

Dose-dependent effect of aqueous extract from *Dendrobium officinale* on blood lipids and lipid peroxidation in hyperlipidemic rats

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Abstract: *Dendrobium officinale* is a traditional Chinese herbal medicine exhibiting multiple bioactivities, showing antitumor and immune-enhancing effects. The purpose of the study is to explore the effect of aqueous extract from *Dendrobium officinale* on blood lipids and lipid peroxidation in hyperlipidemic rats. Hyperlipidemic rats were prepared and daily given an intragastric administration of *Dendrobium officinale* at doses of 0.25g/kg, 0.5g/kg, or 1g/kg, or an intragastric administration of 8mg/kg simvastatin. We determined increased serum levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate transaminase (AST), reduced serum levels of HDL-C, elevated MDA levels, decreased activity of GSH-Px, SOD and CAT in liver tissues of hyperlipidemic rats. Intragastric administration of *Dendrobium officinale* reduced serum levels of TC, TG, LDL-C, ALT, AST, increased serum levels of HDL-C, reduced MDA levels, and enhanced activity of GSH-Px, SOD and CAT in liver tissues of hyperlipidemic rats in a dose-dependent manner. Taken together, aqueous extract from *Dendrobium officinale* plays an inhibitory role in the formation of high blood lipid and strengthens the antioxidant capacity in hyperlipidemic rats.

Keywords: *Dendrobium officinale*, aqueous extract, hyperlipidemia, blood lipids, lipid peroxidation.

INTRODUCTION

Hyperlipidemia is a group of metabolic disorders with the characteristics of increased levels of lipids or lipoproteins in the bloodstream (Karam *et al.*, 2015). It is widely acknowledged as a risk factor for the occurrence and development of atherosclerosis, for the reason of increasing serum cholesterol levels and causing systemic inflammation (Papapanagioutou *et al.*, 2015; Bagley *et al.*, 2015). Hyperlipidemia accelerates the possibility of cardiovascular diseases, especially in combination with such prevalent diseases as hypertension and diabetes mellitus (Bahmani *et al.*, 2015). The treatment regimen for hyperlipidemia remains among the major therapeutic goals in cardiovascular diseases (la Paz *et al.*, 2016). Multiple studies have demonstrated the association between hyperlipidemia and liver injury, and it is useful to attenuate liver damage by suppressing hyperlipidemia (Ponce-Canchihuaman *et al.*, 2010; Zhu *et al.*, 2008). Additionally, oxidative stress is commonly involved in the treatment studies of hyperlipidemia and atherosclerosis; for example, hyperlipidemia and oxidative damage caused by chronic stress lead to atherosclerosis and lipofundin-induced hyperlipidemia which enhances oxidative stress and atherosclerotic lesions in rabbits (Devaki *et al.*, 2013; Delgado Roche *et al.*, 2012). Lipid peroxidation, as a process during which oxidants including radicals interact with lipids, has been revealed to correlate with multiple diseases such as cancer, atherosclerosis and diabetes (Ayala *et al.*, 2014; Yin *et al.*, 2011). Due to the severe toxic side effects of

biochemical drugs, including statins, which lower cholesterol levels in the liver, increasing attention was laid to the application of traditional herbs to balance blood lipids (Rouhi-Boroujeni *et al.*, 2015).

Dendrobium officinale (Tie-Pi-Shi-Hu) is an orchid commonly distributed in Yunnan Province, Anhui Province and Zhejiang Province of China, and the dried stem is a Yin-nourishing medicine to strengthen immunity and mediate blood sugar (Yue *et al.*, 2017; Yang *et al.*, 2015; Yang *et al.*, 2016). *Dendrobium officinale*, as the most valuable species of all the genus *Dendrobium*, is recorded in the China Pharmacopoeia (2010 edition) as an individual entry (Lin *et al.*, 2011). In terms of the pharmacological activity and basic constituents, it has been revealed that the most active constituents include alkaloids, glycosides, stilbenoids and polysaccharides (Hua *et al.*, 2004). Polysaccharide, as the key constituent of *Dendrobium officinale*, plays such pharmacological roles as anti-cancer, immunomodulation and anti-oxidative effects (Zhang *et al.*, 2016). The therapeutic effects of *Dendrobium officinale* has been revealed in hypertension and atherosclerosis, and its polysaccharides have antioxidant capacities (Zhao *et al.*, 2017). *Dendrobium officinale* intensifies cellular immunity, nonspecific immunity and humoral immunity (Liu *et al.*, 2011). Previous study has demonstrated the cardioprotective effects of *Dendrobium officinale*, such as decreasing lipid per oxidation injury and cardiomyocyte apoptosis in response to oxidative stress (Zhang *et al.*, 2017). Furthermore, herbal medicine or herbal extract has been suggested with lipid-modulating effects in hyperlipidemia, such as Yun-Cai Tea (Lee *et al.*, 2015)

