EVALUATION OF ANTIHYPERLIPIDEMIC POTENTIAL OF *DENDROBIUM OFFICINALE* COMBINED WITH *CAMELLIA HAKODAE* IN POLOXAMER-407-INDUCED EXPERIMENTAL MODEL OF MICE

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Herbal medicine has been used in folk medicine in many parts of the world due to its potential medicinal properties. This study was conducted to evaluate the antihyperlipidemic effects of a natural-derived combination of Dendrobium officinale and Camellia hakodae, abbreviated as VHL, in a Poloxamer 407-induced hyperlipidemia model in Swiss mice. An endogenous hyperlipidemia model was established by intraperitoneal administration of Poloxamer-407 at 200 mg/kg body weight. The VHL extract was administered at doses of 1.14 and 3.42 g/kg body weight, once daily for seven consecutive days. At the end of the study, serum lipid parameters were determined. The results show that serum levels of total cholesterol (TC), triglycerides (TG), and non-high-density lipoprotein cholesterol (Non-HDL-C) were significantly increased in poloxamer 407-induced hyperlipidemic control mice. In contrast, TG parameters were markedly reduced in mice treated with the VHL capsules at 1.44 g/kg body weight and 3.42 g/kg body weight. VHL also improved serum HDL-C levels and trendedd to reduce TC and non-HDL-C compared to the cholesterol control group. In conclusion, a naturally derived combination of Dendrobium officinale and Camellia hakodae showed TG-lowering potential and may help prevent hypercholesterolemia in a P407-induced hyperlipidemia model.

Keywords: ***Dendrobium officinale, Camellia hakodae,*** **VHL capsule hyperlipidemia, serum lipid levels.**

I. INTRODUCTION

Lipids play a crucial role in maintaining substances in the human body. Dyslipidemias, including hyperlipidemia (hypercholesterolemia) and low levels of high-density lipoprotein cholesterol (HDL-C), are notable sources of atherogenic risk; therefore, their measurement and control are integral to ASCVD risk assessment and prevention.[1] Plasma TC and TG levels are regulated by a complex network of metabolic pathways; disruption of these pathways by disease or environmental factors can alter the concentrations of lipoproteins responsible for lipid transport in the circulation. The efficacy of cholesterol-lowering agents has been well established in patients with established cardiovascular disease.[2] Effective management of hyperlipidemia requires appropriate lipid-lowering interventions. While mild forms of hyperlipidemia are generally managed through lifestyle modifications, pharmacological treatment is recommended for patients with more severe disease. 3-Hydroxy-3-methylglutaryl-coenzyme A

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(HMG-CoA) reductase inhibitors ("statins"), a key recommendation of cholesterol-lowering therapy, have been shown to prevent and treat both CV events and all-cause mortality. Other lipid-lowering measures, including pharmacological and nonpharmacological, have also been illustrated in clinical trials to reduce CV outcomes. The currently available hypolipidemic drugs have been associated with a number of side effects. There is an increased risk of myopathy and rhabdomyolysis, typically when used in combination with other medications. For most of the hypocholesterolemic drugs to be effective, they must be used for several weeks, which may further aggravate the side effects, such as liver damage.

