Screening for Anti-lipase Properties of 37 Traditional Chinese Medicinal Herbs

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Background: To find new, crude anti-obesity drugs from natural sources through the inhibition of adsorption of dietary lipids, *in vitro* porcine pancreatic lipase (PPL; triacylglycerol lipase, EC 3.1.1.3) inhibitory tests were carried out on selected plants with weight-reducing or related potential, used in Chinese traditional medicine.

Methods: The methanolic extracts of 37 traditional Chinese herbal medicines of different families were assayed for their *in vitro* activity against PPL by using spectrophotometry with 2,4-dinitrophenyl butyrate as a synthetic substrate. Coexistent phytochemicals, or those present in high levels, in the 3 most promising Chinese herbs were tested for their anti-lipase activity.

Results: Extracts from 2 herbs, *Prunella vulgaris* L. (Labiatae) and *Rheum palmatum* L. (Polygonaceae), at a concentration of 200 μg/mL, significantly inhibited PPL—by 74.7% and 53.8%, respectively. Quercetin exhibited better activity (27.4%) than all the other phytochemicals at a final concentration of 25 μg/mL in the assay system, followed by luteolin, with an activity of 17.3%.

Conclusion: The results support the view that herbs represent a rich source of anti-lipase compounds. The screening of the methanolic extracts of 37 Chinese medicinal plants *in vitro* led to the identification of several extracts with potential activity against PPL, in particular, *P. vulgaris* and *R. palmatum*. We also found that several monomeric chemicals in these herbs exhibited good or moderate activity against PPL. To the best of our knowledge, these traditional Chinese herbal medicines or phytochemicals have not been previously screened for their lipase inhibitory activity. [*J Chin Med Assoc* 2010;73(6):319–324]

Key Words: anti-lipase activity, anti-obesity agents, Chinese herbal drugs, *Prunella vulgaris* L., *Rheum palmatum* L.

Introduction

Obesity is an increasingly serious global problem, not only for the harm it causes in its own right, but also due to the associated health threats, especially type 2 diabetes, systemic hypertension, cardiovascular disease, certain cancers, asthma, and sleep apnea.[1–3] The prevalence of obesity has been steadily increasing in children and adolescents in recent years,[4–6] which suggests the likelihood of worsening obesity trends in the future adult population. Therefore, it is essential to develop ways of preventing more people from becoming obese. However, diet and physical exercise are usually not very effective, and most patients regain weight even after successful weight loss.[7] Thus, treatment might be necessary when prevention fails.[8]

The significant progress in unveiling the molecular mechanisms of body weight regulation has provided potential therapeutic targets for obesity.[9,10] For a drug to have a significant impact on body weight, it must ultimately affect energy intake and/or expenditure.[9] The development of inhibitors of nutrient digestion and absorption, which reduce energy intake through gastrointestinal mechanisms without altering any central mechanisms, is one of the most important strategies in the treatment of obesity.[11]

Dietary lipids represent the major source of unwanted calories;[12,13] therefore, lipid metabolism is

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a vital and subtle balance that maintains energy homeostasis.[14] Once this balance is lost, obesity or hyperlipidemia develops, followed by a series of severe diseases, including atherosclerosis, hypertension, diabetes, and dysfunction of certain organs. Obviously, drug control of lipid metabolism offers a possible way to prevent or treat these diseases. The identification and characterization of several enzymes involved in lipid metabolism have yielded a rich pool of potential targets for drugs to treat obesity and other metabolic disorders.[14] Pancreatic lipase, the main lipid-digesting enzyme, removes fatty acids from the α and α′ position of dietary triglycerides, which yields the lipolytic product β-monoglyceride and long-chain saturated and polyunsaturated fatty acids. Inhibition of pancreatic lipase is an attractive targeted approach for the treatment of obesity.[13] For instance, orlistat, a hydrogenated derivative of lipstatin, which is obtained from *Streptomyces toxytricini*, is the only pancreatic lipase inhibitor currently approved for long-term treatment of obesity. Its use can result in up to 10% weight loss when used in combination with dietary, behavioral and exercise therapy,[15] but it also has unpleasant and non-negligible side effects.[9] Therefore, there is a need for more lipase inhibitors or medicinal products that are safe and effective.

