Red cabbage (Brassica oleracea L.) extract reverses lipid oxidative stress in rats

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Abstract: Red cabbage (Brassica oleracea L. var. capitata f. rubra DC.) extract has been demonstrated hypolipidemic and antioxidant capacity. Herein, we investigated the effect of red cabbage aqueous extract (RC) or fenofibrate (FF) in oxidative stress induced by Triton WR-1339 in rats. The antioxidant capacity was evaluated through the superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) activities and, thiobarbituric reactive species (TBARS) and protein carbonyl (PC) levels in erythrocytes, liver, kidneys, cerebral cortex and hippocampus of male rats. The alterations promoted by Triton WR-1339 in enzymatic antioxidant defense in the liver, kidneys and hippocampus were reversed by RC or FF treatments. The TBARS and PC levels increased in the liver, cerebral cortex and hippocampus of hyperlipidemic rats were decreased by the treatments with RC or FF. These findings demonstrated that RC is a potential therapy to treat diseases not only involving dyslipidemic condition but also oxidative stress.

Key words: red cabbage, Brassica oleracea, oxidative stress, antioxidants, Triton WR-1339.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of disability and death worldwide being estimated by 2030 about 23.6 million people affected (Mendis et al. 2011, WHO 2016). Hyperlipidemia is a risk factor of CVD involved in the production of reactive oxygen species (ROS) which cause lipid peroxidation resulting in loss of membrane integrity and cell death (Schwab et al. 2000). As an end product of membrane lipid peroxidation, malondialdehyde (MDA) has shown to cross-link erythrocytes membrane causing impairment of its functions (Dumaswala et al. 1999). MDA have been implicated in neurodegenerative diseases such as Alzheimer, Parkinson, depression and aging process (Bhat et al. 2015, Ng et al. 2008). In addition, protein carbonyl has also been suggested as a marker for oxidative injury (Cao & Cutler 1995, Lucca et al. 2009). Besides, hyperlipidemic conditions modify enzymatic antioxidant defense system composed by superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) (Araujo et al. 1995, Rony et al. 2014).

Since oxidative stress could be an early event in hyperlipidemic condition antioxidants potentially can break the progress of the diseases (Roberts & Sindhu 2009, Rony et al. 2014). In line, natural compounds possessing hypocholesterolemic and antioxidant properties are of highly interest to the health community because they might prevent and treat dislipidemic disorders, since the use of statins and fibrates have demonstrated side effects and great drug dependence (Kahl & Kappus 1993) or intolerance (Ray et al. 2010). Additionally, the
frequent use of synthetic antioxidants is related to toxicity (WHO 1996).

Red cabbage (Brassica oleracea L. var. Capitata f. rubra DC.) methanolic extract in a previous study was responsible for reducing the cholesterol concentration in erythrocytes of hypercholesterolemic subjects (Duchnowicz et al. 2012) and, decreasing lipids, cholesterol and triglycerides, in rats fed with an atherogenic diet (Sankhari et al. 2012). Our previous study (Cruz et al. 2016) showed that red cabbage aqueous extract at 500 mg/kg administered twice a day has a hypolipidemic effect without toxicity in hyperlipidemic rats. Furthermore, Thounaojam et al. (2011) administered a single-dose of red cabbage ethanolic extract at 1000, 2000, 3000, 4000 or 5000 mg/kg in mice without signs of toxicity. Also, chronic administration of the extract, 1000 or 2000 mg/kg for 28 d did not register any significant alterations. Since there was no mortality up to a dose of 5000 mg/kg, LD50 of RC extract was assumed is >5000 mg/kg. Therefore, the authors mentioned considered consumption of RC extract for medicinal purposes safe.

Considering that CVD and neurodegenerative diseases share common risk factors and overlapping pathogenic mechanisms (Cechetto et al. 2008, Kalaria 2010, O’Brien & Markus 2014), the objective of this study was to investigate the effects of red cabbage extract and fenofibrate, a cholesterol reducing agent in Triton WR-1339- induced hyperlipidemic rats on the enzyme activities and oxidative stress markers in the blood, liver, kidneys, cerebral cortex and hippocampus.