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and blackcurrant oil soft capsule (Fa-lin *et al.*, 2010). Hereby, the central objective of this study was to investigate effect of aqueous extract from *Dendrobium officinale* on hyperlipidemia in rat models and its mechanism of mediating blood lipids and lipid peroxidation.

MATERIALS AND METHODS

Experimental animals

Healthy and clean Sprague Dawley (SD) rats (n=48), weighing 180-200g, were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. (Certificate NO. SCXK (Beijing): 2011-0011; Beijing, China). The rats were bred under controlled environmental conditions (19~22°C; 12h light/dark cycle; regular sterilization and ventilation) with ad libitum access to food and water. Before being used in the subsequent experiments, the rats were allowed to adapt to the new conditions for 3 days. The animal experiments were performed according to the Helsinki Declaration (Hellmann *et al.*, 2014), and the ethical approval issued by the Animal Ethics Committee of Hunan Yandi Biotech Co.

Animal grouping and treatment

Totally, 48 rats were assigned into 6 groups with 8 for each group: normal group (rats fed with normal diet), model group (rats fed with high-fat diet), low dose of aqueous extract from *Dendrobium officinale* (LDD) group (rats fed with high-fat diet and intragastrically administered with 0.25 g.kg⁻¹.d⁻¹ aqueous extract from *Dendrobium officinale*), medium dose of aqueous extract from *Dendrobium officinale* (MDD) group (rats fed with high-fat diet and intragastrically administered with 0.5 g.kg⁻¹.d⁻¹ aqueous extract from *Dendrobium officinale*), high dose of aqueous extract from *Dendrobium officinale* (HDD) group (rats fed with high-fat diet and intragastrically administered with 1g.kg⁻¹.d⁻¹ aqueous extract from *Dendrobium officinale*) and positive control drug (PD) group (rats fed with high-fat diet and intragastrically administered with 8mg.kg⁻¹.d⁻¹ simvastatin [Beijing Sihuan Pharmaceutical Co., Ltd., Beijing, China]). *Dendrobium officinale* was purchased from Bright Food Group. Yunnan Dendrobium Biotechnology Development Co., Ltd. It was extracted in boiling water bath for three times after freezing and drying. The aqueous extract was obtained after drying by distillation. The experiment lasted for six weeks. The weight of rats from every group was measured and recorded for subsequent detection.

Indexes for blood lipids and liver function in rat serum

Rats of all the groups were deprived of food but not water 12 h before experiment. After the experiment, blood was collected from aorta abdominalis and centrifuged at 3000 rpm for 10 min. The serum was separated and stored at

-20°C for further use. The liver was taken out immediately after blood collecting. Subsequently, pre-cooled normal saline was used to wash the bloodstain, and the liver was then dried by filter paper. The middle part (~1cm³) of the left lobe of liver was extracted for pathological sections in hematoxylin-eosin (HE) staining. The left part was used to prepare tissue homogenate for detection of indexes. The serum levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT) and aspartate transaminase (AST) were determined using an automatic biochemical analyzer (AU640, Olympus Company, Tokyo, Japan).

HE staining

Tissue sections of rat liver for HE staining were baked at 62°C for 2h and immersed successively in xylene I for 10 min and xylene II for 10 min. After that, the sections were soaked in anhydrous ethanol, 95% ethanol and 80% ethanol (each for 5 min), followed by rinsing in distilled water. There was no need for high-pressure or high-temperature antigen retrieval. Hematoxylin was adopted for 5 min counter stain. Subsequently, the sections were soaked in ethanol-hydrochloric acid to separate colors for 1min and successively in distilled water for 1min, 70% ethanol for 2 min and 80% ethanol for 2 min. After being stained in eosin-ethanol solution for 1~2 min, the sections were soaked again in 95% ethanol for 2 min and anhydrous ethanol for 3 min. Then, the sections were permeabilized in xylene and mounted in neutral balsam. The staining results were observed and photographed under an optical microscope (Wang *et al.*, 2015).

