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Antioxidant and antihyperlipidemic activities of unique nicotinyl polysaccharide from the green seaweed *Ulva pertusa*

Yuzhou Wan[1], Xintao Chang[2], Lin Liu[1], Shaopeng Wang[1], Huimin Qi[1*] and Fang Yan[1]

[1]College of Pharmacy, Weifang Medical University, Weifang, Baotong Road 7166, 261053, China.
[2]People's Hospital of Zhangqiu District, Jinan, Huiquan Road, No. 1920, 250200, China.

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Nicotinyl derivative of polysaccharide (NU) from the green seaweed *Ulva pertusa* (Chlorophyta) has unique structure and strong antioxidant activity *in vitro*. In the present study, *in vivo* antioxidant and antihyperlipidemic activities were tested in the livers of hyperlipidemic mice. Activity levels of superoxide dismutase, glutathione peroxidase (GSH-P_X), catalase, and malondialdehyde were observed. At the 500 mg/kg dose, NU showed strongest antioxidant activity compared with the hyperlipidemic mice. This dose also increased GSH-Px compared with ulvan. NU at a dose of 125 mg/kg showed the strongest antihyperlipidemic activity, significantly decreasing total cholesterol (TC), triglyceride (TG), and low-density lipoprotein levels (LDL-C), as well as elevating high density lipoprotein. The antioxidant and antihyperlipidemic mechanisms of NU may be related to the nicotinyl group in its chemical structure. NU may be effective in protecting liver tissue from the damage of a cholesterol-rich diet in mice and may be of use as a novel antihyperlipidemic agent.

Key words: *Ulva pertusa*, polysaccharide, nicotinyl ulvan, antioxidant activity, hyperlipidemic activity.

INTRODUCTION

Dyslipidemia is characterized with high levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and a low level of high-density lipoprotein cholesterol (HDL-C) in clinical investigations. Disordered lipid metabolism is a primary cause of atherosclerosis and cardiovascular disease (Arnett et al., 2019). In China, related report indica-ted that the prevalence and mortality from cardiovascular disease (CVD) were significantly increased with a rise in living standard and worsening lifestyle habits in the past 20 years (Hu et al., 2017). Reactive oxygen species (ROS) are free radicals with the center of oxygen. The massive production of ROS induces the hyperlipidemia (Miah et al., 2021; Steven et al., 2017; Zhang et al., 2016). Their extreme unstableness and ability to react very quickly with other substances and groups in the body can lead to injury of cells or tissues (Zimmerman and Case, 2019).

ROS can be scavenged by many enzymes, such as

*Corresponding author. E-mail: wfqihuimin@126.com. Tel: +86 536- 8462493.

superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-P_X) and peroxiredoxin (Prx) (Garcia and Blesso, 2021).

A polysaccharide is a large molecule comprised of a chain or ring of smaller monosaccharides, or simple sugars, which are linked by glycosidic bonds. The biological activities of antioxidant, anti-inflammatory and so on are reasons polysaccharides are being studied intensively (Liu et al., 2015). Much attention has been focused on polysaccharides isolated from algae (Cao et al., 2021; Li et al., 2020; Liu et al., 2019). *Ulva pertusa,* (sea lettuce), is an edible green alga. Off the eastern coast of China, it is distributed in the Bohai Sea and the Yellow Sea. *U. pertusa* is a low-calorie food containing abundant vitamins, dietary fiber, and trace elements (Tanna and Mishra, 2019). Polysaccharides extracted from *U. pertusa* show a wide range of pharmacologic activities such as antioxidant, antiviral, anti-hyperlipidemia, and anticancer properties (Li et al., 2018; Liu et al., 2019; Sun et al., 2018). Ulvan is a water-soluble polysaccharide extracted from *U. pertusa*, and is in a group of sulphated heteropolysaccharides mainly composed of rhamnose, xylose, glucose, glucuronic acid, iduronic acid, and sulfate (Gao et al., 2020; Li et al., 2020, 2018).

Synthetic antihyperlipidemic agents may be effective for treating dyslipidemia; however, their adverse effects are well known. Natural sources of antioxidants and antihyperlipidemics may potentially mitigate these side effects. It has been found that natural antioxidants possess potential antihyperlipidemic activities (Mu et al., 2021; Adigun et al., 2016). In previous research, our team has prepared the nicotinyl ulvan (NU) and demonstrated its antioxidant activities *in vitro* (Chang et al., 2017). Thus, in the current study we firstly explored the antihyperlipidemic and antioxidant activities of NU in the mice model of hyperlipidemia.