Traditional herbal medicine is a vital component of complementary and alternative approaches to managing hyperlipidemia. Bioactive constituents derived from selected parts of herb plants, administered singly or in combination, modulate lipid profiles through diverse regulatory pathways.[3] VHL hard capsule combining *Dendrobium officina*le and *Camellia hakodae* represents a promising candidate for investigation. *Dendrobium officina*le has a long history of being consumed as a functional food and medicinal herb for disease prevention and treatment. Phytochemical analyses have identified a wide range of bioactive constituents, including bibenzyls, polysaccharides, flavonoids, and alkaloids. Experimental evidence indicates that Dendrobium officinale and its active compounds exhibit diverse biological activities, such as antioxidant, anti-dyslipidemia, anti-inflammatory, and immunomodulatory effects, and provide multiple health benefits, including anticancer, antidiabetic, cardiovascular-protective, gastrointestinal-regulatory, hepatoprotective, pulmonary-protective, and neuroprotective properties.[4,5] ***Camellia hakodae*** has a natural distribution limited to North Vietnam and Southwest China. Recent phytochemical studies on ***C. hakodae*** have revealed the presence of many useful flavonoids, polysaccharides, saponins, volatile compounds, and other components, including mineral elements and amino acids. It was demonstrated to have pharmacological activities such as anti-inflammatory, antioxidant, hypoglycemic, antibacterial, anti-cancer, hypolipidemic, antiallergic, immunomodulatory, anxiolytic, and antidepressant properties.[6,7] Although the individual hypolipidemia and cardiovascular benefits of these herbs have been documented, their combined effects have not yet been investigated. Besides, evidence from traditional use, modern scientific validation of this herbal combination remains insufficient. Therefore, to provide scientific proof of its efficacy in treating dyslipidemia, in the present study, we attempted to depict the underlying effect by which *Dendrobium officinale* combined with *Camellia hakodae* improves hyperlipidemia induced by P407 in the experiment.

II. MATERIALS AND METHODS

1. Plant materials and preparation of extract

Specimens of *Dendrobium officinale* and *Camellia hokadae* were collected from the Soc Son medicinal plant garden (Bac Son Commune, Soc Son District, Hanoi) in February 2018. The taxonomic identification of *Camellia hokadae* was performed by Professor Tran Ninh (Department of Plant Chemistry, Hanoi University of Science). A voucher specimen (No. 5817; leg. Hieu, Ninh; collected on 15 December 2017; identified by Tran Ninh) has been deposited at the Department of Plant Chemistry, Hanoi University of Science, and at the Soc Son Medicinal Plant Conservation and Development Cooperative (Bac Son, Soc Son, Hanoi).

Extracts of *Dendrobium officinale* and *Camellia hakoda*e were combined at a ratio of 1:5 (w/w) and formulated into VHL capsules at the Institute of Marine Biochemistry, Vietnam Academy of Science and Technology. The quality of the capsules was evaluated by the Department of Pharmaceutical Chemistry and confirmed to meet basic quality standards

Animals

Swiss mice (6 - 8 weeks old) of both genders, weighing 24-28 g, were supplied from the National Institute of Hygiene and Epidemiology. The animals were housed in a 12 h light/12 h dark cycle at 25°C with relative humidity of 50-60% throughout the experimental period. All animals were acclimated to the laboratory environment for seven days prior to experimentation, with free access to food and water.

Chemicals

Poloxamer 407 was purchased from Sigma (Singapore). Atorvastatin 10mg was supplied by Stellapharm J.V. Co., Ltd. Biochemical analyzer ERBA Chem. (India) and commercial ERBA diagnostic kits used for serum analysis of total cholesterol (TC), triglyceride (TG), and high-density lipoprotein-cholesterol (HDL-C).

2. Methods

A hyperlipidemia model in mice by poloxamer 407 (P-407) induced a dyslipidemia model according to the endogenous mechanism.[8-10] In the experimental design, animals were randomly divided into five groups of ten animals each.

- Group I - Normal control vehicle-treated distilled water 1 mL/100 g b.w/day.
- Group II - P-407 control group.
- Group III - Atorvastatin at 100 mg/kg b.w/day.
- Group IV - VHL at 1.14 g/kg b.w/day (low dose).
- Group V - VHL at 3.42 g/kg b.w/day (high dose).

Groups I-II received distilled water, while groups III-IV received atorvastatin and VHL at 1.14 and 3.42 mg/kg orally once daily for 7 days. At the end of the study, the animals' weight were recorded-using a digital balance. Both the P407 group and groups III-V received bolus intraperitoneal (i.p.) injections of P407 (200 mg/kg) to establish the hyperlipidemia model, and the control group received 0.9% saline. P407 was dissolved in cold saline (0.9%) and kept overnight at 4°C for complete dissolution according to the cold method.

