

# In vitro Screening and Evaluation of 37 Traditional Chinese Medicines for Their Potential to Activate Peroxisome Proliferator-activated Receptors- $\gamma$

Die Gao, Yonglan Zhang, Fengqing Yang, Yexin Lin, Qihui Zhang, Zhining Xia

Department of Pharmacy, College of Chemistry and Chemical Engineering, Chongqing University, Chongqing 400030, P.R. China

Submitted: 10-08-2015

Revised: 08-09-2015

Published: 02-03-2016

## ABSTRACT

**Background:** Peroxisome proliferator-activated receptors (PPAR)- $\gamma$  is widely used as an attractive target for the treatment of type 2 diabetes mellitus. Thiazolidinediones, the agonists of PPAR $\gamma$ , has been popularly utilized as insulin sensitizers in the therapy of type 2 diabetes whereas numerous severe side-effects may also occur concomitantly. **Objective:** The PPAR $\gamma$  activation activity of different polar extracts, including petroleum ether, ethyl acetate, n-butanol, residual of ethanol, the precipitate part of water and the supernatant of water extracts, from 37 traditional Chinese medicines were systematically evaluated. **Materials and Methods:** HeLa cells were transiently co-transfected with the re-constructed plasmids of GAL4-PPAR $\gamma$ -ligand binding domain and pGL4.35. The activation of PPAR $\gamma$  by different polarity extracts were evaluated based on the PPAR $\gamma$  retransactivation assay and rosiglitazone was used as positive control. **Results:** Seven medicines (root bark of *Lycium barbarum*, *Anoectochilus sroxburghii*, the rhizome of *Phragmites australis*, *Pteroccephalus hookeri*, *Polygonatum sibiricum*, fruit of *Gleditsia sinensis*, and *Epimedium brevicornu*) were able to significantly activate PPAR $\gamma$ . **Conclusion:** As seven medicines were able to activate PPAR $\gamma$ , the anti-diabetic activity of them is likely to be mediated by this nuclear receptor.

**Key words:** Diabetes mellitus, different polarity extracts, peroxisome proliferator-activated receptor- $\gamma$ , traditional anti-diabetic medicines

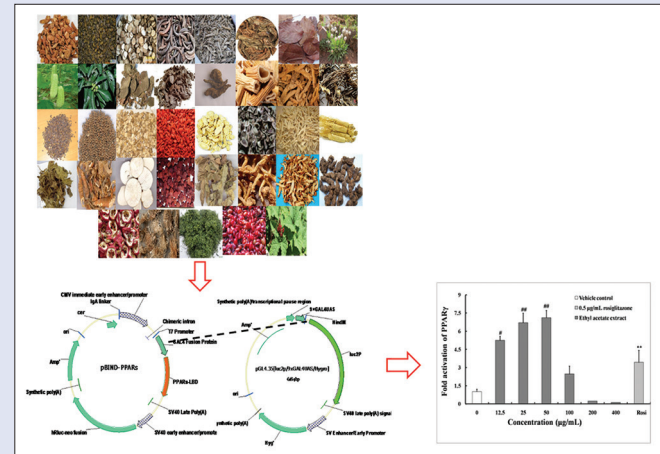
## SUMMARY

- Lots of the tested medicinal products had activation effects on activating PPAR $\gamma$
- Ethyl acetate extracts of root bark of *L. barbarum*, rhizome of *P. australis* and fruit of *G. sinensis* showed good PPAR $\gamma$  activation effect similar or higher than that of positive control, 0.5  $\mu$ g/mL rosiglitazone
- Petroleum ether extracts of *A. sroxburghii*, *P. hookeri*, *P. sibiricum*, *E. brevicornu* also can significantly activate PPAR $\gamma$ , the effects of them were higher than 10.5  $\mu$ g/mL rosiglitazone
- *Schisandra chinensis* (Turcz.) Baill., the fruit *Cornus officinalis* Siebold and Zucc., *Alisma plantago-aquatica* L. and the root of *Trichosanthes Kirilowii* Maxim., traditional anti-diabetic medicines in China, had no effects on the activation of PPAR $\gamma$ .

## INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by insulin resistance coupled with a lackage of enough insulin to control blood glucose.<sup>[1]</sup> It is well-known that chronic hyperglycemia results in many diabetic complications such as diabetic nephropathy, obesity, and atherosclerosis.<sup>[2]</sup>

Peroxisome proliferator-activated receptors (PPARs) have been implicated to participate in many critical physiological and pathological processes, especially in the treatment of diabetes mellitus, obesity, and atherosclerosis.<sup>[3,4]</sup> They play important roles in the expression of various genes which are crucial to lipid and glucose metabolism.<sup>[5]</sup> There are three PPAR subtypes, PPAR $\alpha$ , PPAR $\beta/\delta$ , and PPAR $\gamma$ , which have respective expression patterns and regulate different biological processes based on the requirement of a specific tissue.<sup>[6]</sup> PPAR $\gamma$  is expressed in



**Abbreviations used:** PPAR $\gamma$ : Peroxisome Proliferator-activated Receptors- $\gamma$ , TCMs: Traditional Chinese medicines, TZDs: Thiazolidinediones, LBD: Ligand binding domain, DMSO: Dimethyl sulfoxide, FBS: Fetal bovine serum, DMEM: Dulbecco's modified Eagle's medium.