MATERIAL AND METHODS

Preparation of plant material and extract

The sample of red cabbage (Brassica oleracea L. var. capitata f. rubra DC.) harvested in January, 2013 in Urubici city (highlands region of Santa Catarina State, Southern Brazil - latitude 28°15'0"S, longitude 49°35’30"W). The plant material dried at 45 °C with forced ventilation, grinded using liquid nitrogen for preservation of the antioxidants, and then stored at -10 °C (Cruz et al. 2016).

In order to obtain the aqueous extract, 2 g of plant material were added into 100 ml of distilled water and boiled for 10 min. The phenolic acids, dicaffeoylquinic and cinnamic (7.10 ± 1.41 and 2.08 ± 0.30 g/100g, respectively), and flavonoids, gallocatechin and epicatechin (2.12 ± 0.42 and 1.99 ± 0.28 g/100 g, respectively) are the majority compounds of red cabbage aqueous extract (RC - Cruz et al. 2016). The RC was filtered, lyophilized, stored in freezer at -20 °C and dissolved in distilled water at the time of administration.

Animals

Male Wistar rats (200-300 g) were maintained at 21–23 °C with free access to water and food, under a 12:12h light/dark cycle. In this study, all procedures were performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals. The experiments were developed after approval of the protocol by the Institutional Ethics Committee (CEUA/FURB – 009/13). All efforts occurred in order to minimize the animals’ suffering and to reduce their numbers to the minimum necessary to demonstrate consistent effects in the experiments.

Experimental protocol

The rats were allowed to acclimatize for 1 week before the experiments and then divided into five groups (n=5-6 animals/group). The hyperlipidemic control group named Triton control (TC) performed with a single intraperitoneal administration (i.p.) of Triton...
WR-1339 (400 mg/kg—Sigma Chemical Company, Saint Louis, MO, USA) and, normal control (NC) with distilled water, red cabbage aqueous extract (RC – 125 or 250 mg/kg) and fenofibrate (FF- 65 mg/kg—EMS S/A, SP, Brazil), were given by blunt gavage twice a day, for three consecutive days. On the first day, when administered the Triton WR-1339 injection the others treatments started immediately after. The doses of Triton WR-1339, RC and FF were chosen based on previous studies (Cruz et al. 2016, Zeni et al. 2017).

**Tissue preparation**

After experimental protocol all the animals were euthanized by decapitation and the blood, liver, kidneys and brain removed and kept in ice-cold buffered saline (154 mM NaCl, 5 mM Tris–HEPES, pH 7.5). The cerebral cortex, hippocampus, liver and kidneys were carefully dissected and 10% (w/v) homogenate prepared in 20 mM sodium phosphate buffer with 140 mM KCl, pH 7.4, using a Potter-Elvehejem homogenizer (five pulses). The homogenates were centrifuged at 3000 g, 4 ºC for 15 min to remove cell debris. After, the supernatants saved in aliquots, stored at -20 ºC for assaying the free-radical scavenging enzymes, estimation of lipid peroxidation and damage to protein (Lenzi et al. 2015).

**Biochemical analyses**

**Catalase (CAT) assay**

CAT activity was assayed according Aebi (1984); hydrogen peroxide (H₂O₂) disappearance was continuously monitored with a spectrophotometer at 240 nm for 90 s. One unit of the enzyme defined as 1 μmol of H₂O₂ consumed per minute and the specific activity reported as units per mg protein.

**Glutathione peroxidase (GSH-Px) assay**

GSH-Px activity was measured through the concentration of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) adjusted to 0.1 mM, after previous tests performed in our laboratory. Tert-butyl-hydroperoxide was used as a substrate. NADPH disappearance was continuously monitored with a spectrophotometer at 340 nm for 4 min. One GSH-Px unit defined as 1 μmol of NADPH consumed per minute and the specific activity reported as units per mg protein (Wendel 1981).

**Superoxide dismutase (SOD) assay**

The SOD assay activity was based on the capacity of pyrogallol to autoxidize, a process highly dependent on O₂, which is a substrate for SOD (Marklund 1985). The inhibition of this process occurs in the presence of SOD, whose activity can then be indirectly assayed spectrophotometrically at 420 nm. A calibration curve was performed with SOD as a standard, to calculate the enzyme activity present in the samples. The results were reported as units per mg protein.

