



Research Paper

Antihyperlipidemic activity of *Paeonia anomala* L.

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ABSTRACT

The present study investigated the antihyperlipidemic activity of ethanolic and water extracts, as well as dichloromethane, ethylacetate, *n*-butanol fractions of aerial parts and flowers of *Paeonia anomala* L. (200 and 400 mg/kg) and its major 7 compounds (10 mg/kg) in high-fat diet-induced obesity rats. The study clearly showed that all extracts and fractions of aerial parts and flowers of *P. anomala* at a dose of 200 mg/kg significantly lowered plasma lipid profiles especially, triglycerides within 44.71 to 68.28% as compared with the atherogenic group. Whereas, the total cholesterol level in groups treated with only ethylacetate, *n*-butanol fractions and water extract of aerial parts at the same previous dose was reduced by 35.5, 22.57 and 21.56%, respectively. However, only at the high dose of 400 mg/kg, the ethylacetate and *n*-butanol fractions of aerial parts, dichloromethane, and ethylacetate and *n*-butanol fractions of flowers reduced the low density lipid level by 64.3 and 60.75%, 62.84%, and 65.55 and 60.96%, respectively. Seven major compounds have been isolated from the aerial parts and their molecular structures were determined as quercetin (1), kaempferol (2), kaempferol-3-*O*- β -D-glucopyranoside (3), ethyl gallate (4), gallic acid (5), 1,2,3,4,6-penta-*O*-galloyl- β -D-glucopyranose (6) and paeoniflorin (7). All these compounds except paeoniflorin reduced the serum total cholesterol, triglyceride and low density lipid of rats. Especially, quercetin strongly reduced the total cholesterol level by 68.85%, the triglyceride by 66.81% and the low density lipid by 39.09%, respectively, and slightly increased the high density lipid level as compared with other tested compounds. The compound 6 also exhibited blood lipid profiles lowering activity better than other tested compounds 2, 3, 4, 5 and 7. The antihyperlipidemic activity of this plant is strengthened by its major total phenolic constituents, in particular, quercetin and multigalloyl derivatives, which can be considered as the potent lipid-lowering agents, especially the triglyceride level.

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INTRODUCTION

At present, the number of hyperlipidemic people is growing due to the substantial changes in their diet, social psychology and rhythm of lifestyle. Hyperlipidemia is characterized by elevated concentrations of circulating lipids and considered as a major risk factor for cardiovascular diseases which are the leading cause of

death in developed and developing countries (Leeder et al., 2004; Gilbert, 2003). The World Health Organization estimates that about 17.7 million deaths, or 31% of noncommunicable deaths were due to cardiovascular diseases in 2017 (WHO Report, 2017). Atherosclerotic cardiovascular diseases including coronary heart disease,

stroke, heart attack and atherosclerosis are closely linked to the metabolism of lipids, particularly increased levels of total cholesterol and low density lipoprotein, and decreased level of high density lipoprotein in the blood plasma (Whitman et al., 1998; Grundy et al., 1999). Free radicals support lipid oxidation and are also implicated in cardiovascular diseases (Willcox et al., 2004). Reduction of the cholesterol level in serum by 10% reduces the risk of the coronary heart disease by 30% (Ang et al., 1998). The treatment and control of hyperlipidemia are usually achieved with the help of two main classes of drugs: statins and non-statins such as fibrates. However, statins have side effects such as hyperuricemia, diarrhea, nausea, gastric irritation, flushing, dry skin and are also not suitable for use during pregnancy (Wagstaff et al., 2003; Alsheikh-Ali and Karas, 2005). Fibrates help in lowering blood triglyceride levels but are not effective in reducing the LDL level (Reyes-Soffer et al., 2013). It is, therefore, necessary to develop safer agents for lowering blood lipid levels. Natural products, mainly medicinal plants may be an effective source for such drugs.

Therefore, the present study was conducted to evaluate the antihyperlipidemic activity of crude extracts, fractions and major isolated compounds from aerial parts and flowers of *Paeonia anomala* L. in high cholesterol diet induced hyperlipidemia in experimental animals.

