous persistence and detected concentrations during cyanobacterial blooms (above

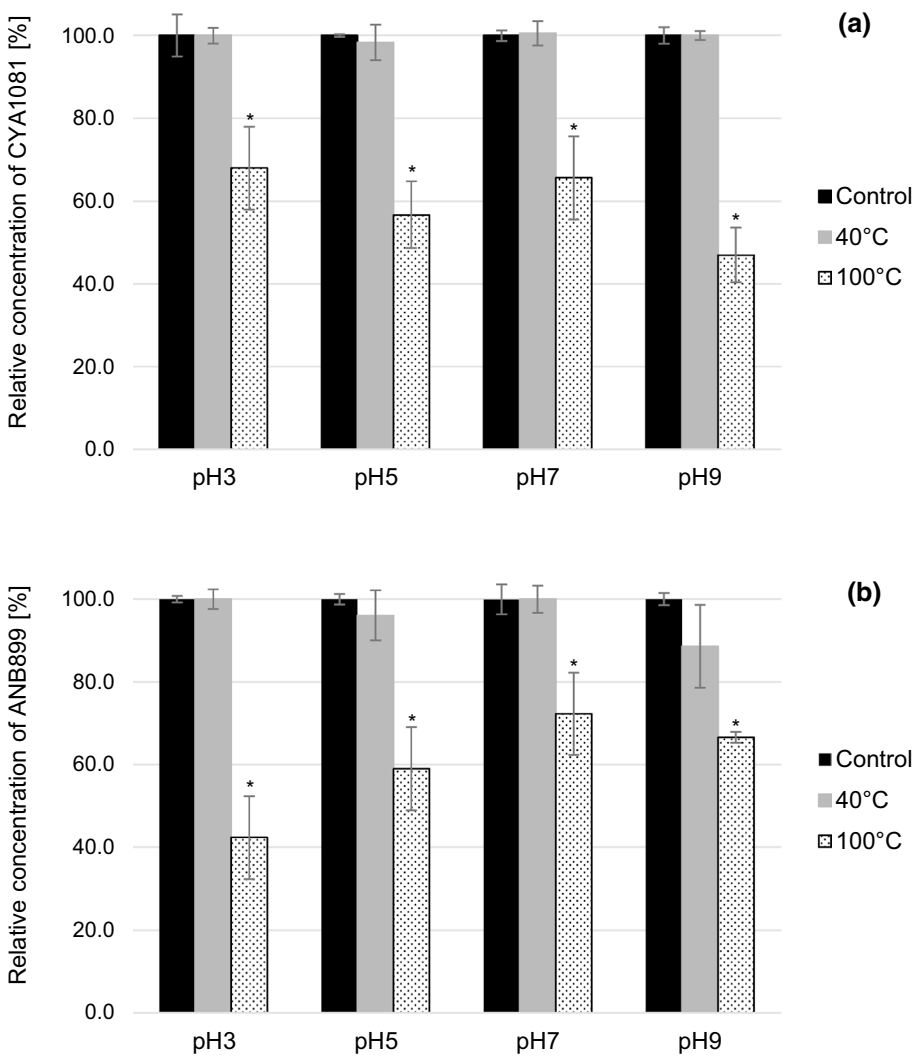

Fig. 3 Effect of temperature on cyanopeptolin 1081 (**a**) and anabaenopeptin 899 (**b**) content after 1 h treatment. Data are expressed as means ± SD ($n = 5$), * significant difference from control at $p < 0.05$

1000 µg L^{-1}; Gkelis et al. 2015), the effect of cyanopeptides should also be considered.

Conclusion

The widespread use of water resources for direct human consumption and food production indicates the high value of research to identify potential hazards in open water. Developing effective treatment strategies requires stability characterisation of the compounds present in the aquatic environment. Presented research is the first attempt to assess the impact of abiotic factors on cyanopeptolin 1081 and anabenopeptin 899 isolated from *W. naegelina* bloom. Although the tested cyanopeptides were relatively stable at room temperature, boiling in combination with pH significantly accelerated their decomposition. CYA-1081 and ANB-899 differ in their sensitivity to visible and UV irradiation. Cyanopeptolin was the most stable under the tested conditions. Given their high persistence, it is important to include the effect of cyanopeptides in the risk assessment. Further experiments will involve implementing the obtained results to develop water treatment techniques.