Sample collection

At the end of the study, the animals were anesthetized, and a blood sample was collected through the carotid artery into nonheparinized tubes for biochemical parameters. Plasma was obtained by centrifugation at 3000 g for 15 minutes.

Measurement of plasma lipid profile

Plasma total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were measured using an enzymatic assay with analytical kits (Erba France). Non-HDL-cholesterol (non-HDL-C) was estimated: Non-HDL-C = TC-(HDL-C).

3. Statistical analysis

All results are presented as the mean± SD. Data were analysed using Microsoft Excel software version 2010. Statistical analysis was performed using the t-test and the Avant-après test. Differences were considered statistically significant at $p < 0.05$.

	$p \leq 0.05$	$p \leq 0.01$	$p \leq 0.001$
Compared with the normal control group	*	**	***
Compared with the cholesterol control group	+	++	+++

III. RESULTS

VHL treatment ameliorates hyperlipidemia induced by P407

To determine whether VHL exhibits lipid-lowering effects, serum lipid concentrations were initially assessed in mice 24h following intraperitoneal administration of P-407. As shown in Figure 1, the experimental mouse model demonstrated a significant increase in serum lipid levels in the P-407 control group compared with the normal control group ($p < 0.001$).

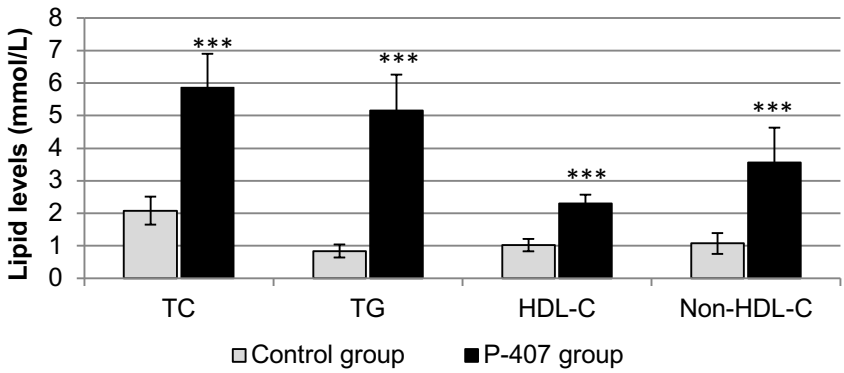

Figure 1. Hyperlipidemia model induced by P-407

*Note: ***: $p < 0.001$ was a significant change compared to the normal control group.*

Table 1. VHL capsules modulate plasma lipid levels induced by Poloxamer 407

Groups	n	Serum lipid levels ($\bar{X}$ ± SD)		
		TG (mmol/L)	TC (mmol/L)	Non-HDL-C (mmol/L)
Normal control	10	0.84 ± 0.20	2.08 ± 0.43	1.07 ± 0.32
P-407 control		5.15 ± 1.11***	5.86 ± 1.04***	3.56 ± 1.07***
Atorvastatin 100 mg/kg	10	4.67 ± 1.05 **(↓9.4%)**	4.48 ± 0.98^{++} **(↓ 23.6%)**	2.02 ± 0.91^{+++} **(↓ 43.2%)**
VHL 1.14 g/kg	10	3.96 ± 1.26^{+} **(↓ 23.1%)**	5.17 ± 1.24 **(↓11.8%)**	2.63 ± 1.03 **(↓ 26.1%)**
VHL 3.42 g/kg	10	1.70 ± 0.51^{+++} **(↓ 67.0%)**	5.47 ± 1.39 **(↓ 6.7%)**	3.07 ± 1.50 **(↓ 13.7%)**

