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Sustainable New Algicidal Effectiveness of Cycloheximide Against *Phaeocystis globosa*

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ABSTRACT

Harmful algal blooms (HABs), a sign of ecosystem imbalance, are frequently brought on by the numerous environmental changes that show the growing global human footprint and climate change. *Phaeocystis globosa* blooms are common in coastal waters and have had detrimental effects on biological environments by producing harmful hemolytic chemicals, creating nuisance foam depleting oxygen, and forming ichthyotoxic algal blooms. Cycloheximide is a fungicide that occurs naturally and is a protein synthesis inhibitor in eukaryotic cells generated by the Gram-positive *Streptomyces griseus* bacteria. The data revealed that cycloheximide treatment (250 µg/ml) with algal cells of *P. globosa* induced a decrease in photosynthetic pigment content (chlorophyll *a*, carotenoid), photosynthetic efficiency, total algal biomass production, total soluble protein, activities of antioxidant enzymes of peroxidase, catalase, and superoxide dismutase, as compared to the control samples. However, there is an increased level of caspase-3 activity, malondialdehyde, and dichlorofluorescein compared to the control samples. The alteration in cell morphology and cell membrane integrity of *P. globosa* was detected by transmission electron microscopy technologies. In control cells, the morphology was normal, with intact organelle structure, typical normal nucleus, chloroplasts, mitochondria, and other organelles. After being exposed to cycloheximide for 72 hours, *P. globosa* algae cells displayed increased cytoplasmic vacuolization and the disintegration of numerous organelles, including the nucleus and chloroplasts. Furthermore, the nucleus was significantly swollen and blurry, and intracellular materials leaked out of the cell via a damaged plasma membrane. The results indicate that application of cycloheximide (250 µg/ml) possesses the potential to be used as an eco-friendly biological control agent for managing harmful effects of *P. globosa* algal blooms, particularly in water treatment processes.

INTRODUCTION

HABs are the most serious consequence of eutrophication. They have become major marine environmental disasters occurring worldwide and have been causing irreversible damage to ecosystems, public health, tourism, and fisheries **(Heisler *et al.*, 2008)**, thereby limiting economic development in fisheries and threatening marine organisms, human health, tourism, and aquaculture **(Anderson *et al.*, 2012; Zhang *et al.*, 2014)**. Algal blooms can seriously compromise human safety and the environment, including the death of aquatic animals, the deterioration in water quality, and the destruction of aquatic environments **(Peperzak & Van Wezel, 2023; Wei *et al.*, 2024)**. An important and common marine haptophyte, *Phaeocystis*

(Prymnesiophyceae), may cause blooms in marine ecosystems with agminated colonies **(Rousseau *et al.*, 2007)**. It has been established that *Phaeocystis* spp. flagellates are dangerous algae which produce enormous blooms that kill fish **(Blauw *et al.*, 2010)**. In tropical marine environments, *P. globose* is the primary cause of toxic algal blooms, where it establishes enormous colonies **(Jun *et al.*, 2020; Liang *et al.*, 2021)**. According to reports, the eukaryotic HAB-producing species *P. globosa* is linked to shellfish mortality and has detrimental effects on the entire ecological system by generating harmful hemolytic chemicals, producing nuisance foam, and depleting oxygen **(Zhang *et al.*, 2014)**. In the meantime, *P. globosa* extracellular polymeric hazardous nanoparticles were detected in marine habitats **(Zhang *et al.*, 2012)**.

P. globosa blooms in the form of colonies floating on the surface of seawater, which can lead to the discoloration of coastal seawater when many colonies are formed, resulting in marine ecosystem disasters (**Wei *et al.*, 2024**). *P. globosa* has been found to produce the following hazardous metabolites: fatty acids with polyunsaturated chains **(van Rijssel *et al.*, 2007)** and dimethylsulfoniopropionate **(Mohapatra *et al.*, 2014)**. According to reports, the most severe toxicities to aquatic organisms are caused by hemolytic glycolipid activity **(Yang *et al.*, 2009)**, and ichthyotoxic activity **(Basti *et al.*, 2021)**. This contributes to cause economic deficits **(Lancelot *et al.*, 2011)** and fish deaths **(Long *et al.*, 2015)**. Scientists have focused on persistent HABs outbreaks in coastal waters, encouraging the development of novel technology and management techniques **(Anderson *et al.*, 2012)**.