## Correspondence:

Prof. Zhining Xia,  
College of Chemistry and Chemical Engineering,  
Chongqing University, Chongqing 400030, P.R. China.  
E-mail: tom\_anal\_cqu@163.com

DOI: 10.4103/0973-1296.177909

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adipose cells as well as islet beta cells.<sup>[7]</sup> Activation of PPAR $\gamma$  can improve insulin sensitization and reduce the risk of the insulin resistance in adipose tissue, liver tissue, and *et al.*<sup>[8,9]</sup> The activation of it affects the

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Cite this article as: Gao D, Zhang Y, Yang F, Lin Y, Zhang Q, Xia Z. In vitro screening and evaluation of 37 traditional chinese medicines for their potential to activate peroxisome proliferator-activated receptors- $\gamma$ . Phcog Mag 2016;12:120-7.

glucose homeostasis and lipid metabolism as well as inflammation.<sup>[10]</sup> Increasing evidence indicated that the activation of PPAR $\gamma$  can promote the adipocyte differentiation, decrease the accumulation of glucose in adipose tissue.<sup>[11,12]</sup> Moreover, PPAR $\gamma$  plays an important role in the regulation of pancreatic functions and activation of PPAR $\gamma$  can decrease  $\beta$ -cell apoptosis.<sup>[13]</sup> It is also known that PPAR $\gamma$  affects glucose-stimulated insulin secretion.<sup>[14,15]</sup> Therefore, the screening of drugs which can activate PPAR $\gamma$  has great significance in the treatment of diabetes mellitus and related metabolic syndromes.

Thiazolidinediones (TZDs), the agonists of PPAR $\gamma$ , had been demonstrated to have a variety of clinical effects such as enhancing insulin sensitivity and improving glucose tolerance.<sup>[16,17]</sup> However, recently evidence demonstrates that TZDs had several side-effects such as cardiovascular risks, liver damage, weight gain, and peripheral edema.<sup>[18,19]</sup> On the other hand, traditional Chinese medicines (TCMs) with fewer side-effects have proven historically to be a potential source for drug discovery. Therefore, numbers of researches have been done to explore the activators of PPAR $\gamma$  from TCMs.<sup>[10,20]</sup>

In previous study, we developed a cell-based PPARs screening model. The model is a stable and effective assay tool to characterize the interactions between PPAR subtype and PPARs activating drugs. Only when a drug bound and activated GAL4-PPAR $\gamma$ -ligand binding domain (LBD) could the luciferase be expressed. The Z'-factor, which was a useful tool and a statistical characteristic of any given assay, was used to evaluate the reliability and the stability of our model. When the value of Z'-factor was between 0.5 and 1, suggesting that the model was suitable for drug screening. The value of Z'-factor of our model was 0.64.<sup>[21]</sup>

Herein, this study aimed to preliminary screen and to evaluate the activation of PPAR $\gamma$  by different polarity extracts from 37 TCMs on the basis of PPAR $\gamma$  transactivation assay, laying the basis of further identifying the effects of active extracts on PPAR $\gamma$ -mediated gene expression, and biological responses and isolating the active compounds from active extracts.

## MATERIALS AND METHODS

### Cells and reagents

HeLa cells were purchased from the Cell Center of the Chinese Academy of Medicinal Sciences (Shanghai, China). Fetal bovine serum (FBS) and Dulbecco's modified Eagle's medium (DMEM) were products of Gibco BRL (Gaithersburg, MD, USA). FUGene<sup>®</sup> HD Transfection Reagent and Bright-Glo<sup>™</sup> Luciferase Assay were purchased from Promega (Madison, WI, USA). Dimethyl sulfoxide (DMSO), penicillin, streptomycin, and rosiglitazone were provided from Sigma-Aldrich Chemical Co, Ltd (St. Louis, MO, USA).

### Plasmid construction

pGL4.35 (luc2P/9XGAL4UAS/Hygro) Vector (Product No. E1370) and GAL4-GR Vector (Product No. E1581) were from Promega Corporation (Madison, WI, USA). The synthetic PPAR $\gamma$ -LBD gene sequences were inserted into GAL4-GR vector, and the sequencing of PPAR $\gamma$ -LBD genes was analyzed by restriction enzyme digestion (XhoI and XbaI) and gel electrophoresis. Then PPAR $\gamma$ -LBD replaced glucocorticoid receptor-LBD (GR-LBD) gene fusion in original GAL4-GR Vector and then formed the GAL4-PPAR $\gamma$ -LBD fusion protein. The pGL4.35 (luc2P/9XGAL4UAS/Hygro) vector containing GAL4 special response element of firefly luciferase was used as reporter gene.

### Collection of medicines material

The TCMs were obtained from the local drug stores, TCMs markets or production place [Table 1]. Further identification of the specimens was authenticated by Professor GuoyueZhong (Jiangxi University of TCM).

All voucher specimens have been deposited at Chongqing Academy of Chinese Materia Medica, Chongqing, China.

### Preparation of different polarity extracts

The dried materials of 37 TCMs were ground into fine powder in a pulverizer, respectively. Reflux extraction was conducted in turn by petroleum ether, 70% ethanol, and water. Then, 70% ethanol extract was liquid-liquid extracted by ethyl acetate, while the concentrated segments of water were treated with absolute ethanol until the absolute ethanol reached to 60%. Afterward, the precipitate and the supernatant were collected, respectively. Finally, petroleum ether, ethyl acetate, the residual of ethanol, the precipitate, and the supernatant of water extracts were obtained. Each part was concentrated to dryness in a vacuum to afford samples for biological tests.

The positive drugs, petroleum ether, and ethyl acetate extracts were dissolved in DMSO. The residual of ethanol, the precipitate part of water, and the supernatant of water extracts were dissolved in water. All of them were stored at  $-20^{\circ}\text{C}$ .