MATERIALS AND METHODS

Plant material

The aerial parts and flowers of *P. anomala* L. were collected from Bulgan (August, 2009) and Tuv provinces (June, 2013) of Mongolia. The plant materials were botanically identified by the ScD., Prof. Sanchir Ch. Institute of General and Experimental Biology, Mongolian Academy of Sciences. A voucher specimen (Pa130622) has been deposited in the herbariums of the Natural Product Chemistry Laboratory of the Institute of Chemistry and Chemical Technology, Mongolian Academy of Sciences.

Preparation of extracts and fractions

Air-dried and powdered aerial parts (2.2 kg) of *P. anomala* were exhaustively extracted 3 times with 80% ethanol (EtOH) at room temperature; each extraction was for 24 h. The EtOH extract was concentrated using a rotary evaporator at low temperature (38-40°C) and under reduced pressure obtained the 720 g thick extract, which was suspended in distilled water and partitioned successively with dichloromethane (DCM fraction 48.4 g), *n*-butanol (*n*-BuOH fraction 425 g) and water soluble residue (WSR 319 g), respectively. Prepared samples were used for phytochemical analysis.

For biological activity tests, each 100 g of aerial parts and flowers were extracted with 80% EtOH and distilled water separately as described above, to yield EtOH extracts 22.98 and 32.93 g, DCM fractions 2.49 and 2.75 g, EA (ethylacetate) fractions 4.81 and 9.49 g, *n*-BuOH fractions 4.29 and 8.13 g, WSR 9.1 and 7.07 g, and water extracts 28.7 and 34.4 g, respectively.

Isolation and identification

The *n*-BuOH fraction of aerial parts of *P. anomala* (100 g) was divided into I - XIX subfractions using column chromatography (CC) by Sephadex LH 20(25 - 100 µm, Pharmacia, Uppsala, Sweden), eluting with a gradient H₂O - MeOH solvent system. Each subfraction was subjected to CC with different absorbents as MCI gel - CHP-20P (75 - 150 µm, Mitsubishi, Chemical Corporation, Japan), Septra C18-E (50 µm, 65A). From the *n*-BuOH fraction, compounds **1** (60.3 mg), **2** (57.9 mg), **3** (1.1 g), **4** (1.9 g), **5** (0.25g), **6** (0.9g) and **7** (1.7 g) have been isolated and purified. The molecular structures of the isolated compounds were determined using one-dimensional nuclear magnetic resonances spectroscopy (NMR) and direct comparison with authentic samples by TLC. ¹H NMR and ¹³C NMR spectra were recorded on JEOL JNM-EX270, using dimethyl sulfoxide (DMSO-*d*₆) and methanol (CD₃OD-*d*₄) as a solvent.

Animals

Male albino "Wistar" rats (250) were obtained from the Research Center for Laboratory Animal Science (Beijing, China). They were housed under standard laboratory conditions (temperature 22±2°C, relative humidity 60±4% and 12 light/dark cycle), fed pellet food and maintained according to the Guide for the Care and Use of Laboratory Animals approved by the Inner Mongolian University.

Experimental design

After one week, the rats were randomly divided into 28 (I-XXVIII) groups of seven rats in each.

Group I, considered as the negative control, was given a standard laboratory diet and administered the vehicle only (5% carboxymethylcellulose). Group II was considered an atherogenic group. To render hyperlipidemia, rats were given a high-fat diet (HFD), enhanced with 3% cholesterol, 0.5% sodium cholate and 10% lard in the administered vehicle. Group III, considered as the positive control, was given HFD and simvastatin (ata dose of 1.5 mg/kg body weight). Other groups, considered as treatment groups, were given HFD and administered the plant extracts (a dose of 200 and 400 mg/kg) and 7 pure compounds (a dose of 10 mg/kg) orally for 14 days. At the end of the experiment,

the rats were fasted overnight and blood samples were collected from the femoral artery of rats. Blood in vials was immediately centrifuged at 3000 rpm for 15 min, serum was separated and stored at -80°C. Total cholesterol (TC) and triglyceride (TG) in serum were measured using enzyme assay kits. Serum lipoproteins as low density (LDL) and high density (HDL) were separated from serum by precipitation and enzymatically measured (Han, 2008).