Cycloheximide is a fungicide that occurs naturally and is a protein synthesis inhibitor in eukaryotic cells generated by the Gram-positive *Streptomyces griseus* bacteria **(Alfred & Dale, 1987; Schneider-Poetsch *et al.*, 2010)**. Cycloheximide blocks eukaryotic translational elongation by interfering with the translocation stage of protein synthesis, which involves the movement of two mRNA molecules and tRNA in proximity to the ribosome **(Müller *et al.*, 2012)**. It is a cell-permeable molecule that binds the ribosome and that specifically prevents eukaryotic translation from reaching its elongation phase **(Schneider-Poetsch *et al.*, 2010; Buchanan *et al.*, 2016)**. Cycloheximide application decreased the photosynthetic pigment content, increased protein degradation, reduced the quantum yield and electron transport of PSII, affected the donor and acceptor sides of PSII, impeded the collection and transduction of light energy, and affected PSI, indicating that cycloheximide can reduce photosynthetic activity **(Buchanan *et al.*, 2016; Gao *et al.*, 2016)**.

The present study aims to investigate the algicidal effectiveness of cycloheximide against *Phaeocystis globosa* by analyzing its physiological responses. Several parameters were assessed, including photosynthetic pigments (chlorophyll *a* and carotenoids), photosynthetic activity, total biomass production, caspase-3 activity, total soluble protein, and the activities of antioxidant enzymes (CAT, POD, and SOD). Lipid peroxidation (MDA) and dichlorofluorescein (DCF) fluorescence were measured to evaluate oxidative damage in the algal cells. In addition, alterations in cell morphology and membrane integrity were examined using transmission electron microscopy (TEM) after seven days of cycloheximide treatment.

MATERIALS AND METHODS

Reagents

Raw powder with a purity of 99.9% of cycloheximide was acquired from the German company Sigma-Aldrich (Sigma-Aldrich Chemie GmbH).

Collection of the *P. globose* algal samples

Sampling collection of the *P. globose*, which belongs to the family Asteraceae, was conducted in the east of the Qaitbay areas (31.22-31.26ºN-29.88-29.98°E), Alexandria, Egypt. These areas are vulnerable to annually recurrent algal blooms triggering between late April and late May 2025.

Culture preparation of *P. globosa* algal cells and algicidal effectiveness of cycloheximide

Phaeocystis globosa algal cells were cultivated for five days to achieve the phase of logarithmic growth (10^6 cells/mL) before being employed as an inoculant in sterile modified Guillard's f/2 nutrient medium, which is suitable for the growth of most algae **(Guillard & Ryther, 1962)**, at 20°C at a cycle ratio of 12h light: 12h dark with a 75 mmol photons $m^{-2}s^{-1}$ light intensity. Cycloheximide dissolved in dimethylsulfoxide at a concentration of 250μg/ ml was incorporated in 500mL of *P. globosa* algal cultured for seven days **(Hartwell *et al.*, 1970; Zheng *et al.*, 2013)**. The previously described conditions were used for the incubation of all samples and controls. Each treatment was performed in triplicate.

Determination of photosynthetic pigments

The level of chlorophyll *a* in the algal medium of *P. globosa* was estimated following the methods outlined by **Moussa (2001)**, **Moussa and Khodary (2003)**, and **Moussa and Hassen (2017)**. Carotenoids were investigated using the technique of **Bazarnova *et al.* (2024)** and **Laylani *et al.* (2024)**.

Estimation of photosynthetic activity

To examine whether cycloheximide affected the photosynthetic efficiency of *P. globosa,* the maximum photochemical quantum yield of photosystem II (Fv/Fm) was measured using a Phyto PAM II phytoplankton & photosynthesis analyzer (WALZ, Effeltrich, Germany). After sub-sampling at the end of this experiment, a 4-mL sample was collected from each bottle and was then subjected to photosynthetic efficiency measurement. Prior to the measurement, the samples were kept in the dark for 10min to relax the reaction centers of photosystem II **(Lürling *et al.*, 2018)**. The Fv/Fm ratio was measured using a saturation pulse and was determined using the following equations:

$$Fv = Fm - F0 \qquad \textbf{(1)}$$

$$Fv/Fm = (Fm - F0) / Fm \qquad \textbf{(2)}$$

Where, F0 is the minimum fluorescence level excited by the very low-intensity measured light, and Fm is the maximum fluorescence level elicited by a saturation pulse **(Park *et al.*, 2025)**. The photosynthetic efficiency was determined assuming the physiological state represented by the highest quantum yield of PSII (Fv/Fm).