Naturally occurring phytochemicals present an exciting opportunity for the discovery of newer anti-obesity agents. Some have already been identified as lipase inhibitors, e.g. licochalcone A, which has been isolated from the roots of *Glycyrrhiza uralensis*,[16] platycodin D from the fresh roots of *Platycodon grandifloru*,[17] dioscin from *Dioscorea nipponica*,[18] phenolic constituents from the leaves of *Nelumbo nucifera*,[19] and other components from other kinds of herbs. However, it remains necessary to search for more efficacious lipase inhibitors from traditional Chinese herbs. Here, we studied 37 Chinese herbs for their lipase inhibitory activity using 2,4-dinitrophenyl butyrate (DNPB) as an artificial substrate.

Methods

Plant materials and chemicals

All traditional Chinese medicinal herbs were purchased from Qian Kun Drugstore of Yangling, a Chinese herb store in China. A collection of voucher specimens is available for confirmation in the Research Centre for Natural Medicinal Chemistry, Northwest Agriculture & Forestry University, Yangling, Shaanxi, China.

Porcine pancreatic lipase (PPL, type II) and orlistat were purchased from Sigma-Aldrich (St Louis, MO, USA). Quercetin, rutin, catechin, and luteolin were all purchased from Indofine (Hillsborough, NJ, USA). Emodin and ursolic acid were purchased from Fluka Chemie (Buchs, Switzerland). All other chemicals and solvents were of analytical grade.

Preparation of plant extracts

The Chinese herbs were air dried and ground into fine powder. The powdered material (50 g) was ultrasonically extracted with 500 mL methanol 3 times at room temperature, and concentrated at 45°C in a rotator vacuum evaporator (Buchi, Flawil, Switzerland). The final extracts were stored at –20°C.

PPL inhibition assay

Lipase activity was measured using DNPB as a substrate.[16] DNPB was synthesized using the method previously described by Mosmuller et al.[20] PPL stock solutions (1 mg/mL) were prepared in 0.1 mM potassium phosphate buffer (pH 6.0), and the solutions were stored at –20°C. To determine lipase inhibitory activity, the extracts (0.2 mg/mL) or phytochemicals (at different concentrations) were pre-incubated with the enzyme for 1 hour in potassium phosphate buffer (0.1 mM, pH 7.2, combined with 0.6 mL/100 mL Tween 80) at 30°C before assaying the enzyme activity.[21] The reaction was then started by adding 0.1 mL 25 mM DNPB, all in a final volume of 5.0 mL. After incubation at 30°C for 5 minutes, the amount of 2,4-dinitrophenol released in the reaction was measured at 360 nm using the Evolution 300 UV-Visible spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). The activity of the negative controls was also checked with and without inhibitor. The inhibitory activity (I) was calculated according to the following formula:[22]

$$I\% = \left(1 - \frac{B - b}{A - a}\right) \times 100$$

where A is the activity of the enzyme without inhibitor, a is the negative control without inhibitor, B is the activity of the enzyme with inhibitor, and b is the negative control with inhibitor.

Statistical analysis

All results were expressed as median ± standard deviation ($n = 3$). Significance of difference from the control was determined by Duncan's test and Kruskal–Wallis test, and a p value < 0.05 was considered significant.

Results

Anti-lipase activity of crude herbal extracts

Thirty-seven extracts were prepared from selected parts of the traditional Chinese herbal medicines and were