Statistical analysis

The results of all experiments performed were presented as Mean±SD (Standard Deviation). The significance of difference among the group was assessed using one-way analysis of variance (ANOVA) followed by Student's *t*-test, where *p*-values < 0.05 and < 0.01 were considered significant.

RESULTS AND DISCUSSION

Crude extracts, fractions and isolated major constituents of aerial parts and flowers of *Paeonia anomala* L. were assayed for their anti-hyperlipidemic effect.

We observed an increase in serum TC, TG, LDL levels and a decrease in the level of good cholesterol carrier HDL in the rats fed with high-fat diet (group II) as compared with the negative control group, suggesting that the hyperlipidemic treatment used was valid.

Oral administration of the different crude extracts and fractions of aerial parts and flowers of *P. anomala* resulted in a significant reduction in serum TC, TG and LDL levels as compared with the group II statistically (Table 1).

The TC level in groups treated with EA, *n*-BuOH fractions and water extract of aerial parts at the dose of 200 mg/kg was reduced by 35.5, 22.57 and 21.56%, and at the dose of 400 mg/kg by 74.09, 79.01 and 79.43%, respectively as compared with the group II. The TC level in groups treated with the EtOH extract and fractions of flowers at the dose of 200 mg/kg were slightly reduced, whereas at the dose of 400 mg/kg the DCM, EA and *n*-BuOH fractions reduced the TC level by 72.99, 69.53 and 72.91%, respectively. The other extracts and fractions did not exhibit any changes in the serum TC level at the dose of 200 mg/kg.

The TG level in groups treated with all extracts and fractions of aerial parts and flowers in both treated doses was strongly reduced by 44.71 and 68.28% as compared with the atherogenic group. In particular, the *n*-BuOH fraction and water extract of aerial parts and the *n*-BuOH fraction of flowers at the dose of 200 mg/kg reduced the TG level by 63.94, 57.21 and 65.38 %, respectively. In our study, it has been observed that the reduction of the TC level by the *P. anomala* fractions was associated with a decrease of its TG level. The standard antihyperlipidemic drug simvastatin at the dose of 1.5 mg/kg reduced the TC and TG

level by 48.43 and 37.98% under the same condition.

All crude extracts and fractions of aerial parts and flowers at the dose of 200 mg/kg did not show any changes in the LDL and HDL levels as compared with the group II. However, at the higher dose of 400 mg/kg, the EA and *n*-BuOH fractions of aerial parts and DCM, EA and *n*-BuOH fractions of flowers reduced the LDL level by 64.3, 60.75 and 62.84 %, 65.55 and 60.96 %, respectively.

Most of the currently used antihyperlipidemic drugs do not reduce the triglycerides level (Veeramani et al., 2012). However, in our study all extracts and fractions of both tested drugs of *P. anomala* at a dose of 200 mg/kg significantly reduced TG level, which consequently might be important in the prevention and management of cardiovascular diseases.

Presently, no report has describes the antihyperlipidemic activity of aerial parts and flowers of *P. anomala* L. However, our results correlate with the findings of Bilalet al. (2014) who stated that the hydroalcoholic and aqueous extracts of *P. emodi* at the dose of 200 mg/kg were able to reduce the TC level by 31.7 and 21.2%, TG by 46.4 and 28.9%, LDL by 46.1 and 64.72%, respectively. Moreover, the root methanol extract of *P. lactiflora* at a dose of 240 mg/kg reduced TC by 15.57%, TG by 33.31%, LDL by 15.16 % and HDL by 15.85% respectively (Yang et al., 2004).

The results of this study suggested that both crude drugs of *P. anomala* may be helpful in controlling the metabolism of blood lipid profiles that demonstrate antihyperlipidemic effect.