### Cell culture

HeLa cells were grown in DMEM, containing 10% FBS and antibiotics (100 units/mL penicillin and 100  $\mu\text{g}/\text{mL}$  streptomycin). All cells were cultivated at  $37^{\circ}\text{C}$  in 5% $\text{CO}_2$  atmosphere.

## IN VITRO PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS $\gamma$ TRANSACTIVATION BIOASSAY

HeLa cells were seeded into 6 well-plates at a density of  $2 \times 10^5$  cells/well in DMEM containing 10% FBS, 100 units/mL penicillin, and 100  $\mu\text{g}/\text{mL}$  streptomycin for 24 h. Then, 0.4  $\mu\text{g}$  GAL4-PPAR $\gamma$ -LBD vector and 1.6  $\mu\text{g}$  of pGL4.35 vector were transiently co-transfections into cells under the condition of FuGENE<sup>®</sup> HD Transfection reagent. After an overnight culture, the cells were replaced into 96 well-plates with new culture medium. 24 h later, negative control, 0.5  $\mu\text{g}/\text{mL}$  rosiglitazone, or test samples were added, respectively. After 24 h, the luciferase activity was detected with Bright-Glo<sup>™</sup>.

### Statistical analysis

Each of these samples was measured in triplicate at various concentrations. Each concentration was tested for sextuplicate. All data are expressed as the mean  $\pm$  standard deviation. The results were analyzed by one-way, and significant differences were determined by the origin 8.0. Statistical significance is displayed as  $P < 0.05$ .

## RESULTS

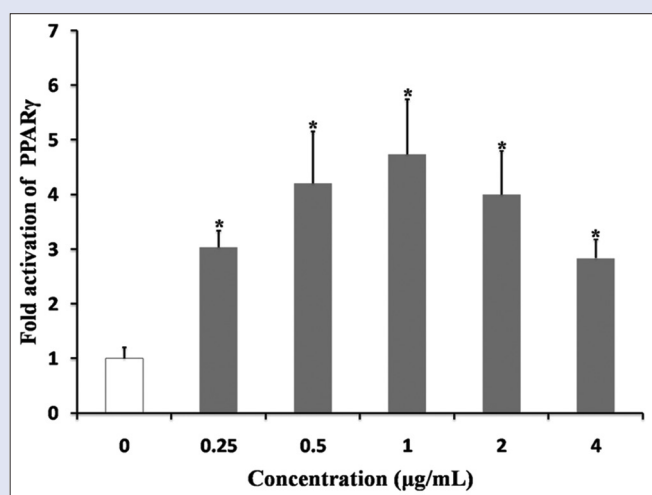
### The dose relationship between positive drug and the activation of peroxisome proliferator-activated receptors $\gamma$

To select an appropriate concentration of positive drug, the activation of PPAR $\gamma$  by rosiglitazone was tested (concentration from 0.5  $\mu\text{g}/\text{mL}$  to 4.0  $\mu\text{g}/\text{mL}$ ) by PPAR $\gamma$  transactivation bioassay. The fold activation of rosiglitazone in dose-dependence manner is shown in Figure 1. The maximum fold on the activation of PPAR $\gamma$  was 1  $\mu\text{g}/\text{mL}$ , and the range of fold activation was from 3.8- to 5.8-folds activation compared to vehicle control (DMSO). On the other hand, there was little change of the fold activation when the concentration of rosiglitazone exceeded 0.5  $\mu\text{g}/\text{mL}$  (the range of fold activation was from 3.2 to 5.1 folds activation). Hence, we chose 0.5  $\mu\text{g}/\text{mL}$  rosiglitazone as a positive control in later experiments.

**Table 1:** The plants species tested for potential peroxisome proliferator-activated receptor gamma activation properties in the screening model