MATERIALS AND METHODS

Ethical approval

This study was approved by the Ethics Committee for Animal Studies, Weifang Medical University and carried out in accordance with the National Academy of Sciences Guide for the Care and Use of Laboratory Animals (2011).

Plant materials

U. pertusa was collected on the coast of Taiping Jiao, Qingdao, China, in October, 2015. The algae specie was identified at the Medical University, China (Figure 1) and thereafter washed, air-dried, and stored at 25°C in plastic bags before use.

Chemical reagents

Malondialdehyde (MDA), SOD, CAT, and GSH-Px assay kits were obtained from Nanjing Jiancheng Bioengineering (Nanjing, China). Serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) assay kits were purchased from Shanghai Rongsheng Biotech (Shanghai, China). All other chemical regents were of analytical grade.

Preparation of nicotinyl ulvan

Ulvan isolated from *U. pertusa* (U) and nicotinyl ulvan (NU) were prepared according to the method described by Chang et al. (2017). NU was prepared using the solvent dimethylformamide (DMF). The mass ratio of ulvan to nicotinoyl was 1:2, with the reaction carried out at 125°C for 4 h. The nitrogen contents of ulvan and NU were 0.60 and 6.62%, respectively. Elemental analyzer (vario EL cube; Elementar Analysensysteme GmbH, Ronkonkoma, NY, USA) was used to measure the nitrogen content of NU.

Experimental design

Seventy (70) male Kunming mice (18 ± 2 g) were purchased from the Animal Laboratory Center, Shandong University, China (license no. SCXK (Lu) 20090001). The mice were housed under controlled conditions of 12 h light:dark cycle, room temperature, and 60% humidity. After three days of acclimatization, mice were randomly divided into 7 groups. Both the normal (NOR) and hyperlipidemia control (MOD) groups received the same daily intragastrically-administered volume (0.7 ml) of deionized water. U group was treated daily with ulvan (250 mg/kg). LNU, MNU, HNU groups were treated with low-dose (125 mg/kg), medium-dose (250 mg/kg), and high-dose (500 mg/kg) of NU in daily, respectively. Positive group received nicotinic acid daily (500 mg/kg). Treatment was for 32 days.

NOR group remained on the standard laboratory diet throughout the study. Animals in all of other groups received a high-cholesterol diet consisting of sodium cholic acid, cholesterol, lard and commercial chow, with the proportion of them being 0.3, 2.0, 8.0 and 89.7%, respectively (Qi et al., 2005). Food intake was recorded daily. During the study period, all animals were weighed every five days during the first 25 days and then weighed for the last time from days 26 to 32 to determine the final weight. After 32 days, the animals were fasted for 12 h. They were then re-weighed, animals were anesthetized with 4% chloral hydrate and blood samples (about 1 ml) were collected retro-orbitally. According to manufacturers' instructions, the levels of TC, TG, HDL-C, and LDL-C in serum were measured. Animals were then euthanized by cervical dislocation; thereafter the livers were removed and immediately stored at −80°C. MDA, SOD, CAT and GSH-Px were detected using the commercial kit following the protocols provided by manufacturer.

Statistical analysis

Data were expressed as mean ± SD and analyzed by one-way ANOVA. Differences were considered to be significant when $P < 0.05$, and very significant when $P < 0.01$.

RESULTS

Food intake and body weight of mice

Among the seven groups, there were no significant changes in food intake, though the normal control group

Figure 1. Appearance of *Ulva pertusa* collected from Qingdao, Shandong province, China.