It is already known that the *Paeonia* sp. are rich in monoterpenoids, flavonols, gallic acid and its derivatives (Wu, 2010; Zhao, 2016). Seven major compounds, which were isolated from the *n*-BuOH fraction of the aerial parts, were investigated for their anti-hyperlipidemic effect. Molecular structures of these known compounds were determined as quercetin (**1**) (Harborne, 1994), kaempferol (**2**) (Harborne, 1994), kaempferol-3-*O*- β -D-glucopyranoside (**3**) (Kamiya et al., 1997), ethyl gallate (**4**) (Sato et al., 1997), gallic acid (**5**) (Lee et al., 2005), 1,2,3,4,6-penta-*O*-galloyl- β -D-glucopyranose (**6**) (Nishizawa et al., 1982) and paeoniflorin (**7**) (Aimi et al., 1969) (Figure 1). They were also detected in flowers and identified as major constituents within the genus *Paeonia* (Purevdorj and Odontuya, 2016).

Flavonols (**1**, **2,3**), gallic acid derivatives (**4**, **5**, **6**) and a "cage-like" a monoterpene paeoniflorin (**7**) at the dose of 10 mg/kg have been tested and results are shown in Table 2.

Compound **1** at the dose of 10 mg/kg strongly reduced the TC level by 65.85%, the TG level by 67.24% and the LDL level by 39.09% and slightly increased the HDL level as compared with other compounds **2-7**. These results correlate with the findings of Ricardo et al. (2001) who evaluated that quercetin at the dose of 5 mg/kg reduced TC level and TG levels by 68.1% and 59.05%, respectively. TC, TG and LDL levels in groups treated with compound **2** and

Table 1: Effect of extracts and fractions of *Paeoniaanomala* L. drugs on lipid levels, *in vivo*.

Treatment groups		Dose, mgkg ⁻¹	Levels (mg/dL)			
			TC	TG	HDL	LDL
Negative control	Group I	-	4.15±0.80**	0.78±0.11**	2.48±0.14**	0.80±0.06**
Atherogenic group	Group II	-	22.81±2.40	2.08±0.55	0.94±0.05	4.79±0.71
Aerial parts						
EtOHextract	Group IV	200	27.88±4.65	0.84±0.28** (-59.61 %)	0.84±0.35	7.91±2.19
DCM fraction	Group V	200	24.09±2.48	0.82±0.12** (-60.57 %)	0.57±0.96*	8.58±4.08
EA fraction	Group VI	200	14.93±2.14 (-35.53 %)	0.86±0.11** (-58.68 %)	0.39±0.16	4.81±1.68
	Group VII	400	5.91±0.71** (-74.09 %)	0.73±0.11** (-65.38 %)	0.51±0.14**	1.71±0.18* (-64.3 %)
n-BuOH fraction	Group VII	200	17.62±3.22 (-22.57 %)	0.75±0.18** (-63.94 %)	0.28±0.19	4.49±1.21
	Group IX	400	4.79±0.57** (-79.01 %)	0.71±0.14** (-65.86 %)	0.51±0.12*	1.88±0.06** (-60.75 %)
Water soluble residue	Group X	200	24.47±2.23	0.93±0.21* (-55.28 %)	0.18±0.08	7.37±1.12
Water extract	Group XI	200	17.89±4.15 (-21.56 %)	0.89±0.12** (-57.21 %)	0.30±0.11	5.11±1.9
	Group XII	400	4.69±0.58** (-79.43 %)	1.15±0.37* (-44.71 %)	0.49±0.15*	3.01±0.58** (-37.16 %)
Flowers						
EtOHextract	Group XIII	200	19.61±3.53 (-14.02 %)	0.75±0.12** (-63.94 %)	0.24±0.07	4.48±1.43
DCM fraction	Group XIV	200	17.69±3.04 (-22.44 %)	0.76±0.12** (-63.46 %)	0.21±0.09	4.72±0.34
	Group XV	400	6.16±0.86** (-72.99 %)	0.81±0.27** (-61.05 %)	0.25±0.08	1.78±0.30** (-62.84 %)
	Group XVI	200	17.79±4.24 (-22.01 %)	0.85±0.15* (-59.13 %)	0.43±0.15	5.13±1.43
EA fraction	Group XVII	400	6.95±0.65** (-69.53 %)	0.76±0.21** (-63.46 %)	0.41±0.05	1.65±0.22* (-65.55 %)
	Group XVIII	200	15.32±3.21 (-32.83 %)	0.73±0.16* (-65.38 %)	0.42±0.13	5.99±1.52
n-BuOH fraction	Group XIX	400	4.61±0.55** (-72.91 %)	0.66±0.06* (-68.28 %)	0.57±0.15**	1.89±0.12* (-60.96 %)
	Group XX	200	19.25±4.67 (-15.61 %)	0.71±0.12** (-65.86 %)	0.13±0.07	5.46±0.45
Water soluble residue	Group XX	200	19.25±4.67 (-15.61 %)	0.71±0.12** (-65.86 %)	0.13±0.07	5.46±0.45
Water extract	Group XXI	200	21.98±2.19 (-3.63 %)	0.93±0.16* (-55.28 %)	0.25±0.08	8.49±1.20
Reference drug						
Simvastatin	Group III	1.5	11.71±1.17 (-48.43 %)	1.29±0.63 (-37.98 %)	1.21±0.29 (+37.23 %)	2.04±0.76 (-57.41 %)