Note: Statistical analysis was done with t-test and Avant-après test, and $p < 0.05$ was considered to be statistically significant; ***+: vs cholesterol control: $p < 0.05$: +; $p < 0.01$: ++; and $p < 0.001$: +++; *** $p < 0.001$ vs normal control.***

The effects of VHL on serum lipid profiles in experimental mice are presented in Table 1. After P-407 injections, the levels of TC, TG, and non-HDL-C in the model group were significantly higher than the normal control group ($p < 0.001$). Administration of VHL at both doses markedly reduced serum triglyceride (TG) levels by 23.1% and 67.0%, respectively, and showed a tendency to decrease total cholesterol (TC) and non-HDL-cholesterol levels compared with those in P-407-induced hyperlipidemic mice.

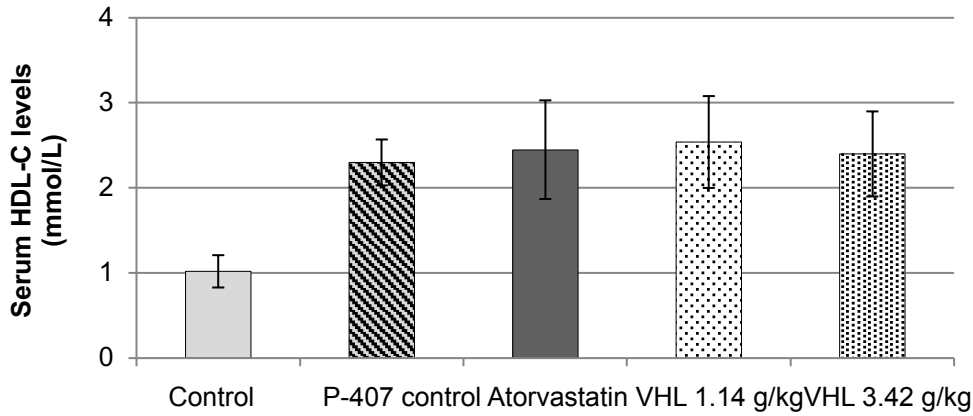

Figure 2. Effect of VHL on serum concentration of HDL-C in hyperlipidemic mice

Figure 2 illustrates the alterations in serum HDL-C levels across all experimental groups. Following treatment with different doses of VHL extract, changes in HDL-C levels were observed relative to the P-407 group. HDL-C concentrations in the VHL-treated groups (1.14 g/kg and 4.32 g/kg) showed a tendency to increase, comparable to those observed in the P-407 group; however, these differences were not statistically significant ($p > 0.05$).

IV. DISCUSSION

Hyperlipidemia is linked to an elevated risk of multiple chronic conditions, including obesity, diabetes, and cardiovascular diseases. Therefore, early management of hyperlipidemia is essential to prevent the onset of related disorders. Hypercholesterolemia is generally induced in several consequences. Among these factors, the etiopathogenesis of hyperlipidemia involves dysregulated triglyceride (TG) synthesis and breakdown. Elevated plasma TG levels arise from increased intestinal absorption of dietary fats and impaired TG catabolism. TG hydrolysis is primarily mediated by plasma lipoprotein lipase (LPL), which progressively converts TGs into free fatty acids and glycerol that are released into the circulation for tissue oxidation.[11] An endogenous hyperlipidemia model was established by intraperitoneal injection of poloxamer-407 (P-407) at 200 mg/kg body weight. P-407, a polyether-based nonionic surfactant, is widely used to induce hyperlipidemia due to its rapid onset of action and lower toxicity compared with Triton WR-1339. It has been shown to induce dose-dependent hypercholesterolemia and hypertriglyceridemia in rodents through multiple mechanisms, including inhibition of lipoprotein lipase, indirect stimulation of HMG-CoA reductase, and increased hepatic cholesterol accumulation. Figure 1 shows that mice injected with P-407 had higher plasma concentrations of TC, TG, and non-HDL-C, as

well as higher serum HDL-C concentrations, than the control group injected with saline. This result indicates that P-407 increases the incidence of hyperlipidemia, consistent with previous findings.[12,13] Our hyperlipidemia model by P-407 is marked by an increase in the serum levels of TC, TG and non-HDL-C, together with an increase in HDL-C at 24 h after a single P-407 injection in rats, confirming the successful establishment of hyperlipidemia.