Number	Botanical name	Family	Part of plant	Voucher specimen number	Local name
1	<i>Alisma plantago-aquatica</i> L.	Alismataceae	Root	GH828	Ze Xie
2	<i>Ampelocissus artemisiifolia</i> Planch.	Vitaceae	Leaves	GH829	Suan Lian Teng
3	<i>Anemarrhena asphodeloides</i> Bunge	Asparagaceae	Rhizome	GH830	Zhi Mu
4	<i>Anoectochilus roxburghii</i> (Wall.) Lindl.	Orchidaceae	Leaves	GH831	Jin Xian Lian
5	<i>Astragalus membranaceus</i> (Fisch.) Bunge	Leguminosae	Root	GH832	Huang Qi
6	<i>Atractylodes lancea</i> (Thunb.) DC.	Compositae	Rhizome	GH833	Cang Zhu
7	<i>Clematis chinensis</i> Osbeck	Ranunculaceae	Root stem	GH834	Wei Lin Xian
8	<i>Cornus officinalis</i> Siebold & Zucc.	Cornaceae	Fruit	GH835	Shan Zhu Yu
9	<i>Crataegus pinnatifida</i> Bunge	Rosaceae	Fruit	GH836	Shan Zha
10	<i>Cuscuta chinensis</i> Lam.	Convolvulaceae	Seed	GH837	Tu Si Zi
11	<i>Cycllobalanopsis glauca</i> (Thunb. ex Murray) Oerst	Fagaceae	Leaves	GH838	Tie Zhou
12	<i>Dendrobium moniliforme</i> (L.) Sw.	Orchidaceae	Root	GH839	Shi Hu
13	<i>Epimedium brevicornu</i> Maxim.	Berberidaceae	Aerial parts	GH840	Yin Yang Huo
14	<i>Gleditsia sinensis</i> Lam.	Leguminosae	Fruit	GH841	Zhu Ya Zao
15	<i>Gynostemma pentaphyllum</i> (Thunb.) Makino	Cucurbitaceae	Whole plant	GH842	Jiao Gu Lan
16	-	-	-	GH843	Hui Dou Ba
17	<i>Ligustrum lucidum</i> W. T. Aiton	Oleaceae	Fruit	GH844	Nv Zhen Zi
18	<i>L. barbarum</i> L.	Solanaceae	Root bark	GH845	Di Gu Pi
19	<i>L. barbarum</i> L.	Solanaceae	Fruit	GH846	Gou Qi
20	<i>Malus doumeri</i> (Bois) Chev.	Rosaceae	Leaves	GH847	Lin Qin Ye
21	<i>Momordica charantia</i> L.	Cucurbitaceae	Fruit	GH848	Ku Gua
22	<i>Moringa oleifera</i> Lam.	Moringaceae	Leaves	GH849	La Mu Ye
23	<i>M. alba</i> L.	Moraceae	Leaves	GH850	Sang Ye
24	<i>M. alba</i> L.	Moraceae	Root bark	GH851	Sang Bai Pi
25	<i>Ophiopogon japonicus</i> (Thunb.) Ker Gawl.	Asparagaceae	Tuber	GH852	Mai Dong
26	<i>Panax ginseng</i> C. A. Mey.	Araliaceae	Tuber	GH853	Ren Sen
27	<i>Phragmites australis</i> (Cav.) Trin. ex Steud.	Gramineae	Rhizome	GH854	Lu Gen
28	<i>Polygonatum odoratum</i> (Mill.) Druce	Asparagaceae	Rhizome	GH855	Yu Zhu
29	<i>Polygonatum sibiricum</i> F. Delaroché	Liliaceae	Rhizome	GH856	Huang Jin
30	<i>Pouzolzia zeylanica</i> (L.) Benn.	Schisandraceae	Fruit	GH857	Wu Shui Ge
31	<i>Pterocephalus hookeri</i> (C. B. Clarke) Hoek	Dipsacaceae	Leaves	GH858	Yi Shou Cao
32	<i>Pueraria lobata</i> (Willd.) Ohwi	Leguminosae	Root	GH859	Ge Gen
33	<i>R. glutinosa</i> (Gaertn.) DC.	Scrophulariaceae	Prepared tuber	GH860	Shu Di Huang
34	<i>R. glutinosa</i> (Gaertn.) DC.	Scrophulariaceae	Tube	GH861	Sheng Di Huang
35	<i>Salvia miltiorrhiza</i> Bunge	Labiatae	Root	GH862	Dan Shen
36	<i>Schisandra chinensis</i> (Turcz.) Baill.	Schisandraceae	Fruit	GH863	Wu Wei Zi
37	<i>Trichosanthes kirilowii</i> Maxim.	Cucurbitaceae	Root	GH864	Tian Hua Fen

*L. barbarum*: *Lycium barbarum*; *M. alba*: *Morus alba*; *R. glutinosa*: *Rehmannia glutinosa*



**Figure 1:** Fold activation of PPAR $\gamma$  by different dosages of rosiglitazone. The data are expressed as the means and standard deviations of three independent experiments with triplicate well. \* $P < 0.05$  vehicle control dimethyl sulfoxide (set to 1.0)

## Effects of different polarity extracts on the activation of peroxisome proliferator-activated receptors $\gamma$

The activation of PPAR $\gamma$  resulted from 185 different kinds of prepared extracts from selected TCMs were tested for six concentrations, respectively. The results [Table 2] indicated that nine extracts resulted in stronger activation on PPAR $\gamma$  than rosiglitazone based on the comparisons of the maximum folds on the activation of PPAR $\gamma$ .

Ethyl acetate extract of root bark of *Lycium barbarum* had the strongest effect on activating PPAR $\gamma$  in all extracts. The maximum fold was 7.11-fold (50  $\mu\text{g/mL}$ ), which equal to 207% of positive drug [Figure 2a]. Besides, ethyl acetate extracts of rhizome of *Phragmites australis* and fruit of *Gleditsia sinensis* also could significantly activate PPAR $\gamma$ . The maximum fold on the activation of PPAR $\gamma$  by rhizome of *P. saustralis* was 5.69 fold, which was 137% of 0.5  $\mu\text{g/mL}$  rosiglitazone [Figure 2b]. The maximum fold activation of the fruit of *G. sinensis* was 5.02-fold, about 105% that of positive control [Figure 2c].

Petroleum ether extracts of *Anoectochilus roxburghii*, *Pterocephalus hookeri*, *Polygonatum sibiricum*, *Epimedium brevicornu* also can significantly activate PPAR $\gamma$ . The maximum folds on the activation of PPAR $\gamma$  by them were higher than that of positive drug. The maximum

**Table 2:** Summary of the results obtained by applying the screening model to 185 different polarity extracts from 37 traditional Chinese medicines

