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PROLONG SUB-CHRONIC EXPOSED TO MICROCYSTIS CELL EXTRACT RESULTS IN OXIDATIVE STRESS IN MICE LIVER

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Abstract: Recent studies have indicated that oxidative damage is involved in the toxicity of microcystins in animals. In the present study, the induction of oxidative stress by Microcystis cell extract in the liver of mice after prolonged exposure to cell extracts of Microcystis aeruginosa was investigated. The extracts were administered by intraperitoneal injection to Kunming mice at a daily dose of 3.3 μg microcystins/kg for 28 days. Toxin-induced damage of the liver was found by histological observation. Determination of lipid peroxidation demonstrated a significant increase in malondialdehyde in the toxin-treated mice compared to the control group. The activities of antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase) and the detoxification enzyme glutathione S-transferase in the liver of microcystin-treated mice were significantly increased compared to the control. These results showed that prolonged exposure to Microcystis cell extract led to oxidative stress in mouse liver, and oxidative stress might play an important role in the pathogenesis of microcystin-induced toxicity.

Key words: Microcystis cell extracts; Antioxidant system; Lipid peroxidation; Oxidative stress; Mice
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Toxic blooms of cyanobacteria, especially Microcystis, pose a health threat to humans and animals due to their ability to produce hepatotoxin heptapeptides called microcystins[1]. Death of domestic and wild animals associated with microcystins has been reported all over the world[2—4]. It has also been reported that development of primary liver cancer in humans can be attributed to long-term chronic exposure to microcystins[5].

Microcystins are taken up into hepatocytes via multi-specific bile acid transporters and can potently inhibit protein phosophatase type-1 and 2A, leading to the disruption of normal cell metabolism and function[4, 6—8]. It has been reported that acute poisoning by microcystins results in rapid disorganization of the hepatic architecture, causing intrahepatic hemorrhage and even death in mammals[9—13]. Chronic uptake of microcystins resulted in generalized hepatocyte degeneration, single-cell necrosis, fibrosis, neutrophil infiltration, and tumor promotion[14—16].

Recent studies indicated that microcystins could induce oxidative stress in animals and cells[17—24]. Oxidative stress in primary cultures of rat hepatocytes treated with cyanobacteria extracts resulted in lactate dehydrogenase leakage, lipid peroxidation, and reactive oxygen species accumulation[25]. Substantial alteration in lipid peroxidation in rat liver due to microcystin administration was also found by Guzman and Soltet[26]. Additionally, anti-oxidants such as Vitamin E and selenium were found to provide some protection against lipid peroxidation induced by microcystins[27, 28].

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Glutathione S-transferases (GSTs) are an important part of the cellular detoxification system, and catalyze the conjugation of eletrophilic xenobiotics to glutathione (GSH)[29]. Pflugmacher et al[30] found the existence of a microcystin-LR-GSH conjugate that formed enzymatically via soluble GST in various aquatic organisms ranging from plants (Ceratophyllum demersum) to invertebrates (Dreissena polymorpha, Daphnia magna) up to fish (Danio retio).

Increased lipid peroxidation and decreased levels of the anti-oxidant enzymes glutathione peroxidase (GPX), superoxide dismutase (SOD), and catalase (CAT) were observed in the liver and kidney of rats after acute exposure to microcystin-LR following intraperitoneal (i.p.) injection[22]. Furthermore, Jayaraj et al[31] found similar results in the liver of mice. Nevertheless, most of these studies examined acute exposure to microcystins in mammals to high doses of microcystins. The possible oxidative damage caused by subchronic exposure to microcystins has not been well studied[26].

The Nanwan Reservoir is located in South of Henan Province, China. It is an important source for agriculture, industrial development and drinking water. Algal samples were collected from the reservoir and the predominant species identified were toxic Microcystis aeruginosa and non-toxic Aphanizomenon flos-aquae. The presence of toxic cyanobacteria in water is a potential health risk for the local habitants.

The aim of this study is to evaluate the prolonged effects of microcystins on the anti-oxidant defense system in the liver of mice. To this end, anti-oxidant GPX, SOD, and CAT activities, detoxification enzyme GST activity and lipid peroxidation levels were determined. In addition, the pathology induced by microcystins was investigated.

1 Materials and methods

1.1 Chemicals Diagnostic reagent kits for SOD, CAT, GPX, malondiadehyde (MDA), and GST were purchased from Nanjing Jiancheng Bioengineering Institute (China). Other chemicals were obtained from Sigma (St. Louis, MO, USA) and were analytical grade.