Table 1. Lipase inhibitory effects of various Chinese herbs

No.	Scientific name	Plant part	Family	Inhibition (%)*
1	*Achyranthes bidentata* Bl.	Root	Amaranthaceae	2.9 ± 3.5
2	*Alisma oriental* (Sam.) Juzep.	Tuber	Alismataceae	15.4 ± 0.0
3	*Angelica sinensis* (Oliv.) Diels.	Root	Umbelliferae	1.2 ± 1.9
4	*Astragalus membranaceus* (Fisch.) Bunge	Root	Leguminosae	–11.0 ± 2.2
5	*Atractylodes macrocephala* Koidz.	Rhizome	Asteraceae	–3.1 ± 3.8
6	*Bupleurum chinense* DC.	Root	Umbelliferae	16.8 ± 4.2
7	*Carthamus tinctorius* L.	Flower	Asteraceae	12.3 ± 3.5
8	*Citrus aurantium* L.	Young fruit	Rutaceae	–3.5 ± 2.4
9	*Cornus officinalis* Sieb. Et Zucc.	Fruit	Cornaceae	7.6 ± 3.8
10	*Dioscorea opposita* Thunb.	Rhizome	Dioscoreaceae	3.5 ± 3.9
11	*Eclipta prostrata* L.	Whole grass	Asteraceae	–3.1 ± 0.3
12	*Ephedra sinica* Stapf	Herbaceous stem	Ephedraceae	25.9 ± 4.3
13	*Epimedium brevicornum* Maxim.	Aerial part	Berberidaceae	–3.8 ± 1.9
14	*Forsythia suspensa* (Thunb.) Vahl	Fruit	Oleaceae	20.4 ± 4.9
15	*Grataegus pinnatifida* Bunge	Fruit	Rosales	11.3 ± 0.1
16	*Leonurus japonicus* Houtt.	Fruit	Labiatae	11.1 ± 5.2
17	*Ligusticum chuanxiong* Hort.	Rhizome	Umbelliferae	16.3 ± 5.6
18	*Ligustrum lucidum* Ait.	Fruit	Oleaceae	8.0 ± 2.2
19	*Millettia reticuiata* Benth.	Rattan cane	Leguminosae	33.3 ± 4.2
20	*Morus alba* L.	Ear	Moraceae	16.4 ± 3.2
21	*Paeonia lactiflora* Pall.	Root	Ranunculaceae	2.8 ± 0.1
22	*Panax notoginseng* (Burk.) F.H.Chen	Root	Araliaceae	–4.3 ± 5.1
23	*Phragmites communis* Trin.	Rhizome	Poaceae	–5.4 ± 0.7
24	*Pinellia ternata* (Thunb.) Breit.	Tuber	Araceae	–8.1 ± 2.7
25	*Plantago asiatica* Linn.	Whole grass	Plantaginaceae	0.7 ± 1.0
26	*Polygonum cuspidatum* Sieb. et Zucc.	Root and rhizome	Polygonaceae	37.8 ± 6.5
27	*Polygonum multiflorum* Thunb.	Root	Polygonaceae	17.0 ± 3.9
28	*Portulaca oleracea* Linn.	Aerial part	Portulacaceae	6.0 ± 3.7
29	*Prunella vulgaris* L.	Ear	Labiatae	74.7 ± 10.0
30	*Pueraria lobata* (Willd.) Ohwi	Root	Leguminosae	–15.9 ± 2.4
31	*Raphanus sativus* L.	Seed	Cruciferae	3.0 ± 1.3
32	*Rheum palmatum* L.	Root and rhizome	Polygonaceae	53.8 ± 9.0
33	*Salvia miltiorrhiza* Bge.	Root and rhizome	Labiatae	32.7 ± 3.8
34	*Saposhnikovia divaricata* (Turcz.) Schischk.	Root	Umbelliferae	–1.9 ± 2.1
35	*Sophora tonkinensis* Gapnep.	Root and rhizome	Leguminosae	2.8 ± 3.4
36	*Taxillus chinensis* (DC.) Danser	Aerial part	Loranthaceae	21.1 ± 5.1
37	*Uncaria macrophylla* Wall.	Aerial part	Alismataceae	30.1 ± 3.3
38	Orlistat			93.5 ± 7.3

*$p < 0.05$ compared with control orlistat, data presented as median ± standard deviation ($n = 3$), and "–" indicates a promotion of lipase activity. The final concentration of the extracts used in this screening was 200 μg/mL.

tested at a concentration of 0.2 mg/mL for PPL inhibition (Table 1). The selected Chinese herbs, which belonged to various families, had different effects on PPL *in vitro*. Six extracts showed moderate to strong anti-lipase activity (> 30%).

Among these 6 plants, *Prunella vulgaris* L. (Labiatae) and *Rheum palmatum* L. (Polygonaceae), were found to have strong inhibitory activity of > 50% against PPL: 74.7% with *P. vulgaris*, and 53.8% with *R. palmatum*. *Millettia reticulata* Benth. (Leguminosae), *Polygonum cuspidatum* Sieb. et Zucc. (Polygonaceae), *Salvia miltiorrhiza* Bge. (Labiatae), and *Uncaria macrophylla* Wall. (Alismataceae) showed > 30% inhibition of PPL. Additionally, there were several herbs that displayed weak inhibitory activity against PPL. Some of the herbs slightly promoted the activity of PPL, such as *Pueraria lobata* (Willd.) Ohwi (Leguminosae), which increased the activity of the enzyme by 15.9%, which was distinct from the other herbs.