Number	Botanical name	Extracts <sup>a</sup>	Concentration at max fold activation ( $\mu\text{g/mL}$ )	Max fold activation mean $\pm$ SD (positive drug fold activation)	Percentage versus positive drug
1	Root bark of <i>L. barbarum</i>	Ethyl acetate	50	7.11 $\pm$ 0.60 (3.43)	207
2	<i>Anoectochilus roxburghii</i>	Petroleum ether	200	5.15 $\pm$ 0.50 (3.22)	160
3	Rhizome of <i>P. australis</i>	Ethyl acetate	200	5.69 $\pm$ 0.27 (4.16)	137
4	<i>P. hookeri</i>	Petroleum ether	400	4.06 $\pm$ 0.49 (3.36)	121
5	<i>P. sibiricum</i>	Petroleum ether	100	4.67 $\pm$ 0.57 (3.99)	117
6	<i>P. hookeri</i>	The residual of ethanol	400	3.65 $\pm$ 0.58 (3.36)	109
7	<i>P. hookeri</i>	The supernatant of water	25	3.61 $\pm$ 0.62 (3.36)	107
8	Fruit of <i>G. sinensis</i>	Ethyl acetate	50	5.02 $\pm$ 0.63 (4.78)	105
9	<i>E. brevicornu</i>	Petroleum ether	200	5.76 $\pm$ 0.72 (5.54)	104
10	Root bark of <i>M. alba</i>	Petroleum ether	50	3.17 $\pm$ 0.22 (3.20)	99
11	<i>A. membranaceus</i>	Ethyl acetate	100	3.31 $\pm$ 0.62 (3.36)	99
12	<i>A. membranaceus</i>	Petroleum ether	50	3.71 $\pm$ 0.26 (3.73)	99
13	<i>Clematis chinensis</i>	Petroleum ether	200	4.83 $\pm$ 0.76 (4.94)	98
14	Leaves of <i>M. alba</i>	Petroleum ether	12.5	4.37 $\pm$ 0.56 (4.53)	96
15	<i>P. lobata</i>	Petroleum ether	400	4.31 $\pm$ 0.37 (4.57)	94
16	<i>P. sibiricum</i>	Ethyl acetate	400	3.67 $\pm$ 0.62 (3.99)	92
17	<i>P. lobata</i>	Ethyl acetate	200	4.13 $\pm$ 0.38 (4.57)	91
18	Leaves of <i>M. alba</i>	The residual of ethanol	12.5	3.99 $\pm$ 0.41 (4.53)	88
19	<i>A. artemisiifolia</i>	Petroleum ether	200	4.40 $\pm$ 0.47 (5.07)	87
20	<i>Cuscuta chinensis</i>	Petroleum ether	200	4.29 $\pm$ 0.73 (4.91)	87
21	<i>E. brevicornu</i>	Ethyl acetate	50	4.54 $\pm$ 0.83 (5.54)	82
22	<i>M. doumeri</i>	Ethyl acetate	200	3.11 $\pm$ 0.60 (3.82)	81
23	Hui Dou Ba	Petroleum ether	200	2.73 $\pm$ 0.33 (3.48)	78
24	<i>Pouzolzia zeylanica</i>	Petroleum ether	400	2.88 $\pm$ 0.36 (3.48)	78
25	<i>A. artemisiifolia</i>	Ethyl acetate	12.5	3.97 $\pm$ 0.32 (5.07)	78
26	<i>Cyclobalanopsis glauca</i>	The supernatant of water	200	3.26 $\pm$ 0.36 (4.257)	77
27	<i>G. pentaphyllum</i>	Ethyl acetate	12.5	2.69 $\pm$ 0.32 (3.65)	74
28	<i>R. glutinosa</i>	Petroleum ether	400	2.90 $\pm$ 0.71 (4.25)	68
29	Root bark of <i>M. alba</i>	Ethyl acetate	400	2.19 $\pm$ 0.32 (3.20)	68
30	<i>S. miltiorrhiza</i>	Ethyl acetate	50	3.02 $\pm$ 0.66 (4.54)	66
31	<i>C. pinnatifida</i>	Ethyl acetate	50	3.08 $\pm$ 0.35 (4.68)	66
32	<i>Clematis chinensis</i>	Ethyl acetate	200	3.23 $\pm$ 0.67 (4.94)	65
33	<i>R. glutinosa</i>	Ethyl acetate	12.5	2.23 $\pm$ 0.03 (3.43)	65
34	Hui Dou Ba	Ethyl acetate	50	2.26 $\pm$ 0.22 (3.48)	65
35	<i>O. japonicas</i>	Petroleum ether	100	2.08 $\pm$ 0.68 (3.32)	63
36	<i>P. ginseng</i>	Ethyl acetate	200	3.20 $\pm$ 0.36 (5.10)	63
37	<i>M. oleifera</i>	Ethyl acetate	200	2.54 $\pm$ 0.43 (4.10)	62
38	Rhizome of <i>P. australis</i>	Petroleum ether	25	2.56 $\pm$ 0.43 (4.16)	61
39	<i>G. pentaphyllum</i>	Petroleum ether	50	2.23 $\pm$ 0.25 (3.65)	61
40	<i>M. oleifera</i>	Petroleum ether	400	2.42 $\pm$ 0.16 (4.10)	59
41	<i>A. membranaceus</i>	Ethyl acetate	6.25	2.17 $\pm$ 0.34 (3.73)	58
42	<i>O. japonicas</i>	Ethyl acetate	50	1.90 $\pm$ 0.14 (3.32)	57
43	<i>A. lancea</i>	Ethyl acetate	50	2.84 $\pm$ 0.56 (5.01)	57
44	Fruit of <i>G. sinensis</i>	Petroleum ether	100	2.69 $\pm$ 0.26 (4.78)	56
45	<i>D. moniliforme</i>	Ethyl acetate	100	2.60 $\pm$ 0.35 (4.70)	55
46	<i>Anemarrhena asphodeloides</i>	Ethyl acetate	200	2.53 $\pm$ 0.59 (4.67)	54
47	<i>A. lancea</i>	Petroleum ether	50	2.71 $\pm$ 0.53 (5.01)	54
48	<i>S. miltiorrhiza</i>	The supernatant of water	25	2.43 $\pm$ 0.27 (4.54)	54
49	<i>M. doumeri</i>	The supernatant of water	200	1.74 $\pm$ 0.14 (3.82)	52
50	<i>Polygonatum odoratum</i>	Petroleum ether	400	2.31 $\pm$ 0.46 (4.60)	50
51	Fruit of <i>L. barbarum</i>	Petroleum ether	400	2.02 $\pm$ 0.51 (4.03)	50
52	<i>P. ginseng</i>	Petroleum ether	200	2.46 $\pm$ 0.36 (5.10)	48
53	Hui Dou Ba	The residual of ethanol	400	1.63 $\pm$ 0.14 (3.48)	47
54	<i>M. doumeri</i>	Petroleum ether	200	1.74 $\pm$ 0.14 (3.82)	46
55	Fruit of <i>L. barbarum</i>	Ethyl acetate	400	1.83 $\pm$ 0.25 (4.03)	45
56	<i>S. miltiorrhiza</i>	Petroleum ether	2.5	2.02 $\pm$ 0.17 (4.54)	44
57	<i>Cuscuta chinensis</i>	Ethyl acetate	200	2.16 $\pm$ 0.54 (4.91)	44
58	<i>C. pinnatifida</i>	Petroleum ether	100	2.03 $\pm$ 0.17 (4.68)	43
59	<i>Momordica charantia</i>	Petroleum ether	100	2.30 $\pm$ 0.46 (5.34)	43
60	<i>E. brevicornu</i>	The residual of ethanol	100	2.35 $\pm$ 0.67 (5.54)	42
61	<i>Ligustrum lucidum</i>	Petroleum ether	200	1.69 $\pm$ 0.22 (4.52)	37
62	Fruit of <i>G. sinensis</i>	The supernatant of water	100	1.72 $\pm$ 0.28 (4.78)	36
63	<i>D. moniliforme</i>	Petroleum ether	50	1.67 $\pm$ 0.33 (4.70)	35
64	<i>D. moniliforme</i>	The supernatant of water	200	1.60 $\pm$ 0.31 (4.70)	34