In our study, plasma levels of these markers in mice exposed to VHL capsules for 7 days were comparable to those in normal control and atorvastatin-treated (positive control) groups, suggesting that VHL significantly prevented dyslipidemia and exhibited hypotriglyceridemic effects. Given that P407-induced abnormal TG levels were also prevented by VHL, we hypothesize that the extract's hypolipidemic activity may be mediated by inhibiting LPL activity. Several studies have shown that *Dendrobium officinale* and *Camellia hakodae* in the VHL capsule can ameliorate dysregulated lipid metabolism in pathological conditions such as diabetes and obesity. Extensive evidence indicates that *Dendrobium officinale* is rich in diverse bioactive constituents, including polysaccharides, flavonoids, bibenzyls, and alkaloids. Tissue-specific analyses have revealed that polysaccharides are predominantly concentrated in the stems, flavonoids in the leaves, and alkaloids in protocorm-like bodies. Among these constituents, polysaccharides, primarily composed of mannose and glucose with (1⟶4)-linked β-D-mannopyranosyl and β-D-glucopyranosyl residues, represent the principal medicinal components and are most frequently investigated for the therapeutic potential of *Dendrobium officinale*. *Dendrobium officinale* polysaccharides could decrease the levels of fasting blood glucose, insulin, glycated serum protein, and serum lipid profile and could decrease the levels of fasting blood glucose, insulin, glycated serum protein, and serum lipid profile.[4] In Jian Qu's research, polysaccharides from *Dendrobium officinale* ameliorated lipid metabolic disorders in obese mice. The treated mice group exhibited significantly lower liver TG levels than the untreated mice. In addition, free fatty acid, serum TC, TG, and LDL-C levels in the treated mouse group were lower than in the control group and were effective in increasing HDL-C levels.[14]

Moreover, *Camellia hakodae* demonstrates considerable pharmacological potential, largely attributable to its high levels of flavonoids and phenolic constituents. Recent investigations indicate that yellow camellias are primarily composed of flavonoids and phenolic compounds, with smaller amounts of saponins, triterpenoids, phytosterols, essential oils, lipid constituents, polysaccharides, amino acids, and trace elements. Among these constituents, flavonoids, phenols, and saponins are considered the principal bioactive compounds underlying the biological activities of yellow camellias. These compounds confer a broad spectrum of biological activities, including potent antioxidant, cytotoxic (anticancer), anti-inflammatory, antibacterial, and antihyperglycemic effects. Emerging evidence further suggests a beneficial role for *C. hakodae* in regulating obesity and lipid metabolism.[15] According to Ngo Thi My Binh et al. (2023), *Camellia hakodae* had an effect on reducing TC, TG, and non-HDL-C. The *dry extracts from the leaves of the yellow tea plant* (*Camellia hakodae*) in the model of endogenous dyslipidemia. At 0.6 g/kg and 1.8 g/kg, TC (26.5% and 28.3%), TG (21.2% and 17.3%), and non-HDLC (31.1% and 33.8%) were reduced.[16]

V. CONCLUSION

In conclusion, the present study assessed the hypolipidemic properties of the extract of *Dendrobium officinale* and *Camellia hakodae* (abbreviated as the VHL capsule), used in traditional medicine. In P407 -induced hyperlipidemia mice model, VHL extract corrected dyslipidemia; this combination had hypotriglyceridemic effects, while plasma total cholesterol, HDL-C, and non-HDL-C were trend affected. It suggests future studies addressing the mechanism of this combination.

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