Detection for parameters of oxidation in rat liver tissues

Rat liver tissues for parameter detection were homogenized on the ice with the supplement of homogenate buffer to prepare 10% tissue homogenate, followed by centrifugation and supernatant collection. Thiobarbituric acid (TBA) method, 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), xanthine oxidase method and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were performed respectively to identify the malondialdehyde (MDA) levels and the activity of glutathione peroxidase (GSH-Px), super oxide dismutase (SOD) and catalase (CAT) in the supernatant of rat liver tissues from each group. The kit was supplied by Nanjing Jiancheng Bioengineering Institute (Nanjing, Jiangsu, China). Coomassie Brilliant Blue G250 assay was performed to determine protein concentration.

STATISTICAL ANALYSIS

SPSS 21.0 (IBM Corp, Armonk, NY, USA) was employed to analyze data obtained in this study. Quantitative data were expressed as mean ± standard deviation. Comparisons between two groups of normally

distributed quantitative data were conducted by using *t*-test, pairwise comparisons by the least significant difference (LSD) and comparisons among multiple groups by one-way analysis of variance (ANOVA). $P < 0.05$ was accepted as indicative of significant differences.

RESULTS

Hyperlipidemia in relation to the formation of high blood lipid

When compared with rats fed with normal diet, rats that were consecutively fed with high-fat diet for six weeks exhibited significantly increased serum levels of TC, TG and LDL-C (all $P < 0.05$) and decreased serum levels of HDL-C ($P < 0.05$). It suggested the successful establishment of rat models of hyperlipidemia (fig. 1).

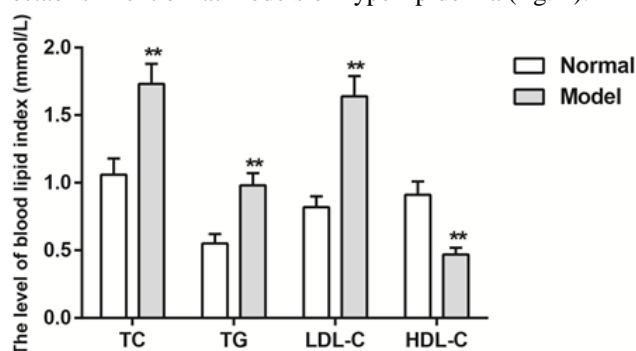


Fig. 1: Changes of serum levels of blood lipid indexes in normal rats (normal group) and hyperlipidemic rats (model group).

Note: **, $P < 0.01$ compared with the normal group; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

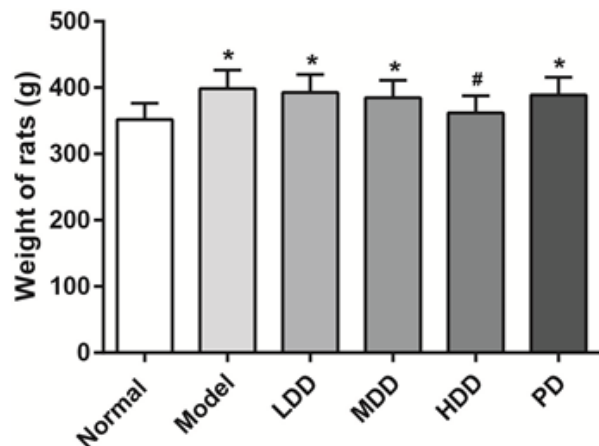


Fig. 2: Comparison on the weight of rats of different groups.

Note: *, $P < 0.05$ compared with the normal group; #, $P < 0.05$ compared with the model group; LDD, low dose of aqueous extract from *Dendrobium officinale*; MDD, medium dose of aqueous extract from *Dendrobium officinale*; HDD, high dose of aqueous extract from *Dendrobium officinale*; PD, positive control drug.

Intragastric administration of aqueous extract from *Dendrobium officinale* decreases weight increase in a dose-dependent manner

The weight of rats from all the groups obviously increased after the experiment. In comparison to the normal group, rat weight substantially elevated in the model, LDD, MDD and PD groups (all $P < 0.05$). Compared with the model group, rats lost weight in the HDD group ($P < 0.05$). The rat weight did not differ significantly among the model, LDD, MDD and PD groups (all $P > 0.05$). These results indicated that high dose of aqueous extract from *Dendrobium officinale* exerted inhibitory effects on the weight increase of hyperlipidemic rats (fig. 2).