Estimation of total algal biomass

After 7 days of growth, aliquots of one liter were centrifuged at 7000 x*g* for 30min. The algal biomass following centrifugation was dried at 100°C to a stable constant weight, cooled, and weighed. The results were calculated and presented in g L^{-1} **(Helal *et al.*, 2025)**.

Estimation of activities of antioxidant enzymes (CAT, POD, and SOD), malondialdehyde (MDA), total soluble protein, reactive oxygen species (ROS), and caspase-3 activity

POD and CAT activities were assessed in accordance with the study of **Qian *et al.* (2009b)**. SOD activity was measured following the outlines of **Trenzado *et al.* (2006)**. Each enzyme's activity was represented on a protein basis. The malondialdehyde level was estimated by the method of **Dogru *et al.* (2008)** and **Kong *et al.* (2013**) to measure the level of lipid peroxidation. **Bradford (1976)** calculated the concentrations of total soluble proteins using the bovine serum albumin as the reference standard. Reactive oxygen species (ROS) accumulation was estimated by the fluorescent probe, 2',7'-dichlorofluorescein diacetate using the method of **Rastogi *et al.* (2010)**. A caspase-3 like activity assay kit (Solarbio, China) was used to assess *P. globosa* caspase-3 activity.

Transmission electron microscopy (TEM)

Ultrathin sections stained with lead citrate and 6% uranyl acetate were examined with a JEM2100F TEM to investigate the ultrastructural changes in *P. globosa* cells treated with cycloheximide **(Kong *et al.*, 2013)**.

Statistical analysis

The statistical program (SPSS version 17), United States, Illinois, Inc., was used to conduct analytical statistics. Tukey's analysis was used and treatment means were compared at $P \leq 0.05$ **(Moussa, 2004; Moussa & Galad, 2015b; Abdel-Alim *et al.*, 2023)**.

RESULTS AND DISCUSSION

Effect of cycloheximide treatment on chlorophyll *a*, carotenoid, photosynthetic activity, biomass production, caspase-3 activity, and total soluble protein in *P. globosa* after 7 days of growth

The effect of cycloheximide treatment on chlorophyll *a*, carotenoid, photosynthetic activity, biomass production, caspase-3 activity, and total soluble protein in *P. globosa* are shown in Table (1).

Cycloheximide application (250µg/ ml) severely inhibited the photosynthetic pigment content of chlorophyll *a*, carotenoid, photosynthetic activity, biomass production, and total soluble protein by 50.5, 55.1, 50.0, 50.0, and 55.6 %, respectively, in *P. globosa* algal cells as compared to the control after 7 days of growth. However, cycloheximide treatment increased caspase-3 activity by 400%, compared to the control (Table 1). The photosynthetic pigment is a crucial marker of photosynthesis and algal growth **(Ahmed *et al.*, 2025)**. Decreased photosynthetic efficiency is related to a reduction in the ability of the cells to perform photosynthesis, impacting their energy production **(Lawlor & Tezara, 2009)**.

Cycloheximide severely inhibited the photosynthetic pigment content of chlorophyll *a* and carotenoids, photosynthetic activity, and biomass production since it is a translation inhibitor that prevents the synthesis of new proteins essential for pigment biosynthesis, such as enzymes **(Gao *et al.*, 2016)**.

Cycloheximide is frequently used to cause apoptosis through cleaving polymerase (ADP-ribose), boosting caspase-3 activity, DNA fragmentation, and loss of cell-cell adhesion, all of which cause a developmental arrest and cell death **(Negron & Lockshin, 2004; Wu *et al.*, 2004)**. Recent evidence indicates that cycloheximide greatly inhibits protein synthesis **(Croons *et al.*, 2008)**.

Table 1. Effect of cycloheximide application on chlorophyll *a*, carotenoid, photosynthetic activity, total biomass production, caspase-3 activity, and total soluble protein in *P. globosa* after 7 days of growth

Parameter	Control	*P. globosa*
Chlorophyll *a* (mg g^{-1}FW)	9.3^a	4.7^b
Carotenoid (mg g^{-1}FW)	25.6^a	14.1^b
Photosynthetic activity (F_v/F_m)	0.6^a	0.3^b
Total biomass production (g L^{-1})	2.6^a	1.3^b
Caspase-3 activity (fold change)	1.0^a	4.0^b
Total soluble protein (mg L^{-1})	72^a	40^b

The three-triplicate mean is used to express values. Significant means are those with different superscript letters ($P<0.05$), whereas those with the same superscript letters are not-significant ($P>0.05$).