**Thiobarbituric acid-reactive substances (TBARS)**

TBARS levels were determined according to the method described previously (Ohkawa et al. 1979). TBARS measures malondialdehyde (MDA), a product of lipoperoxidation caused mainly by hydroxyl free radicals. Briefly, plasma or homogenate in 1.15% KCl was mixed with 20% trichloroacetic acid and 0.8% thiobarbituric acid and heated in a boiling water bath for 60 min. TBARS levels were determined by the absorbance at 532 nm. The calibration curve was performed using 1,1,3,3-tetramethoxypropane and each curve point was subjected to the same treatment as that of the supernatants. TBARS levels were calculated as nmol per mg of protein of MDA.
**Protein carbonyl (PC)**

The protein carbonyl content was assayed by Reznick & Packer (1984) method with modifications. After the homogenate preparation, supernatant was discarded and the pellet resuspended in 10 mM 2,4-dinitro-phenyl hydrazine (DNPH). The protein was precipitated with 20% trichloroacetic acid and the pellet was washed with 1 ml ethanol:ethyl acetate (1:1 v/v) solution. Finally, the pellets dissolved in 6 M guanidine hydrochloride at 37 °C were centrifuged at 14000 rpm for 3 min and the samples read at 370 nm. The carbonyl content was expressed in nmol per mg of protein.

**Protein determination**

Protein was measured using serum bovine albumin as standard (Lowry et al. 1951).

**Statistical analysis**

The results were expressed as means ± standard deviation (SD). Comparisons between treatments and control groups were performed by one-way or two-way analyses of variance (ANOVA) followed by Tukey's HSD test, when appropriate. A value of $p<0.05$ was considered significant.

**RESULTS**

**Effects of Red Cabbage aqueous extract (RC) or Fenofibrate (FF) on TBARS and PC levels in the kidneys, liver, serum, cerebral cortex and hippocampus of Triton WR-1339-induced lipid oxidative stress in rats**

As shown in Figures 1a, b, c and 2a, b Triton WR1339 caused an increase on TBARS level in the kidneys and liver ($p<0.05$), as well as, in the serum, cerebral cortex and hippocampus ($p<0.001$), respectively. While, Triton WR-1339 also caused an increase in PC level in the kidneys ($p<0.01$), liver, serum ($p<0.001$) and in the cerebral cortex ($p<0.01$), but none in the hippocampus of rats compared to the control (Figure 1d, e, f and Figure 2c, d, respectively).

The RC 125, RC 250 and FF were effective in decreasing TBARS levels in the liver (Figure 1b) although did not abolish the increase of TBARS in the kidneys and serum (Figure 1a and c). Only FF decreased lipid peroxidation in the liver ($p<0.05$) and serum ($p<0.01$). In the cerebral cortex and hippocampus the effect was dose dependent with statistical difference between RC 125 and RC 250 ($p<0.05$ and $p<0.001$, Figure 2a and b, respectively).

Furthermore, the increase in the PC level was counteracted by both doses of RC in kidneys ($p<0.01$; $p<0.001$) and cerebral cortex ($p<0.05$; $p<0.01$), with a dose dependent effect (Figure 1d, 2c). Moreover, just RC 125 decreased the PC level in the liver ($p<0.01$) and RC 250 caused the decrement in the serum ($p<0.001$) and, FF decreased the content in both structures ($p<0.05$ and $p<0.001$) (Figure 1e, f). Also, neither RC nor FF altered the PC level in the hippocampus (Figure 2d).

**Effects of Red Cabbage aqueous extract (RC) or Fenofibrate (FF) on SOD, CAT and GSH-Px activities in the liver, kidneys and erythrocytes of Triton WR-1339-induced lipid oxidative stress in rats**

The results depicted in Figure 3 show that Triton WR-1339 caused a decrease on SOD ($p<0.01$) and CAT ($p<0.001$) activities in the kidneys (Figure 3a and d) while in both, liver and erythrocytes, happened an increase on SOD and a decrease on CAT activities ($p<0.001$) (Figure 3b, c and e, f, respectively). The activity of GSH-Px also was modified; in kidneys and liver (Figure 3g and h) occurred an increase ($p<0.001$), but it did not cause any alterations in the erythrocytes (Figure 3i).