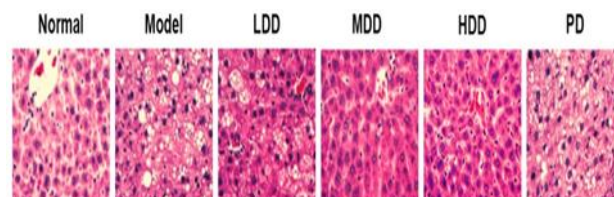


Fig. 3: Pathological changes of rat liver tissues of different groups detected by hematoxylin-eosin staining ($\times 400$).

Note: LDD, low dose of aqueous extract from *Dendrobium officinale*; MDD, medium dose of aqueous extract from *Dendrobium officinale*; HDD, high dose of aqueous extract from *Dendrobium officinale*; PD, positive control drug.

Intragastric administration of aqueous extract from *Dendrobium officinale* reduces formation of high blood lipid in a dose-dependent manner

Compared with the normal group, rats in the model group showed increased serum levels of TC, TG and LDL-C as well as decreased HDL-C (all $P < 0.05$). The MDD and HDD groups had reduced serum levels of TC, TG and LDL-C as well as increased HDL-C (all $P < 0.05$) when compared with the model group. The PD group showed lower serum levels of TC and TG than the model group (both $P < 0.05$), with no significant difference in LDL-C and HDL-C levels (both $P > 0.05$). As compared with the model group, the LDD group also showed relatively but not significantly reduced serum levels of TC, TG and LDL-C as well as increased HDL-C (all $P > 0.05$) (table 1).

Intragastric administration of aqueous extract from *Dendrobium officinale* decreases serum levels of ALT and AST in a dose-dependent manner

Rats in the model group had higher serum levels of ALT and AST than normal rats (both $P < 0.05$). Compared with the model group, rats in the PD and MDD groups displayed decreased serum levels of ALT and AST (all $P < 0.05$). Furthermore, rats in the HDD group showed even lower serum levels of ALT and AST (all $P < 0.05$) as compared with the PD and MDD groups. No difference was identified in serum levels of ALT and AST between the LDD and model groups (all $P > 0.05$) (table 2).

Table 1: Changes of serum levels of blood lipid indexes in normal rats and hyperlipidemic rats.

Group	TC	TG	LDL-C	HDL-C
Normal	1.06±0.12	0.55±0.07	0.82±0.08	0.91±0.10
Model	1.73±0.15*	0.98±0.09*	1.64±0.15*	0.47±0.05*
LDD	1.68±0.16*	0.92±0.08*	1.55±0.12*	0.52±0.06*
MDD	1.18±0.12 [#]	0.68±0.07 [#]	1.02±0.10* [#]	0.79±0.08 [#]
HDD	1.09±0.11 [#]	0.59±0.06 [#]	0.84±0.09 [#]	0.88±0.10 [#]
PD	1.31±0.13* [#]	0.89±0.08* [#]	1.57±0.16*	0.49±0.05*

Note: *, $P < 0.05$ compared with the normal group; [#], $P < 0.05$ compared with the model group; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; LDD, low dose of aqueous extract from *Dendrobium officinale*; MDD, medium dose of aqueous extract from *Dendrobium officinale*; HDD, high dose of aqueous extract from *Dendrobium officinale*; PD, positive control drug.

Table 2: Comparison on serum levels of ALT and AST to test liver function in normal rats and hyperlipidemic rats treated with low/medium/high dose of aqueous extract from *Dendrobium officinale* as well as positive control drug (U/L).

Group	ALT	AST
Normal	226.38±37.45	55.14±4.07
Model	351.26±49.72*	140.68±16.28*
LDD	334.58±50.31*	129.85±15.92*
MDD	292.73±43.64* [#]	87.68±8.06* [#]
HDD	239.85±35.47 [#]	61.49±4.18 [#]
PD	294.46±45.18* [#]	94.85±8.47* [#]

Note: *, $P < 0.05$ compared with the normal group; [#], $P < 0.05$ compared with the model group; ALT, alanine aminotransferase; AST, aspartate transaminase; LDD, low dose of aqueous extract from *Dendrobium officinale*; MDD, medium dose of aqueous extract from *Dendrobium officinale*; HDD, high dose of aqueous extract from *Dendrobium officinale*; PD, positive control drug.

Table 3: Changes of parameters of oxidation in normal rats and hyperlipidemic rats treated with low/medium/high dose of aqueous extract from *Dendrobium officinale* as well as positive control drug.