Impact of cycloheximide treatment on antioxidant enzyme activities (POD, CAT, and SOD), malondialdehyde (MDA), and dichlorofluorescein (DCF) in *P. globosa* after 7 days of growth

The effect of cycloheximide treatment (250µg/ ml) on POD, CAT, SOD, MDA, and DCF in *P. globosa* after 7 days of growth is illustrated in Table (2).

Cycloheximide application (250µg/ ml) severely decreased the antioxidant enzyme activities of SOD, POD, and CAT by 54.6, 68.4, and 60.3 %, respectively, in *P. globosa* algal cells, compared to the control after 7 days of growth. However, cycloheximide treatment increased MDA and dichlorofluorescein by 292 and 154 %, respectively, compared to the control (Table 2).

Cycloheximide is a common protein synthesis inhibitor used in research on apoptosis, or programmed cell death, and decreased antioxidant enzyme activities of POD, CAT, and SOD **(Furukawa *et al.*, 1997; XU *et al.*, 2015)**. Treatment with cycloheximide decreased cell viability, increased caspase-3 activity, induced apoptosis, reduced antioxidant enzyme activities, and increased ROS production **(Babu *et al.*, 2012; Geng *et al.*, 2015)**. Cycloheximide increased lipid peroxidation **(Pushpendran *et al.*, 1983; Abe & Hiraki, 2009)**. Application of cycloheximide increased oxidative stress and increased ROS (reactive oxygen species) formation **(Mattson & Furukawa, 1997)**.

Table 2. Effect of cycloheximide treatment on catalase (CAT), superoxide dismutase (SOD), peroxidase (POD), malondialdehyde (MDA), and dichlorofluorescein (DCF) in *P. globosa* after 7 days of growth

Parameter	Control	*P. globosa*
SOD (U mg^{-1} protein)	183^a	100^b
POD (U mg^{-1} protein)	98^a	67^b
CAT (U mg^{-1} protein)	63^a	38^b
MDA (µmol L^{-1})	26^a	76^b
DCF fluorescence (Arbitrary units)	523^a	806^b

The three-triplicate mean is used to express values. Significant means are those with different superscript letters ($P<0.05$), whereas those with the same superscript letters are not significant ($P>0.05$).

Morphological and ultrastructural changes of *P. globosa* algal cells after cycloheximide treatment

The structure of subcellular TEM analysis was used to compare *P. globosa* algal cells treated with cycloheximide (250µg/ ml) to control cells (Fig. 1). In control cells, we could see that the morphology was normal, with intact organelle structure and typical normal nucleus, chloroplasts, mitochondria, and other organelles (Fig. 1A, B). After cycloheximide treatment for 24 hours, algal cells appeared to have distinct plasmolysis; nuclear morphology was still normal at this time, but cytoplasmic hypervacuolization was less compact than in the control cells.

Nevertheless, the treated cells displayed noticeable vacuolization and plasmolysis (Fig. 1C- E). After 48h of treatment, nearly every organelle in the treated cells became compromised, and in certain instances, the chloroplasts suffered significant damage (Fig. 1F, G). After being exposed to cycloheximide (250µg/ ml) for 72 hours, *P. globosa* algae cells displayed increased cytoplasmic vacuolization and the disintegration of numerous organelles, including the nucleus and chloroplasts in addition to extreme plasmolysis and vacuolization. Furthermore, the release of cellular inclusions from cells, which left the cell wall mostly intact, showed that the cells had entirely stopped performing essential functions with extreme plasmolysis and vacuolization. Furthermore, the nucleus was significantly swollen and blurry, and intracellular materials leaked out of the cell via a damaged plasma membrane (Fig. 1H- J).