1.2 Culture of *M. aeruginosa* and determination of microcystins Algal samples were collected from the Nanwan Reservoir using a 64 μm mesh plankton net. Microscopic examination revealed that *M. aeruginosa* and *A. flos-aquae* were the dominating alga. These strains were isolated according to the method of Watanabe[32]. Mouse bioassay revealed that *M. aeruginosa* was toxic to mice while *A. flos-aquae* was non-toxic. The strain of *M. aeruginosa* has been stored in FACHB (Freshwater Algae Culture Collection, Institute of Hydrobiology, Chinese Academy of Sciences) and CCTCC No. is FACHB-1125.

M. aeruginosa were cultured in MA medium[33] at (25±1)℃ and employed as a toxin source. Microcystis cell extracts from the cultures were prepared as previously described[34]. Briefly, cells were incubated in boiling water for 15 min, and then samples were removed, cooled on ice, and centrifuged at 12 000× g for 10 min. The supernatant was collected and stored at −20℃.

Microcystin content in the extracts was determined by HPLC according to the method of Harada et al[35] by comparison with authentic standards. The concentrations of microcystin-LR and microcystin-RR were 1.510 μg/mg and 0.008 μg/mg dry weights of cell extracts, respectively. Microcystin-YR was below the limits of detection by HPLC analysis. Therefore, the total concentration of toxin in the cell extracts was considered to be 1.518 μg microcystins/mg dry weights.

1.3 Animals Male Kunming (KM) mice (body weight from 20—22 g) were provided by the Experimental Animal Center of Henan Province, China. The animals were housed in groups (4—5 mice per cage) with wood shavings as bedding in a constant temperature of 21—22℃ and humidity of 55±5% throughout all tests. The animals were allowed free access to a standard rodent pellet diet and tap water under a 12 h light-dark cycle.

1.4 Toxin exposure Mice were randomly divided into two equal groups, one of which received treatment ($n=6$) and another as a control ($n=6$). Toxin-treated mice were administered an i.p. injection of Microcystis cell extracts daily for 28 days at a dose of 3.3 μg microcystins/kg body weight. The dose was based on our previous result[36] which was approximately one-tenth of the intraperitoneal LD_{50} for Microcystis cell extracts in mice. The control group was injected with the

same volume of 0.9% saline solution. All animals received humane care. The animals were euthanized by ether inhalation after 24 h at the end of toxin exposure. The livers of mice were quickly removed, and the blood immediately washed out with ice-cold 0.9% saline solution. Livers were weighed and sections were taken for histological observation. The remainders of the livers were stored at −70℃.

1.5 Lipid peroxidation The concentration of thiobarbituric acid reactive substances (TBARS), expressed as MDA concentration (nmol/mg protein), was determined using the diagnostic reagent kit. Liver homogenates were made in cold phosphate buffered saline (PBS, pH 7.4).

1.6 Enzyme assays Liver homogenates were prepared at 10% (w/v) in 4℃ PBS (pH 7.4). The homogenates were then centrifuged at 12 000× g for 20 min at 4℃ to remove nuclei and cellular debris. The resulting supernatants were collected and stored at −70℃ until antioxidant enzyme activity was determined.

SOD (U/mg protein), CAT (U/mg protein), GPX (U/mg protein), and GST (U/mg protein) in the livers of mice were determined using the diagnostic reagent kit.

Total protein content in the liver of mice was measured using the diagnostic reagent kit (Coomassie protein assay dye).

1.7 Histopathology Liver sections were fixed in 10% neutral-buffered formalin for 24 h, and then dehydrated and embedded in paraffin. These sections (5—6 μm thick) were stained with hematoxylin and eosin (H&E) for examination under a light microscope.

1.8 Statistics SPSS 11.0 for Windows was used for all statistical analysis. Differences between the treated and control groups were evaluated by Student's *t*-test. A level of $P<0.05$ was used to indicate statistical significance.

2 Results

2.1 Body weight, hepatosomatic index and liver protein

After the experimental period of 28 days, no significant difference in final body weight was found between the treated and control groups of mice. Hepatosomatic index was increased significantly in toxin-treated mice compared to control. The protein content in liver was reduced significantly in the toxin-treated mice compared to control mice (Tab.1).