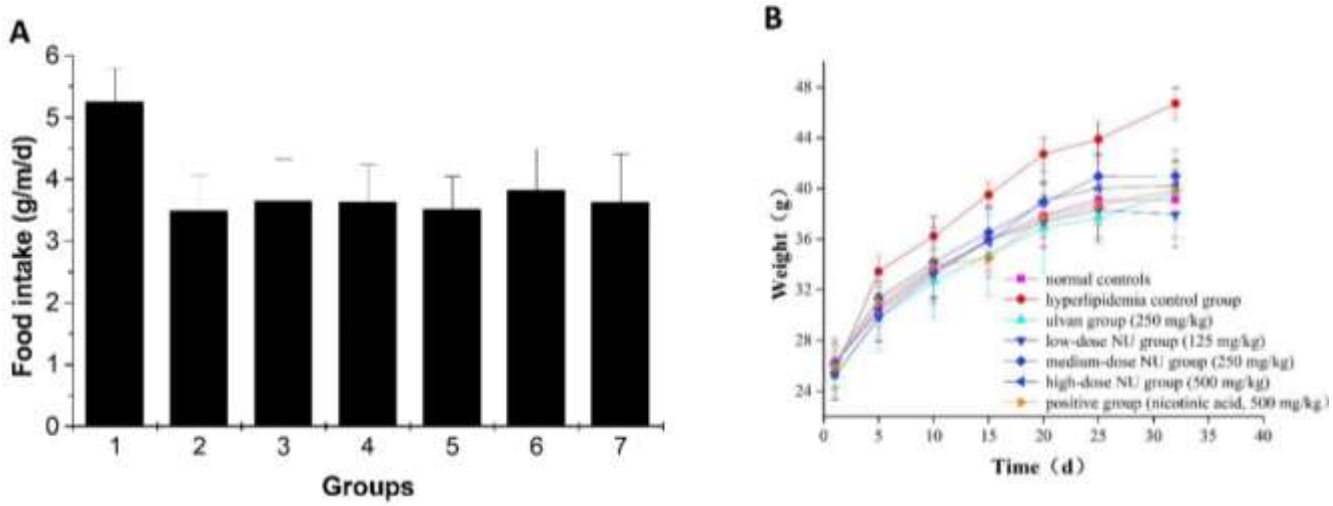

Figure 2. Effect of nicotinyl ulvan on food intake and body weight of mice (A. food intake, 1: NOR group; 2: MOD group; 3: U group (250 mg/kg); 4: LNU group (125 mg/kg); 5: MNU group (250 mg/kg); 6: HNU (500 mg/kg); 7: Positive group (nicotinic acid, 500 mg/kg); B. body weight).

did exhibit an elevated but insignificant level of food intake (Figure 2A). Hyperlipidemia is typically accompanied by an increase in body weight (BW). Throughout this study, all mice remained in good health, without mortalities. In the first 5 days, BW gain was observed in all of the groups without significant difference. From the 6th day, BW gain in the hyperlipidemia group increased rapidly, and was significantly higher compared with the normal control group ($P < 0.05$) (Figure 2B). There were no significant differences in BW gain of the other six groups. Of note, BW decreased during the last week of the study, although not significantly between low-dose

Table 1. Activities of antioxidant enzymes in high-cholesterol diet mice liver.

Group	Dose (mg/kg)	SOD (U/mg prot)	GSH-Px (U/mg prot)	CAT (U/mg prot)	MDA (nmol/mg prot)
1	-	99.47±13.80	452.39±68.00	331.49±53.30	0.86±0.27
2	-	75.32±8.84*	289.85±85.91**	188.63±47.40*	1.08±0.17*
3	250	94.99±14.41#	336.76±60.34	313.54±59.00#	0.84±0.24#
4	125	94.13±14.04	436.28±86.56#	334.91±61.80#	0.87±0.17
5	250	91.58±21.35	384.11±69.21	274.56±46.10	0.87±0.16
6	500	96.37±25.32#	450.59±72.34##△	326.84±51.30#	0.93±0.19
7	500	98.10±19.96#	355.75±73.51	305.17±34.70#	0.84±0.16#

1: NOR group; 2: MOD group; 3: U group (250 mg/kg); 4: LNU group (125 mg/kg); 5: MNU group (250 mg/kg); 6: HNU (500 mg/kg); 7: Positive group (nicotinic acid, 500 mg/kg), *P < 0.05, **P < 0.01 vs. NOR group; #P < 0.05, ##P < 0.01 vs. MOD group. △P < 0.05 vs. U group.

Table 2. Changes of serum lipid profiles in high-cholesterol diet mice.