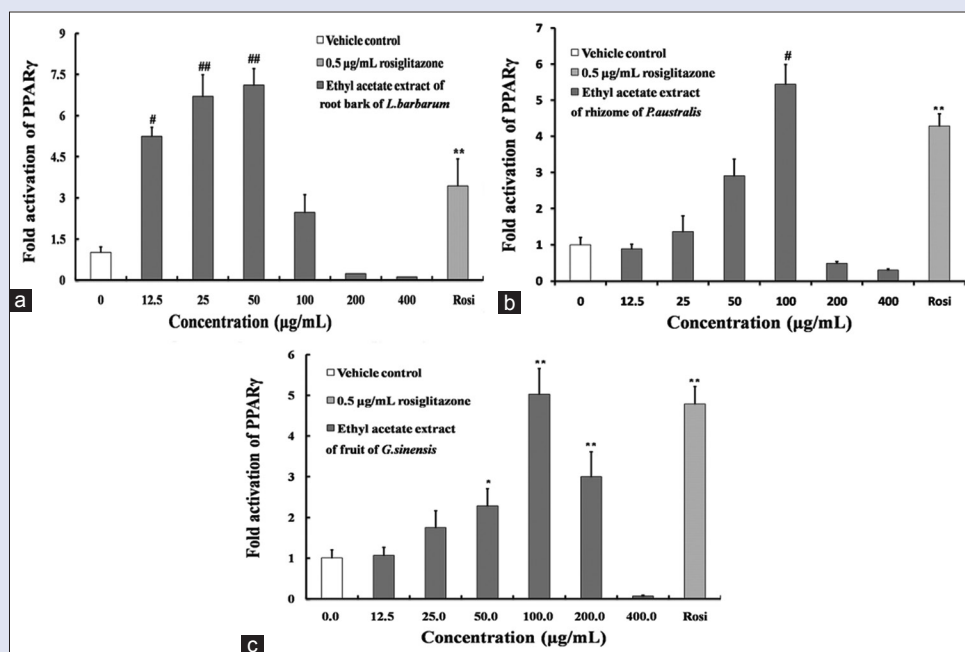
<sup>a</sup>Only the extracts inducing transactivation of PPAR $\gamma$  have been included in this table. PPAR $\gamma$ : Peroxisome proliferator-activated receptor gamma; SD: Standard deviation; *D. moniliforme*: *Dendrobium moniliforme*; *G. sinensis*: *Gleditsia sinensis*; *E. brevicornu*: *Epimedium brevicornu*; *C. pinnatifida*: *Crataegus pinnatifida*; *S. miltiorrhiza*: *Salvia miltiorrhiza*; *L. barbarum*: *Lycium barbarum*; *M. doumeri*: *Malus doumeri*; *P. ginseng*: *Panax ginseng*; *A. lancea*: *Attractylodes lancea*; *O. japonicas*: *Ophiopogon japonicas*; *A. membranaceus*: *Astragalus membranaceus*; *M. oleifera*: *Moringa oleifera*; *G. pentaphyllum*: *Gynostemma pentaphyllum*; *P. australis*: *Phragmites australis*; *R. glutinosa*: *Rehmannia glutinosa*; *M. alba*: *Morus alba*; *A. artemisiifolia*: *Ampelocissus artemisiifolia*; *P. lobata*: *Pueraria lobata*; *P. sibiricum*: *Polygonatum sibiricum*; *P. hookeri*: *Pteroccephalus hookeri*