Values are mean ± SD of 7 rats.

* p < 0.05, ** p < 0.01 significantly different from group II (Students *t*-test).

3 were somewhat reduced, while the significant difference in the HDL level was not observed.

Among the gallic acid derivatives, compound **6** more effectively reduced TC, TG and LDL levels by

39.1, 42.3 and 21.3% than compounds **4** and **5**. Park et al. (2002) reported that PGG at the same dose of our experiment reduced both serum TC and TG by

22.7 and 33.3%, respectively. Our results are in line with this report.

Compound **7** did not show any antihyperlipidemic

activity under our experimental condition. However, it has been reported that compound **7** from *P. lactiflora*, at the high doses of 200 and 400 mg/kg strongly reduced the serum lipid level in high fat induced hypercholesterolemia (Yang et al.,

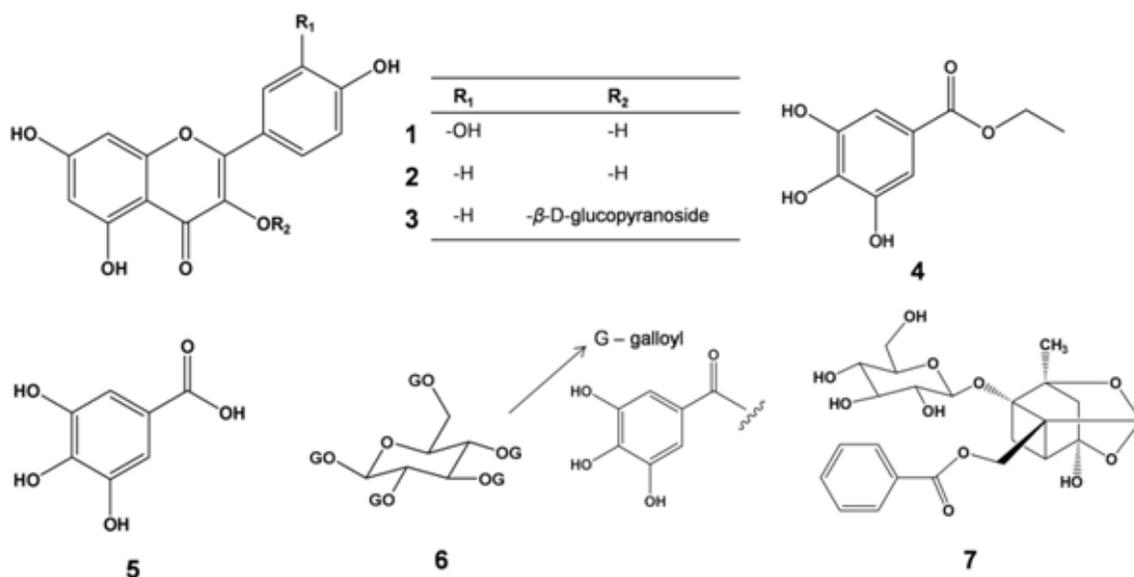


Figure 1: Major constituents in the aerial parts and flowers of *P. anomala* L.

Table 2: Effect of major compounds of *Paeonia anomala* L. on lipid levels, *in vivo*.