The RC 250 or FF treatment by oral route was capable to counteract all alterations on enzyme
activities. The higher dose of RC was necessary to normalize CAT activities in liver and erythrocytes and, GSH-Px in kidneys.

**Effects of Red Cabbage aqueous extract (RC) or Fenofibrate (FF) on SOD, CAT and GSH-Px activities in the cerebral cortex and hippocampus of triton wr-1339-induced lipid oxidative stress rats**

As shown in Figure 4, the injection of Triton WR-1339 was capable to decrease significantly SOD (Figure 4a) activity in the cerebral cortex of rats, compared to the control (p<0.001), without significant alterations on CAT and GSH-Px activities (Figure 4c and e). In this structure, the RC higher dose (250 mg/kg) and FF were able to abolish the effect induced by the hyperlipidemic drug. Although, analyzing hippocampus reaction to the detergent, was observed a significant decrement on SOD and CAT (Figure 4b and d, respectively) and an increment on GSH-Px (Figure 4f) activities compared to the control group. Furthermore, RC 250 and FF treatments were efficient in normalizing the activity of the enzyme SOD and RC 125 and 250, as well as FF treatments were able to prevent the alterations on CAT and GSH-Px activities.

**DISCUSSION**

The consumption of red cabbage (*Brassica oleracea* var. *capitata f. rubra* - *Brassicaceae*) has been linked to the reduction risk of chronic illness, including cardiovascular diseases (Cartea et al. 2011, Jahangir et al. 2009). Previously, we demonstrated that RC has a hypolipidemic effect against Triton WR-1339- induced hyperlipidemia.
in rats that markedly increased cholesterol (4 times) and triglycerides (9 times) compared to the control (Cruz et al. 2016). The hyperlipidemic effect of Triton WR-1339 is caused by the inhibition of the lipoprotein lipase (LPL) decreasing of triglycerides hydrolysis as a consequence raising the levels of triglycerides and cholesterol. Furthermore, Zarzecki et al. (2014) demonstrated an elevation of lipid peroxidation in the liver of mice in the same model.

Since the lipid peroxidation is an event in acute hyperlipidemic condition, the model used for induction of hyperlipidemia would be able to alter other parameters of antioxidant defense showing evidence that oxidative stress is an early event in hyperlipidemia. Herein, Triton increases the production of free radicals by enhancing mitochondrial respiration and down regulating the antioxidant system. The increased levels of triglycerides and cholesterol in blood are associated with mitochondrial dysfunction since induce an overproduction of superoxide radicals possibly due exacerbated xanthine oxidase activity in the endothelium which causes oxidative alterations on their lipids, proteins, and DNA (Chowdhury et al. 2010, Ohara et al. 1993, Puddu et al. 2005). Furthermore, it has been reported that antioxidant enzymes can be inactivated by lipid peroxides and ROS (Halliwell & Gutteridge 1984). Yang et al. (2008) concluded that oxidative stress is an early event in the hyperlipidemia condition and antioxidant supply prevent or delay the development of the illness.

In this sense, we hypothesized that RC might be beneficial for erythrocytes, liver, kidneys, cerebral cortex and hippocampus of rats submitted to hyperlipidemia since cited tissues and organs with high quantity of polyunsaturated fatty acids being more susceptible to oxidative stress (Gomes et al. 2011, Horton et al. 2002, Ozbek 2012).

The principal enzymatic antioxidant defense includes SOD enzyme, which promotes the
dismutation to superoxide radical in hydrogen peroxide, which can be removed by two types of enzymes, CAT and GSH-Px, that catalyses the reduction of hydrogen peroxide into water and oxygen, considering important to scavenge free radicals (Horton et al. 2002). Moreover, the compatibility of enzymes to the free radicals could be variable; the affinity of GSH-Px for H$_2$O$_2$ is higher at low levels, at the same time that CAT’s affinity increases with the rise of the H$_2$O$_2$ level (Herbette et al. 2007). Furthermore, the increase of enzymes activity denotes a response to the rise of ROS production (Laaksonen et al. 1999). Therefore, it has been reported that these enzymes can be inactivated by lipid peroxides and ROS in general (Sarandol et al. 2007).