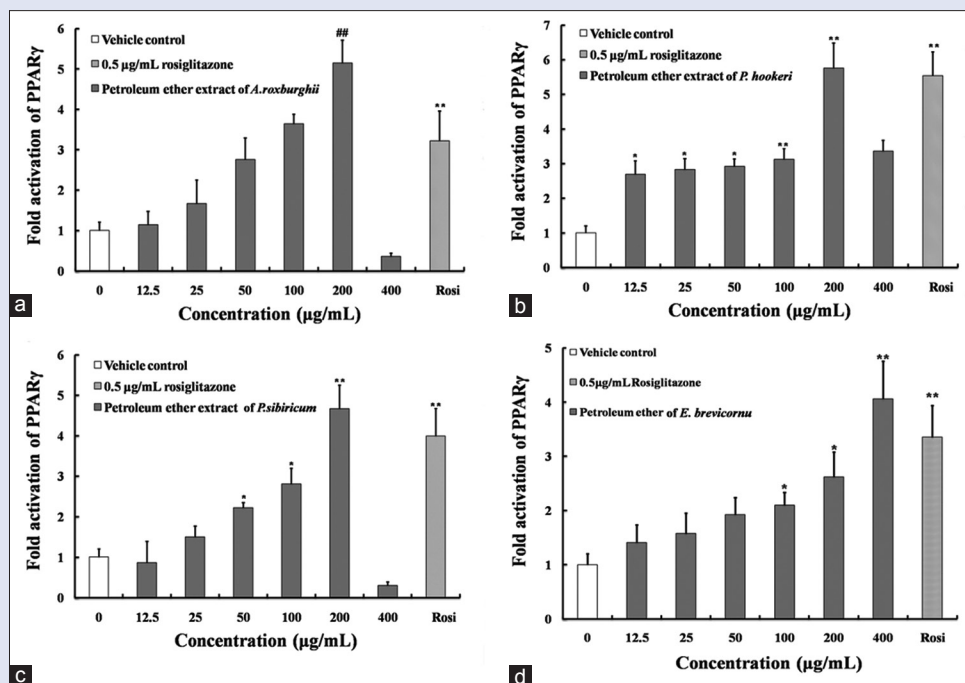
fold to activate PPAR $\gamma$  by *A. sroxburghii* was 5.15 fold, about 160% compared to 0.5  $\mu\text{g/mL}$  rosiglitazone [Figure 3a]. The maximum fold to activate PPAR $\gamma$  by *P. hookeri* was 4.06 fold, 121% of positive control [Figure 3b]. The maximum folds on the activation of PPAR $\gamma$  by

*P. sibiricum* and *E. brevicornu* were 4.67 fold and 5.76 fold, which equaled to 117% and 104% of 0.5  $\mu\text{g/mL}$  rosiglitazone [Figure 3c and d].

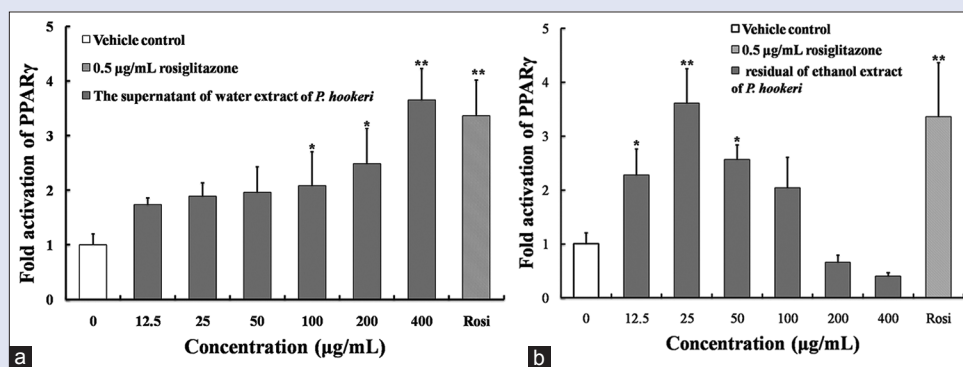
In addition, the residual of ethanol and the supernatant of water extracts of *P. hookeri* also had remarkable activation effects on PPAR $\gamma$  [Figure 4a and b].



**Figure 2:** Fold activation of PPAR $\gamma$  by ethyl acetate extracts of Root bark of *Lycium barbarum*, (a) rhizome of *Phragmites australis*, (b) fruit of *Gleditsia sinensis*. (c) The data are expressed as the means and standard deviations of three independent experiments with triplicate well. \* $P < 0.05$  versus vehicle control dimethyl sulfoxide, \*\* $P < 0.01$  versus vehicle control dimethyl sulfoxide (set to 1.0), \* $P < 0.05$  versus 0.5  $\mu\text{g/mL}$  rosiglitazone, \*\* $P < 0.01$  versus 0.5  $\mu\text{g/mL}$  rosiglitazone



**Figure 3:** Fold activation of peroxisome proliferator-activated receptors- $\gamma$  by n-hexane extracts of *Anoectochilus sroxburghii*, (a) *Pterocephalus hookeri*, (b) *Polygonatum sibiricum*, (c) *Epimedium brevicornu* (d). The data are expressed as the means and standard deviations of three independent experiments with triplicate well. \* $P < 0.05$  versus vehicle control dimethyl sulfoxide, \*\* $P < 0.01$  versus vehicle control dimethyl sulfoxide (set to 1.0), \* $P < 0.05$  versus 0.5  $\mu\text{g/mL}$  rosiglitazone, \*\* $P < 0.01$  versus 0.5  $\mu\text{g/mL}$  rosiglitazone



**Figure 4:** Fold activation of peroxisome proliferator-activated receptors- $\gamma$  of the supernatant of water extract (a) and residual of ethanol extract (b) of *Pterocephalus hookeri*. The data are expressed as the means and standard deviations of three independent experiments with triplicate well. \* $P < 0.05$  versus vehicle control dimethyl sulfoxide, \*\* $P < 0.01$  versus vehicle control dimethyl sulfoxide (set to 1.0)

The maximum folds on the activation of PPAR $\gamma$  by them were similar to positive drug. The maximum folds to activate PPAR $\gamma$  by the residual of ethanol and the supernatant of water extracts were 3.65 fold and 3.61 fold, which were 107% and 104% that of positive control, respectively.