Group	MDA (nmol/mg)	GSH-Px (U/mg)	SOD (U/mg)	CAT (U/mg)
Normal	0.41±0.04	238.24±32.07	91.65±8.39	0.78±0.08
Model	1.08±0.11*	160.68±24.28*	54.34±5.31*	0.32±0.04*
LDD	1.02±0.09*	189.85±21.92*	61.08±7.05*	0.41±0.06*
MDD	0.65±0.07* [#]	205.68±27.06* [#]	78.92±7.68* [#]	0.69±0.07 [#]
HDD	0.47±0.05 [#]	231.49±31.18 [#]	89.19±8.98 [#]	0.73±0.08 [#]
PD	0.97±0.10*	195.02±20.09*	63.02±7.09*	0.39±0.05*

Note: *, $P < 0.05$ compared with the normal group; [#], $P < 0.05$ compared with the model group; MDA, malondialdehyde; GSH-Px, glutathione peroxidase; SOD, superoxide dismutase; CAT, catalase; LDD, low dose of aqueous extract from *Dendrobium officinale*; MDD, medium dose of aqueous extract from *Dendrobium officinale*; HDD, high dose of aqueous extract from *Dendrobium officinale*; PD, positive control drug.

Intragastric administration of aqueous extract from *Dendrobium officinale* affects pathological changes of liver tissues

In the normal group, the hepatocytes in the liver tissues did not show any swelling, fatty degeneration and necrosis, formation of pseudolobules or pathological changes in the central and portal vein area, with regular structures in plates of liver lobule. As for rats in the model group, obvious fatty degeneration and necrosis was identified in plenty of hepatocytes in the liver lobule; fat vacuoles, vague and irregular structures of liver lobule

were also observed; the hepatocytes were unevenly aligned and sinusoids got narrow or disappeared. The LDD group exhibited a large number of small fat vacuoles in many hepatocytes, and large fat vacuoles merged by small fat vacuoles in some hepatocytes. In the MDD group, small fat vacuoles were identified in a few hepatocytes, as well as regular and clear liver plates but slightly disordered alignment of hepatocytes. The liver lobule of the HDD group had nearly normal structures. Compared with the model group, the liver structures of the PD group were not significantly different, with still vague lobule

structures, obvious hepatocyte swelling and fatty degeneration, unevenly aligned hepatocytes and narrowed hepatic sinusoids (fig. 3).

Intragastric administration of aqueous extract from *Dendrobium officinale* promotes antioxidant capacity of hyperlipidemic rats

In order to assess the effect of aqueous extract from *Dendrobium officinale* on lipid peroxidation, parameters related to oxidation were detected in rat liver tissues. Compared with the normal group, the model group showed increased MDA levels and decreased activity of GSH-Px, SOD and CAT (all $P < 0.05$), which indicated that high-fat diet could induce lipid peroxidation injury in rat liver tissues. In comparison to the model group, the LDD and PD groups displayed no significant difference in MDA levels and activity of GSH-Px, SOD and CAT (all $P > 0.05$), which suggested that low dose of aqueous extract from *Dendrobium officinale* had little influence on lipid peroxidation in hyperlipidemia. The MDD and HDD groups showed significantly reduced MDA levels and enhanced activity of GSH-Px, SOD and CAT and the HDD group had even obvious effects (all $P < 0.05$), which demonstrated that high dose of aqueous extract from *Dendrobium officinale* could facilitate the antioxidant capacity of hyperlipidemic rats (table 3).

DISCUSSION

Hyperlipidemia is one of the prevalent diseases with increasing morbidity and mortality, and the adverse effects of lipid-lowering therapies have attracted accumulating attention to alternative or traditional treatments (Bahmani *et al.*, 2015). In recent years, herbs are crucial sources for anti-hyperlipidemia therapies, and over 80% of individuals in the developing world depend on traditional herbal medicine for palliation of hyperlipidemia (Rouhi-Boroujeni *et al.*, 2015). In this study, high dose of aqueous extract from *Dendrobium officinale* was proved to ameliorate hyperlipidemia in rats by decreasing lipid levels and enhancing antioxidant capacity.