The crude extracts of *P. vulgaris* and *R. palmatum* at different concentrations were also tested for their PPL inhibitory effects, and a dose–response curve was obtained (Figure 1). To avoid inaccurate test results, extracts with a concentration > 200 μg/mL were not

tested for a sudden increase in ultraviolet absorption from the extracts themselves. With weaker effects than the positive control orlistat at each concentration, both *P. vulgaris* and *R. palmatum* exhibited increasing inhibitory activities as concentration rose from 5 to 200 μg/mL.

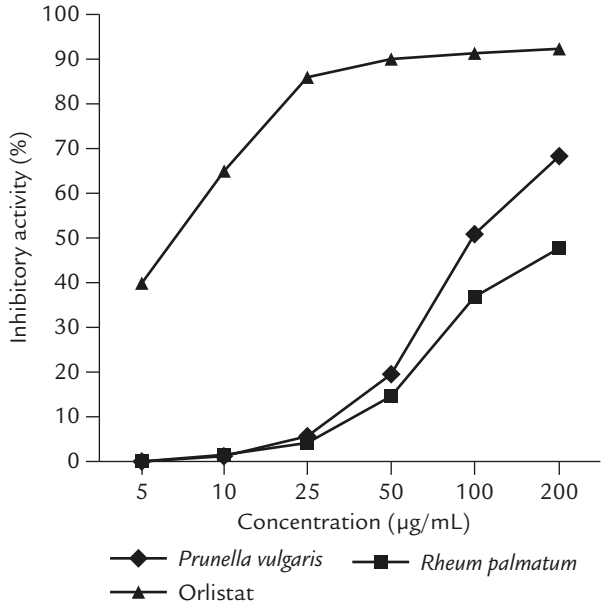

Figure 1. Porcine pancreatic lipase inhibitory activities of *Prunella vulgaris* L. and *Rheum palmatum* L. Orlistat was used as a positive control.

Anti-lipase activity of coexistent or phytochemicals appearing at high levels in promising herbs

The anti-lipase activity of the coexistent phytochemicals or phytochemicals found at high levels in the 3 most promising Chinese herbs (Table 2) were also tested, and the results are shown in Table 3.

All the chemicals tested displayed increasing inhibition of PPL with increasing concentration. We tried to determine their activity at 3 different concentrations (25 μg/mL, 50 μg/mL and 100 μg/mL), but some could not be tested because of too large an absorbance from the chemicals, which could have resulted in inaccurate data. Thus, lower concentrations (5 μg/mL and 10 μg/mL) were also used when the data for higher concentrations were unavailable.

Quercetin, which is present in *P. vulgaris* and *Pol. cuspidatum*, exhibited a good inhibitory effect (27.4%) on PPL at a concentration of 25 μg/mL. Luteolin, another phytochemical that coexists in these 2 herbs, had an inhibitory activity of 17.3% at the same concentration. Ursolic acid also contributed to a better performance of these 2 herbs, with an anti-lipase activity of 11.0%. For *P. vulgaris*, the effect might also have been

Table 2. Coexistent phytochemicals or phytochemicals present at high levels in the most promising Chinese herbs for porcine pancreatic lipase activity

Chinese herbs	Phytochemicals					
	Luteolin	Rutin	Catechin	Quercetin	Ursolic acid	Emodin
Prunella vulgaris L.	*	*		*	*	
Rheum palmatum L.			*		*	*
Polygonum cuspidatum Sieb. et Zucc.	*		*	*	*	*

**Indicates the existence of a compound in the corresponding herb.*

Table 3. Inhibitory effects (%) of coexistent phytochemicals or phytochemicals present at high levels in promising Chinese herbs for porcine pancreatic lipase activity*