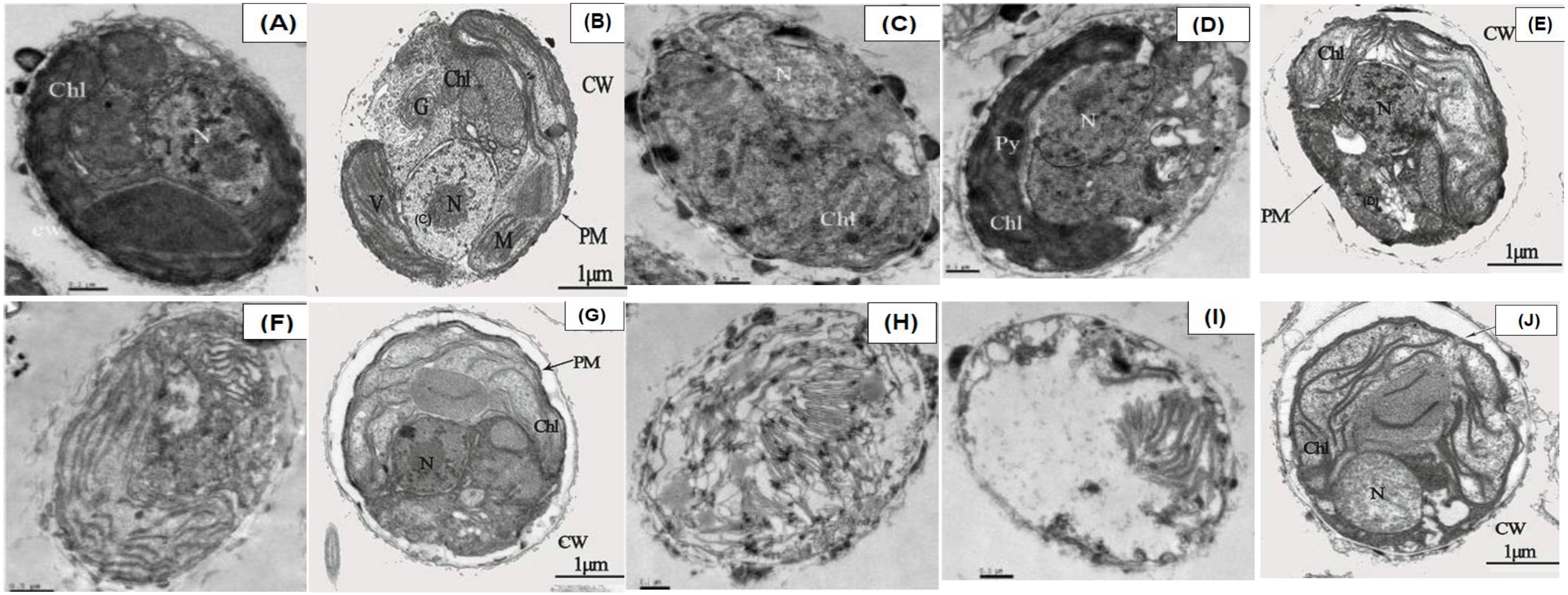

Fig. 1. TEM images of cycloheximide-treated *P. globosa* algal cells demonstrating the ultrastructure. Control cells (A-B). However, (C-E), (F-G), and (H-J) represent treatment for 24, 48, and 72h, respectively. nucleus; Py, pyrenoid; CW, cell wall; Chl, chloroplast; M, mitochondria; G, golgi body; PM, plasma membrane.

CONCLUSION

The results imply that cycloheximide administration (250µg/ ml) may be utilized as a sustainable biological control agent to mitigate the negative impacts of *P. globosa* algal blooms, especially in water treatment procedures. Current studies indicate that the mechanisms of inhibition on algal growth mainly take some pathways: photosynthesis inhibition, destruction of cell structure, inhibition of antioxidant enzymatic activities (POD, CAT, and SOD), and micromolecular compounds, including carotenoids, which increased reactive oxygen species (ROS) accumulation leading to cellular damage that can result in cell death of *P. globosa*. Cycloheximide treatment increased caspase-3 activity-induced apoptosis, reduced antioxidant enzyme activities, and increased ROS production. The main manifestations were the induction of oxidative stress, increasing malondialdehyde content, ROS formation, an impaired cell membrane structure, damage to the cell membrane structure, and potentially disrupting its barrier function, leading to cellular damage.

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Author contribution
Participation in the conceptualization, design, material preparation, data collecting, analysis, and paper draft of this study was shared by all authors. After reading the finished manuscript, each author signed for his/her approval.

Declaration of Conflict of Interest
All authors declare that there is no conflict of interest.

Data availability
Contact the author for data**.**

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