Group	Dose (mg/kg)	TC (mmol/L)	TG (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	LDL/HDL
1	-	3.06±0.56	0.98±0.04	0.26±0.08	1.00±0.30	0.26
2	-	4.70±0.84**	1.52±0.46*	0.46±0.08**	0.57±0.11*	0.81
3	250	3.56±0.45##	1.05±0.38#	0.34±0.05#	0.79±0.21#	0.43
4	125	3.85±0.61#	0.79±0.25##, △	0.30±0.10#	0.84±0.32#	0.36
5	250	4.23±0.27	1.04±0.29#	0.41±0.07	0.88±0.02#	0.47
6	500	4.37±0.51△	0.99±0.25##	0.38±0.08	1.06±0.18#	0.36
7	500	3.69±0.29##	1.04±0.27#	0.33±0.12#	1.02±0.28#	0.32

1: NOR group; 2: MOD group; 3: U group (250 mg/kg); 4: LNU group (125 mg/kg); 5: MNU group (250 mg/kg); 6: HNU (500 mg/kg); 7: Positive group (nicotinic acid, 500 mg/kg), *P < 0.05, **P < 0.01 vs. NOR group; #P < 0.05, ##P < 0.01 vs. MOD group. △P < 0.05 vs. U group.

NU group (125 mg/kg) and the normal controls.

Antioxidant activities of ulvan, NU, and nicotinic acid in high-cholesterol diet mice liver

Compared with the MOD group, the HNU group exhibited more optimal effects on antioxidant enzyme (SOD, CAT, and GSH-Px). After treating with high dose of NU, the activities of these enzymes increased by 27.9, 55.5, and 73.3% (P < 0.05), respectively (Table 1). Moreover, compared with the U, HNU significantly increased GSH-Px (33.8%; P < 0.05). However, all U and three dose NU-treated groups exhibited no significant effects on MDA. Furthermore, MDA levels were not affected by U nor by the three dose levels of NU.

Effects of ulvan, NU, and nicotinic acid on serum lipid indicators in high-cholesterol diet mice

In the serum, MOD group showed significant levels of TC, TG, and LDL-C is about 1.5, 1.6, and 1.8 times higher than that of the NOR group (P < 0.05), respectively (Table 2). Compared with the NOR group, HDL-C levels in MOD group were obviously reduced by 43.0% (P < 0.05). All above data indicated that the hyperlipidemic model was successfully established. After 32 days of treatment, levels of TG were decreased significantly in the NU groups than in the MOD group, with the LNU group exhibiting the most robust response. TG reduced by 48.0% (P < 0.01) than the MOD group and reduced by 24.8% (P < 0.05) compared with the U group. However, these declines were not in a dose-independent manner. In the LNU group, the levels of TC, LDL-C, and TG were significantly decreased by 18.1, 34.8, and 48.0% than MOD group (P < 0.05), respectively, while the level of HDL-C in serum improved by 47.4% (P < 0.05). On the other hand, compared with the MOD group, U and three NU dose groups all had significant effects on HDL-C levels. The results indicated that LNU group may be beneficial for the treatment of hyperlipidemia.

DISCUSSION

The antioxidant enzymes (SOD, CAT, and GSH-Px)

prevent against the production of ROS under oxidative stress (Irazabal and Torres, 2020). It has been demonstrated in hyperlipidemic rat model that the vigours of SOD, CAT, and GSH-Px were decreased (Li et al., 2020). The activities of these antioxidant enzymes were also decreased in the liver of hyperlipidemic mice (Ru et al., 2019; Wang et al., 2019). In the present study, ulvan and NU showed that strong activity improved the ability of these three enzymes in the livers of hyperlipidemia mice, especially under those treated with high dose of NU, which exhibited the strongest activity. SOD as crucial endocellular compound plays a role in protecting against oxidative stress caused by superoxide anion. For NU groups, only HNU (500 mg/kg) significantly improved the activity of SOD. CAT, enriched in hepatocytes, is crucial in catalyzing dismutation of toxic H_2O_2 (Hong and Park, 2021). Except for the MNU group (250 mg/kg), the activity of CAT showed significant difference between other drug administration groups and hyperlipidemic mice. MDA as the marker of oxidative stress mainly produced by endogenous lipid peroxidation, a process induced by free radicals (Mas-Bargues et al., 2021). However, in this study, as compared with the positive and ulvan groups, all three doses of NU showed lesser activity on MDA.