		Dose, mgx kg ⁻¹	Levels (mmol/L)			
			TC	TG	HDL	LDL
Negative control	Group I		1.61±0.21**	0.67±0.26**	0.45±0.08**	2.98±1.14**
Atherogenic group	Group II		9.87±1.95	2.29±0.98	0.22±0.03	3.99±0.62
Major constituents of <i>P. anomala</i>						
1		10	3.37±0.77** (-65.85 %)	0.75±0.15** (-67.24 %)	0.23±0.7 (+4.45 %)	2.43±0.59** (-39.09 %)
2		10	7.19±0.84 (-27.15 %)	1.41±0.27* (-46.99 %)	0.22±0.06	3.32±0.47 (-16.79 %)
3		10	8.42±1.41* (-14.6 %)	1.21±0.19 (-47.16 %)	0.21±0.04	3.58±0.39* (-10.27 %)
4		10	6.01±0.48** (-39.1 %)	1.32±0.32* (-42.35 %)	0.19±0.12*	3.14±0.75* (-21.3 %)
5		10	6.87±0.89 (-30.39 %)	1.51±0.27 (-34.06 %)	0.21±0.12	3.53±0.56 (-11.52 %)
6		10	4.96±1.04** (-49.74 %)	1.04±0.23** (-53.98 %)	0.15±0.05**	3.98±0.55** (-10.27 %)
7		10	14.26±2.81	2.04±0.48 (-10.91 %)	0.21±0.11	3.75±0.72 (-6.01 %)
Reference drug						
Simvastatin	Group III	1.5	4.38±0.73** (-55.62 %)	0.86±0.13** (-62.44 %)	0.25±0.05** (+16.63 %)	3.08±1.13* (-22.81)

Values are mean ± SD of 7 rats.

* p < 0.05, ** p < 0.01 significantly different from group II (Students *t*-test)

2004).

The present study demonstrated that the oral administration of compound **1** and **6** exhibited higher antihyperlipidemic activity than other tested compounds. Consequently, the antihyperlipidemic activity of crude drugs of *P. anomala* could be characterized by the presence and amount of the quercetin and its glucosides, as well as multigalloylglucopyranosides.

The antiatherosclerotic effect of phenolic compounds and its influence on the regulation of cholesterol biosynthesis have been discussed in numerous studies (Attaway and Buslig, 1998; Garcia-Saura et al., 2005; Abbass, 2011; Bok et al., 2002; Affana et al., 1989; Koo and Noh, 2007). Especially, quercetin has gained considerable attention mainly due to their broad spectrum of health beneficial effects for treating atherosclerosis. Quercetin reduced the high cholesterol level in HFD and it can inhibit HMG-CoA reductase, a rate-limiting enzyme in cholesterol biosynthesis and decrease oxidative stress through stimulation of lipolysis activity (Ricardo et al., 2001; Attaway and Buslig, 1998; Garcia-Saura et al., 2005; Abbass, 2011; Bok et al., 2002)

It has been suggested that polyphenols interact with proteins involved in cholesterol translocation from the enterocyte, change their function and effectively reduce intestinal cholesterol absorption (Koo and Noh, 2007). In addition, polyphenols can enhance the endogenous antioxidative system, improve the oxidant and antioxidant balance, inhibit cholesterol lipase enzyme, effectively prevent oxidative damage and decrease lipid peroxidation (Terfiouta et al., 2018; Odontuya et al., 2017). In our previous study, 1,2,3,4,6-penta-*O*-galloyl- β -D-glucopyranose significantly inhibited pancreatic lipase activity with IC₅₀ 0.021 mM (Odontuya et al., 2017). Therefore, PGG inhibited rat microsomal squalene synthase (IC₅₀ 1.0 μ M) which is a key enzyme in cholesterol synthesis (Park et al., 2002).

The findings of the present study to some extent proves the beneficial effects of quercetin and PGG on blood lipid metabolism and suggests that they can be effective anti-hyperlipidemic agents. Moreover, molecular structures of these compounds have similar catechol groups in their skeletons which might be effective in reduction of the serum lipid level.

Conclusion

This study demonstrated that the polar fractions and water extracts of aerial parts and flowers of *P. anomala* L. possess antihyperlipidemic properties. In particular, the treatments selectively reduced triglyceride levels, probably because of its major total phenolic constituents, in particular, quercetin and multigalloyl derivatives.

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