In this study, Triton WR-1339, an LPL inhibitor, produced a consistent oxidative attack demonstrated through altered stress markers, TBARS, PC and enzymatic defense (SOD, CAT, and GSH-Px). Previous studies demonstrated that hyperlipidemia increased TBARS and PC levels (Halliwell & Gutteridge 1984, Zarzecki et al. 2014), reduces the enzymatic antioxidant defense (Anandhi et al. 2013, Ko et al. 2007, Ragheb et al. 2011, Vijayaraj et al. 2013) producing toxic

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**Figure 3. Effects of red cabbage aqueous extract (RC) and fenofibrate (FF) treatments on antioxidant enzymes activities in kidneys (left, panels a, d and g), liver (middle, panels b, e and h) and erythrocytes (right, panels c, f and i) of Triton WR-1339-induced hyperlipidemia in rats. Bars represent means± S.D. (n=5–6). **p <0.001, ***p<0.001 vs normal control (NC) and ###p<0.01, ####p<0.001 vs Triton control (TC), according to one-way ANOVA followed by Tukey’s test. SOD= superoxide dismutase; CAT= catalase; GSH-Px= glutathione peroxidase.**
intermediates (Araujo et al. 1995, Catapano et al. 2000). Herein, the SOD activity increased in the erythrocytes and liver and decreased in the other organs. Discordantly, the decrement of SOD activity in the liver of hyperlipidemic animals was demonstrated (Ling et al. 2012, Zarzecki et al. 2014).

In the present study, CAT activity decreased in the kidneys, liver, hippocampus and erythrocytes while remained without alteration in the cerebral cortex of hyperlipidemic rats. Furthermore, in hyperlipidemic animals GSH-Px activity rose in the kidneys, liver and hippocampus, while did not alter in the cerebral cortex and erythrocytes. Similarly, the decrement on CAT activity in liver of mice without changes on GSH-Px activity is consistent with previous findings (Ko et al. 2007, Oh et al. 2006). The impairment on CAT activity also was found in the kidneys of hyperlipidemic rats induced by Triton WR-1339 (Salama & Ibrahim 2015). However, discrepancies found among studies may be due to the nature of the tissue/organ used, experimental period and Triton dose.

RC and FF presented a consistent effect against the lipid oxidative stress exerted

![Figure 4. Effects of red cabbage aqueous extract (RC) and fenofibrate (FF) treatments on antioxidant enzymes activities in cerebral cortex (left, panels a, c and e) and hippocampus (right, panels b, d and f) of Triton WR-1339-induced hyperlipidemia in rats. Bars represent means±S.D. (n=5–6). ***p<0.001 vs normal control (NC) and ####p<0.001 vs Triton control (TC), according to one-way ANOVA followed by Tukey’s test. SOD= superoxide dismutase; CAT= catalase; GSH-Px= glutathione peroxidase.](image-url)
Figure 5. The schematic diagram shows biochemical pathways underlying Triton WR-1339-induced lipid oxidative stress and the antioxidant effects of RC and FF, a PPARα agonist. In this study, the RC and FF counteracted the alterations induced by Triton beyond the decrement of TBARS and PC levels normalizing the enzyme activities. CAT=catalase; FF= fenofibrate; GSH-Px= glutathione peroxidase; LPL= lipoprotein lipase; PPARα= Peroxisome proliferator-activated receptor alpha; PC= protein carbonyl; RC= red cabbage aqueous extract; SOD= superoxide dismutase; TBARS=thiobarbituric acid reactive substances.

by Triton demonstrated by the reduction of TBARS level in the liver, cerebral cortex, hippocampus, and PC level in the kidneys, liver, erythrocytes, and cerebral cortex. Consistently, the activity of enzymes was normalized such as; SOD in all animal materials tested, CAT in the kidneys, liver, erythrocytes and, hippocampus and GSH-Px in the liver, kidneys, and hippocampus. Therefore, we showed a link between hyperlipidemia and the increase of oxidative stress. The effect exerted by Triton WR-1339 was counteracted by RC and FF treatments showing different oxidative parameters response according to the tissue or organ studied. As a matter of fact, the tests approached depicted suppression of oxidative stress, suggesting that the modulation of the antioxidant defense played a crucial role in the hypolipidemic effect of RC and FF.