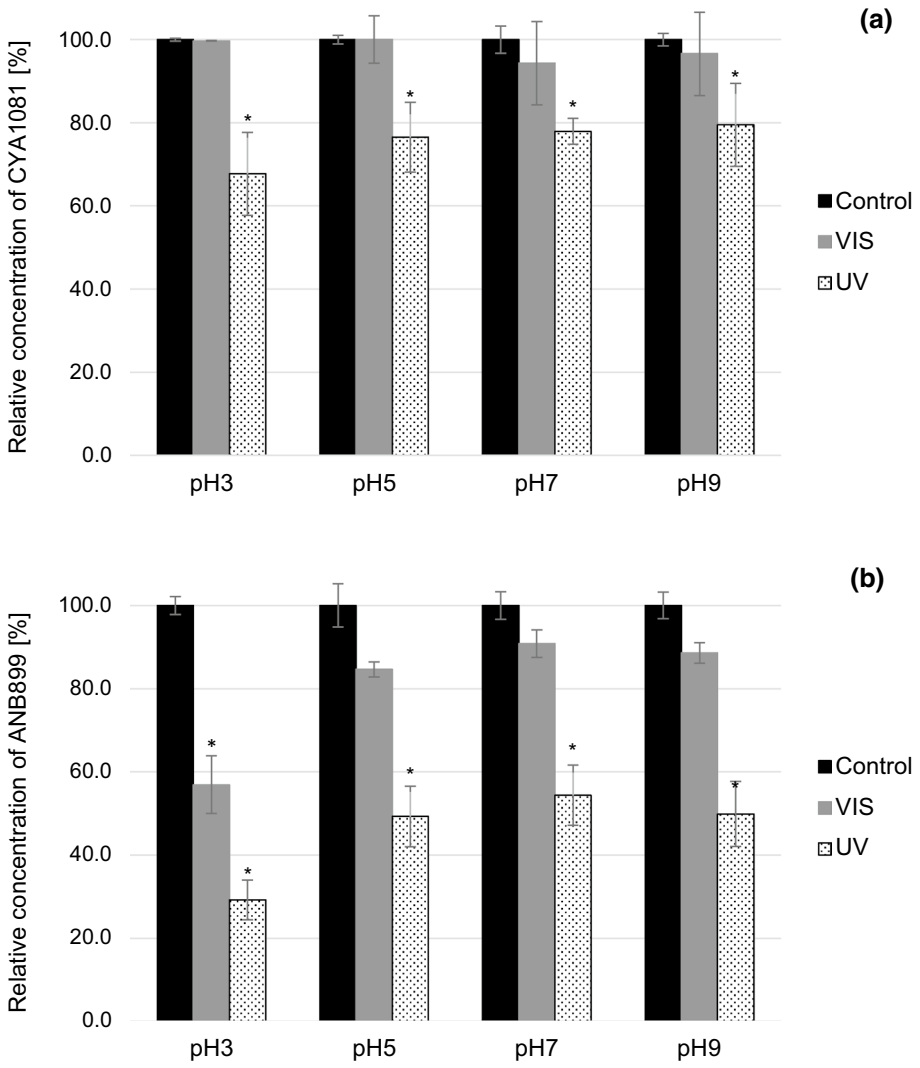

Fig. 4 Change in content of cyanopeptolin 1081 (**a**) and anabaenopeptin 899 (**b**) after 3 h irradiation with VIS (500 µmolm^{-2} s^{-1}) or UV-B (36 µmolm^{-2} s.$^{-1}$). Data are expressed as means ± SD ($n = 5$), *significant difference from control at $p < 0.05$

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13762-022-04474-4.

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Author contributions BB contributed to original concept, analyses, analysis of data and drafting manuscript; JB reviewed the manuscript; ECS contributed to review and editing manuscript.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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