Based on findings of this present study, when hyperlipidemic rats were administered with aqueous extract from *Dendrobium officinale* at a high dose, they had reduced serum levels of TC, TG, LDL-C and increased HDL-C levels as well as decreased weight. Obviously, blood lipid levels of the modeled rats fed with high-fat diet were reduced significantly as a result of high dose *Dendrobium officinale* treatment. Yamato *et al.* has revealed consistent findings that high-fat diet fed mice exhibited hyperlipidemia associated with elevated fatty acids, which in turn promoted an increase in levels of oxidative stress factors (Yamato *et al.*, 2007). Reducing the assimilation and synthesis of TC and TG plays a crucial role in preventing and treating hyperlipidemia

(Fa-lin *et al.*, 2010). According to a study of Karam *et al.*, elevated levels of LDL has association with the progression of atherosclerosis, while HDL is involved in reducing cholesterol and exerts cardioprotective effects (Karam *et al.*, 2015). Cicero *et al.* reported that serum LDL-C levels may be the only reversible factor for cardiovascular diseases (Cicero *et al.*, 2015). Long term hyperlipidemia is implicated in the production of inflammatory cells and cytokines and severe inflammation exacerbates liver damage with declined liver function as well as inhibited glucolipid metabolism and liver lipid depositions (Zhang *et al.*, 2015). *Dendrobium officinale* is a precious traditional Chinese herb plant, with such medicinal qualities as immunomodulatory, antioxidative, antineoplastic and antimutagenic activities (He *et al.*, 2016). Elevated oxidative stress is associated with lipid accumulation, and SOD is a crucial enzyme which reduces reactive oxygen radicals (Pan *et al.*, 2014; Sekiya *et al.*, 2008). Based on the observations and findings of Zhang *et al.* (2015) *Dendrobium officinale* extract exerted cardioprotective effects from diabetic cardiomyopathy through repressing cardiac lipid accumulation, oxidative stress and pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin-1 β and interleukin-6 (Zhang *et al.*, 2016). In the study of Xiang *et al.* *Dendrobium* polysaccharides suppressed the TNF- α -induced apoptosis by inhibiting the plasma membrane-bound complex of TNF- α and the receptors in salivary gland cells (Xiang *et al.*, 2013). In addition, rat models with hyperlipidemia showed reduced serum levels of ALT and AST, as well as improved pathological changes of liver tissues, after the treatment of high dose of aqueous extract from *Dendrobium officinale*. Thus, the liver injuries caused by hyperlipidemia were alleviated. Previous studies have pointed out the associations between hyperlipidemia and liver damages (Zhu *et al.*, 2008; Kawase *et al.*, 1989). Liver injuries could be palliated by traditional herbal drugs, such as hepatic oxidative stress could be alleviated by Yin-Chen-Hao-Tang in obese mice with steatosis (Lee *et al.*, 2010). Traditional Chinese herbal drugs have been proved to treat liver fibrosis and cancer in the clinical evaluations of Luk *et al.* (Luk *et al.*, 2007).

High dose of aqueous extract from *Dendrobium officinale* enabled hyperlipidemic rats to have decreased MDA levels and enhanced activity of GSH-Px, SOD and CAT in liver tissues. It indicated that high dose of aqueous extract from *Dendrobium officinale* inhibited the lipid peroxidation injury caused by hyperlipidemia in rat models. Oxidative stress is a critical factor in the pathological changes of cardiovascular diseases and especially important in cardiomyocyte apoptosis, which, in the study of Zhang *et al.* was inhibited by *Dendrobium officinale* polysaccharide through the PI3K/AKT and the MAPK signaling pathways (Zhang *et al.*, 2017). Hyperlipidemia intensifies production of radicals, which

subsequently facilitates oxidation of low density lipoprotein and oxidative stress, and meanwhile, low density lipoprotein oxidation is implicated in the occurrence of atherosclerotic plaques (Bahmani *et al.*, 2015). As oxidants target lipids, they generate the process of lipid peroxidation to produce breakdown molecules, including MDA and 4-hydroxy-2-nonenal, which are involved in secondary deleterious reactions and accelerate the progression of multiple pathological states (Ayala *et al.*, 2014). The antioxidant activities of *Dendrobium officinale* was reported in an in vitro study, which demonstrated that the polysaccharide of *Dendrobium officinale* showed scavenging activity of hydroxyl radical and 1,1-diphenyl-2-picrylhydrazyl radical and metal chelating activity (Luo *et al.*, 2016).

CONCLUSION

In conclusion, the evidence provided by the study supports that high dose aqueous extract from *Dendrobium officinale* presented anti-hyperlipidemic effects in rat models through reducing blood lipid levels, liver injuries and lipid peroxidation damages as well as promoting antioxidant capacity. Further work should be performed to explore more information of *Dendrobium officinale* and develop clinical values of it in therapies for hyperlipidemia.

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