In this regard, red cabbage ameliorates diabetic nephropathy in rats normalizing TBARS level and SOD activity by possibly compensatory mechanisms for the overproduction of free radicals and oxidative stress (Kataya & Hamza 2008). The protective property of red cabbage is consistent with its ability to counteract oxidative damage induced by toxic agents in animal tissues (Igarashi et al. 2000, Lee et al. 2002). Consistently, plant phenolics and anthocyanins are involved in inhibition of oxidative process (Chong et al. 2010, Thompson et al. 2016, Urso & Clarkson 2003, Vincent & Taylor 2006). Moreover, the RC in a previous study showed high levels of anthocyanins and dicaffeoylquinic and cinnamic acids, and the flavonoids, galocatechin, and epicatechin, as the
majority compounds identified by HPLC (Cruz et al. 2016), are well-known antioxidants. And also, Chrysanthemum mirofolium extracts presented as majority compound, caffeoylquinic acid decreased MDA, elevated GSH-Px activity and up-regulated PPARα decreasing hyperlipidemia (Cui et al. 2014, Lin & Harnly 2010).

Furthermore, the agonist of PPARα, FF, significantly decreased SOD activity in MPTP-lesioned rats and demonstrated, neurological recovery-promoting, anti-inflammatory, and antioxidant effects in traumatic brain injury (Barbiero et al. 2014, Chen et al. 2007). Additionally, the increases of the antioxidant enzymes, SOD and GSH-Px have been studied as markers of neuroprotection (Bordet et al. 2006). In fact, PPARα activation induces expression and activation of SOD and GSH-Px and this receptor has been localized in the cerebral cortex and hippocampus (Moreno et al. 2004). Consistently, the neuroprotective effect against cerebral ischemia of FF treatment after 3 days, the same experimental period used in the present study, has been previously demonstrated (Inoue et al. 2003). In this way, the PPREs (PPAR-responsive elements) have been found in the SOD gene (Moraes et al. 2006). Indeed, it has been an increasing body of evidence on the relation between PPARα and redox signaling. Kunsch & Medford (1999) mentioned that gene activation in aged mice restored the cellular redox balance, effect not observed in null mutated animal and also, administration of vitamin E cause increased expression of the gene. Therefore, suggesting that the redox balance may provide transcriptional regulation for PPARα. Additionally, the liver is protected against ROS via increased expression of antioxidant enzymes genes of SOD and CAT which are controlled by PPARα (Girnun et al. 2002, Inoue et al. 1998, Nakamuta et al. 2008).

Finally, the administration of Triton WR-1339, a non-ionic detergent, inhibits the LPL function leading to an increase of lipids, although, RC or FF decreased cholesterol and triglycerides levels in rats (Cruz et al. 2016). In this study, the administration of RC or FF reversed the Triton WR-1339 induced-lipid peroxidation, protein carbonylation and alterations on antioxidant enzymes activities in the serum, erythrocytes, liver, kidneys and, brain of rats. The in silico analysis showed a weak interaction between RC phenolics and the modulation of PPARα. On the other hand, it showed strong antioxidant activity for dicaffeoylquinic acid, gallocatechin and epicatechin (data not shown) reinforcing the data obtained here. Therefore, we hypothesized these RC phenolics could be acting as indirect ligands of PPARα (Figure 5). However, further studies are needed on ROS production by mitochondrial dysfunction during the hyperlipidemic experimental model, mainly in the mitochondrial complexes and ATP production, to clarify the link between RC lipid-lowering effect and PPARα activation.

CONCLUSIONS

In conclusion, the present investigation has demonstrated the putative antioxidant activity of RC extract in Triton WR-1339-induced lipid oxidative stress in rats. The lipid-lowering potential previously demonstrated by our research group is accompanied by antioxidant activity that appeared to be more pronounced than FF, the standard lipid-lowering agent used in this study. Further studies on the effects are required. In spite of, we provided evidence about the usage of red cabbage not only as a hypolipidemic agent but also as an organs protector against oxidative damage, mainly the brain.
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BV performed experiments, collected samples, analyzed data and co-wrote the paper. AC and APD performed experiments and co-wrote the paper. BG collected samples, performed experiments and co-wrote the paper. DDDM and DDL supervised the research, designed experiments and co-wrote the paper. ALBZ supervised the research, designed experiments, analyzed data and co-wrote the paper.