Phytochemical	Formula	Hazard†	Concentration (μg/mL)				
			5	10	25	50	100
Luteolin	$C_{15}H_{10}O_6$	Irritant	1.7 ± 0.6‡	10.9 ± 1.8‡	17.3 ± 1.4‡	NT	NT
Rutin	$C_{27}H_{30}O_{16}$	Harmful	NT	NT	11.0 ± 2.0‡	24.4 ± 2.7‡	30.8 ± 1.2‡
Catechin	$C_{15}H_{14}O_6$	Irritant	NT	NT	4.2 ± 0.9‡	8.3 ± 0.3‡	6.5 ± 1.5‡
Quercetin	$C_{15}H_{10}O_7$	Toxic	6.9 ± 0.7‡	18.1 ± 2.1‡	27.4 ± 2.9‡	NT	NT
Ursolic acid	$C_{30}H_{48}O_3$	–§	NT	NT	11.0 ± 1.0‡	22.6 ± 1.9‡	39.6 ± 2.7‡
Emodin	$C_{15}H_{10}O_5$	Irritant	1.5 ± 0.6‡	4.7 ± 0.8‡	12.0 ± 1.3‡	NT	NT
Orlistat	$C_{29}H_{53}NO_5$	–§	40.7 ± 0.8	63.9 ± 1.7	87.1 ± 2.5	91.3 ± 2.9	92.0 ± 3.3

**Data (%) are presented as median ± standard deviation (n = 3); †adapted from the product information at http://www.sigmaaldrich.com; ‡p < 0.05 compared with positive control orlistat; §non-toxic and comparatively safe. NT = not tested.*

enhanced by rutin, which exhibited an activity similar to that of ursolic acid.

Discussion

Besides a wide range of health benefits, extracts of *P. vulgaris* have recently been reported to have an anti-hyperglycemic enhancing effect in diabetic mice,[23] and extracts of *R. palmatum* have been used to treat hyperlipidemia in diabetic rats.[24] Emodin, one of the main effective components in *R. palmatum* and *Pol. cuspidatum*, can not only inhibit cell differentiation and proliferation of 3T3-L1 preadipocytes,[25] but also promotes adipocyte differentiation in 3T3-L1 cells.[26] In the current study, emodin showed an anti-lipase activity of 12.0% at a concentration of 25 μg/mL, which suggests that it can be used as an anti-obesity drug. Polydatin, another important chemical in *Pol. cuspidatum*, has been found to have lipid-lowering activity, and has favorable potency for clinical development as a hypolipemic and/or hepatoprotective agent.[27,28] Our study indicated that the methanol extracts of *P. vulgaris* and *R. palmatum* showed strong inhibitory effects against PPL (>50%), which suggests that these herbs could be candidate anti-obesity drugs.

The anti-lipase properties of the crude herbal extracts might be determined not only by the species of the phytochemicals, but also by their content in the herbs. For example, emodin was not as active as quercetin, but its high concentration contributed to the activity of *R. palmatum*, which demonstrated that emodin was mainly responsible for the anti-lipase activity of *R. palmatum*.

For clinical research in obesity control, the toxicity of the chemicals must be considered. Although quercetin has much better anti-lipase activity than other compounds at the same concentration, it is classified as toxic. Therefore, it might not be a good candidate for further clinical investigation, or structural modification might be needed. Rutin is also harmful to humans. Ursolic acid is relatively non-toxic, and has been used in cosmetics and health products;[29] thus, it could be a much more promising candidate for management of overweight or obesity.

Although good activities were detected from the coexistent or phytochemicals present at high levels in the top 3 promising Chinese herbs, we could not conclude whether or not these chemicals were the only contributors to their excellent anti-lipase characteristics. Thus, further investigations, both *in vitro* and *in vivo*, should be conducted to elucidate the main effective phytochemicals in these candidates, which are responsible for the inhibition of lipase activity, using bioguided fractionation.

For screening, especially when faced with a mass of materials, the testing method used in the assay must be easy to perform and reliable. There are many methods for the determination of lipase activity, but not all of them are well suited to screening because of the complexity of the procedures. In our research, the synthetic substrate DNPB was used, and it enabled the determination of the activity of PPL to be conducted easily using a spectrophotometric method. Furthermore, a positive control, orlistat, was used to ensure the reliability of our results.

In conclusion, the screening of methanolic extracts of 37 Chinese medicinal plants *in vitro* led to the identification of several extracts with potential anti-lipase activity, in particular, *P. vulgaris* and *R. palmatum*. The phytochemicals in the promising herbs also exhibited good to moderate anti-lipase activity, but they might not be the only contributors to the activity of the herbs. Therefore, more studies should be carried out. To the best of our knowledge, these traditional Chinese herbal medicines and monomeric chemicals have not been previously screened for their lipase inhibitory activity.

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