The beneficial effects of a serum high level of HDL-C are well known. In the liver, HDL-C plays a role in cholesterol metabolism by reverse cholesterol transport (Zhao et al., 2012). In our study, mice that received U, the three doses of NU, or the positive controls all showed significantly increased HDL-C levels, with high-dose NU exhibiting similar activity to the positive controls. The increased LDL/HDL ratio and its existence in a positively correlated manner showed that the ratio of LDL-C to HDL-C could be a predictor of atherosclerosis and cardiovascular conditions (Carr et al., 2019). Our data indicated that administration of low and high-dose NU significantly suppressed LDL/HDL ratio by 55.6% compared with the hyperlipidemic group.

Nicotinic acid (vitamin B_3/niacin) has antihyperlipidemic effects, but patients often have side effects such as facial flushing, burning sensation, and upper gastrointestinal discomfort (Meyer-Ficca and Kirkland, 2016). The results of this study revealed that LNU had the strongest antihyperlipidemic activity and HNU had the most robust antioxidant activity in the liver of hyperlipidemia mice. Many studies have demonstrated that acetylated derivative of polysaccharide, high-sulfated polysaccharide, and phosphorylated polysaccharide exhibited stronger biological activities than polysaccharide alone (Chen and Huang, 2019; Li et al, 2020; Lopes et al., 2017; Ren et al., 2020; Jiang et al., 2020). These studies also revealed that some activities can be enhanced through the structural modification.

This current study is an initial investigation of the *in vivo* antioxidative and antihyperlipidemic activity of NU from *U. pertusa*. One of the mechanisms of ulvan inhibiting oxidative stress is that it can directly capture ROS or provide H to act on ·OH and produce H_2O (Huang, 2017). Nicotinyl group was linked to ulvan, on the one hand, that increases the spatial volume of ulvan, thereby increasing the ability of ulvan to capture ROS, and on the other hand, increases the hydrogen-donating ability of ulvan, so that ulvan can react with more ·OH to generate H_2O (Huang, 2017; Qiu et al., 2022; Zhou and Huang, 2021). NU reduces the occurrence of oxygen radical chain reaction by reacting with ROS, thereby reducing the consumption of metal ions (Fe^{2+}, Cu^{2+}) which are an important part of SOD (Wang et al., 2018). It may be that the mechanism of NU improves the activities of antioxidative enzymes. The mechanism of NU's modulation of lipid metabolism is not fully understood. In our previous study, we successfully prepared NU from *U. pertusa* and identified its unique structure (Chang et al., 2017). Based on studies by other investigators, nicotinyl enhanced the ion exchange capacity of ulvan, make it to better act with bile acid in gut, and furthermore decreases the serum TC (Evans, 2020). At the genetic molecular level, ulvan enhances the expression of peroxisome proliferator-activated receptor gamma (PPARγ) in hyperlipidemic rats (Qi and Sheng, 2015). Therefore, our future investigations may focus on the effects of NU on PPARγ gene expression. Of further consideration is that in the atherosclerotic process, oxidative stress contributes to endothelial damage (Yang et al., 2010). Moreover, lipid peroxidation can be induced by massive free radicals, leading to dysfunction of the lipid metabolism pathway in the liver and aggravation of hyperlipidemia. Therefore, research on the antioxidant properties of polysaccharides derived from natural sources such as the seaweed *Porphyra haitanensis* and sea cucumber *Apostichopus japonicus* is garnering importance (Wang et al., 2017; Lin et al., 2012). All of the results revealed that among the three different doses of NU, the high dose (500 mg/kg) showed the strongest antioxidant activity while the low dose (125 mg/kg) had the most robust antihyperlipidemic activity. The mechanisms of these effects remain to be investigated.

Conclusion

NU derivative from the green seaweed *U. pertusa* (Chlorophyta) possess antioxidant and antihyperlipidemic activities *in vivo*. NU showed the more powerful activities of antioxidant and antihyperlipidemic than ulvan. The antioxidant and antihyperlipidemic mechanisms of NU may be related to the nicotinyl group in its chemical structure. As a natural antioxidant, NU is potentially responsible for relieving or treating chronic diseases caused by oxidative stress. In addition, NU has hypolipidemic activity, as it is not only able to treat hypolipidemic conditions, but can also be a potential in preventing cardiovascular and cerebrovascular diseases

caused by hyperlipidemia.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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