Tab.1 Effects of *Microcystis* cell extract administration on body weight, hepatosomatic index in mice

	Body weight (g)	HSI (%)	Liver protein (mg protein/g liver)
Control	37.60±2.50	5.06±0.78	152.10±5.90
Treatment	34.15±2.96	6.39±0.70*	116.70±10.70**

Data shown as mean± standard deviation. Asterisk denotes a response that is significantly different from the control (* $P<0.05$; ** $P<0.01$). HSI: hepatosomatic index (liver weight/body weight)×100

2.2 Lipid peroxidation

Lipid peroxidation levels in the livers of toxin-treated mice were significantly increased after 28 days of exposure as compared to the control group (Tab.2).

2.3 Enzyme activities

The activities of anti-oxidant enzymes (SOD, CAT and GPX) were increased significantly in the liver of toxin-exposed mice, as compared to the control group. In addition, GST activity was also increased in the liver of mice after exposure to microcystins for 28 days (Tab.2).

Tab.2 Effects of *Microcystis* cell extract administration on lipid peroxidation, anti-oxidant enzymatic activity, and GST activity in the liver of mice

	Lipid peroxidation (nmol MDA/mg protein)	SOD (U/mg protein)	CAT (U/mg protein)	GPX (U/mg protein)	GST (U/mg protein)
Control	1.88± 0.34	35.92± 2.43	2.76± 0.66	47.44± 10.05	17.36± 1.27
Treatment	2.77± 0.38**	51.47± 5.79**	5.27± 1.98*	62.78± 12.58**	26.13± 3.37**

Data shown as mean± S.D. Asterisk denotes a response that is significantly different from the control (* $P<0.05$; ** $P<0.01$)

2.4 Histopathology

The livers of control mice presented with normal histology (Fig.1A). Liver from microcystin-treated mice exhibited a disorganization of cell structure and a loss of adherence between hepatocytes; in addition, some hepatocytes showed condensed chromatin (Fig.1B). Cytoplasm became dense and cytoplasmic vacuolation appeared. Inflammatory cell infiltration was also observed in the portal space (Fig.1C-D).

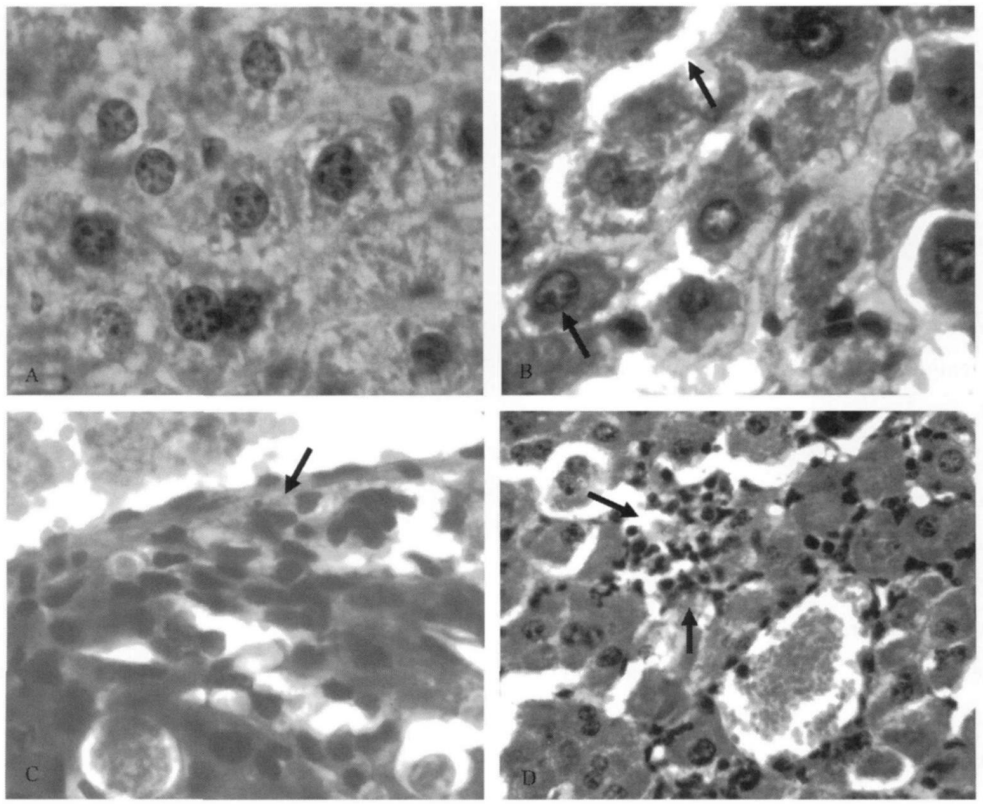

Fig. 1 Hepatic lesions in the liver of mice exposed intraperitoneally to Microcystis cell extracts for 28 days (H&E, 10×40)
A. Control liver with normal hepatic structure; B. Livers from Microcystis cell extract-treated mice showing a loss of adherence between hepatocytes and condensed chromatin (arrows); C, D. Microcystis cell extract-damaged livers with inflammatory cell infiltration (arrows)

3 Discussions

In this study *M. aeruginosa* was cultured and Microcystis cell extracts were used as a toxin source. Several studies also have used algal extracts rather than pure toxin[27, 28, 37, 38]. An advantage is that the extract is more closely to the real environmental situation[39]. A disadvantage is that the extract may contain various bioactive substances such as lipopolysaccharide.

The toxic effects of microcystins on mammals have been well studied both in vivo and in vitro[4, 40, 41]. A well-studied mechanism of microcystins is their inhibition of serine/threonine phosphatases 1 and 2A in animals. However, some recent studies indicated that oxidative damage was involved in the toxicity of microcystins in animals[17, 20, 21, 25, 26]. To evaluate the prolonged effects of Microcystis cell extracts exposure on the anti-oxidant defenses in mouse liver, this study examined the levels of MDA, anti-oxidant enzyme activities, and GST activity. These parameters are the most commonly used biomarkers of oxidation in animals[13, 28].

In the present study, an increase in the level of MDA showed that exposure to Microcystis cell extracts led to lipid peroxidation in the liver of mice, indicating that Microcystis cell extracts induced oxidative stress in the mouse liver. The finding was similar to the results observed in mouse liver[13, 24], rat liver[22, 26, 42] and primary cultured rat hepatocytes[25].

With respect to anti-oxidant enzymes, SOD activity was found increased in this study, suggesting that a rise in the O_2^- generation rate might occur. This result was consistent with our previous study in loach (*Misgurnus mizolepis*)[43]. In tilapia fish (*Oreochromis* sp.) exposed to microcystins for 21 days, an increase of hepatic SOD activity was also reported[44].

The increase of SOD activity in the liver of mice would result in a higher generation of H_2O_2. However, CAT and GPX are responsible for inactivation of H_2O_2, converting it to H_2O and O_2. In the present study, the activities of CAT and GPX in the liver of mice were significantly increased after 28 days of microcystin exposure. Similar results were observed in tilapia fish

(Oreochromis sp.)[44] and loach (Misgurnus mizolepis)[43]. In contrast to our results using a subchronic prolonged exposure Moreno, et al.[22] observed that acute exposure to microcystin-LR resulted in a decrease in these anti-oxidant enzymes in rat liver.

GSTs participate in the defense against oxidative stress by detoxifying electrophilic xenobiotics and/or reactive intermediates formed during their biotransformation[29]. Conjugation of microcystins with GSH via the action of GST was found in a previous study[30]. In the present study, the activity of GST was significantly increased in the liver of toxin-treated mice. A higher GST activity implies a greater detoxification capacity through conjugation of microcystins with GSH[28].

As MDA is considered a valuable indicator of oxidative damage of cellular components, the present results suggested that microcystin exposure enhanced reactive oxygen species generation in the liver of toxin-treated mice, and cellular anti-oxidant defenses were insufficient to maintain these harmful molecules below a toxin threshold level, leading to lipid peroxidation. These results indicated that oxidative stress might play an important role in the pathogenesis of microcystin-induced toxicity.

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微囊藻细胞抽提物亚慢性暴露导致小鼠肝脏氧化应激

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摘要: 研究了微囊藻细胞抽提物亚慢性暴露对小鼠肝脏抗氧化系统的影响。采用腹腔注射进行连续染毒 28 d, 染毒组剂量为 3.3 μg microcystins/kg 体重。结果显示, 超氧化物歧化酶、过氧化氢酶、谷胱甘肽过氧化物酶在第 4 周时发生显著性升高, 提示微囊藻细胞抽提物激活了小鼠肝脏抗氧化系统。谷胱甘肽-S-转移酶和对照组相比也显著提高, 表明谷胱甘肽-S-转移酶作为解毒Ⅰ相酶加快了对肝脏微囊藻毒素的清除。脂质过氧化产物丙二醛也显著升高, 说明抗氧化系统未能清除微囊藻细胞抽提物对小鼠肝脏的氧化损伤, 导致了氧化应激的产生。结果表明低剂量微囊藻细胞抽提物长时间暴露能够导致小鼠肝脏氧化损伤。

关键词: 微囊藻细胞抽提物; 抗氧化系统; 脂质过氧化; 氧化应激; 小鼠