However, traditionally anti-diabetic medicine including *Schisandra chinensis*, the fruit of *Calendula officinalis*, *Alisma plantago-aquatica* and the root of *Trichosanthes kirilowii*, had no effects on the activation of PPAR $\gamma$ .

## DISCUSSION

Nuclear receptors are large family of receptors which allow an access to the control of gene regulation. The family contains steroid receptors, metabolic receptors, retinoid receptors, Vitamin D receptor and *et al.*<sup>[22,23]</sup> They play important roles in normal development, reproduction, and metabolism.<sup>[24-26]</sup> Most nuclear receptors, share a similar basic structure that contains two important domains named LBD and DNA-binding domain. The two domains are crucial for the regulation of the transcription of nuclear receptors. Especially, the LBD fulfills the functions of ligand binding, dimerization, and recruitment of co-regulators.<sup>[27-29]</sup> Ligand binding and activation of nuclear receptor induces a conformational change of it and participates in the regulation of transcription via many approaches such as activation of phosphorylation of the receptor, replacement of corepressors by coactivators and *et al.*<sup>[30,31]</sup> Considering that nuclear receptor family binds to a wide range of lipophilic ligands derived from daily life, targeting nuclear receptors have been a major source for the development of new drugs.<sup>[32]</sup> It is noteworthy that researchers have found some active compounds from traditional medicines which are the ligands for some of these nuclear receptors.<sup>[23,33]</sup> For example, honiolol, a compound isolated from magnolia bark, is a partial PPAR $\gamma$  agonist which binds directly to PPAR $\gamma$  LBD.<sup>[20]</sup> On accounting that honokiol can prevent hyperglycemia and weight gain in mice, it becomes a clinically interesting compound which has opportunity to replace TZDs.

In the past few decades, the prevalence of diabetes mellitus has increased, especially type 2 diabetes. Type 2 diabetes mellitus are closely related to unhealthy diet, sedentary lifestyle, as well as the rise of obesity in the population, which in turn impel the search for new preventive and treatment strategies.<sup>[34,35]</sup> In recent years, metabolic receptors from nuclear receptor family get more and more attention due to their regulation of metabolic homeostasis.<sup>[36,37]</sup> It is noteworthy that PPAR $\gamma$ , which belongs to PPAR family, is widely used as an important target for the treatment of diabetes mellitus. Ligand binding of PPAR $\gamma$  can induce the expression of a lot of genes which in turns changes the lipids and glucose metabolism.<sup>[38,39]</sup>

However, common agonists of PPAR $\gamma$  such as TZDs, have many serious side-effects such as cardiovascular risks, liver damage, weight gain, and peripheral edema.<sup>[40]</sup> Hence, significant research efforts have recently been undertaken to explore the potential drugs of activating PPAR $\gamma$  with less adverse effects.<sup>[40-43]</sup> TCMs seem to be an ideal replacement of TZDs for the treatment of hyperglycemia, insulin resistance, and the diabetic complications with less adverse effects.<sup>[44-46]</sup>

Based on the cell-based PPARs screening model.<sup>[47]</sup> In this study, thirty-seven traditionally used anti-diabetic TCMs were selected and to evaluate their activation activities of PPAR $\gamma$ . The activations of PPAR $\gamma$ -LBD by different polarity extracts from 37 TCMs were evaluated. The results indicated that the ethyl acetate extracts of root bark of *L. barbarum*, rhizome of *P. saustralis* and fruit of *G. sinensis* could significantly activate PPAR $\gamma$ . The activities of them were higher than that of 0.5  $\mu\text{g/mL}$  rosiglitazone. Besides, petroleum ether extracts of *A. sroxburghii*, *P. hookeri*, *P. sibiricum*, *E. brevicornu* also can significantly activate PPAR $\gamma$ . The activities of them were also higher than that of 0.5  $\mu\text{g/mL}$  rosiglitazone. Furthermore, the residual of ethanol and the supernatant of water extracts of *P. hookeri* had remarkable activation effects on PPAR $\gamma$ . Thus, three extracts (petroleum ether, the residual of ethanol and the supernatant of water) of *P. hookeri* were found to have a significant effect on the activation of PPAR $\gamma$  compared to 0.5  $\mu\text{g/mL}$  rosiglitazone. On the other hand, previous studies showed that *P. hookeri* had good anti-inflammatory effects, and it was used to treat inflammation and analgesic in Tibet of China.<sup>[48]</sup> Other evidence also demonstrated that the ligands of PPAR $\gamma$  can treat inflammation in the development of diabetes mellitus.<sup>[49,50]</sup> Therefore, it is speculated that the significant activation of PPAR $\gamma$  by *P. hookeri* might be related to its remarkable anti-inflammatory activity.

On the contrary, we found that all extracts of *S. chinensis*, *C. officinalis*, *A. plantago-aquatica*, and the root of *T. kirilowii* could not activate PPAR $\gamma$ . Previous studies showed that extracts of *S. chinensis* were effective when used as aldose reductase inhibitors for the treatment of diabetes mellitus.<sup>[51]</sup> The petroleum ether extract of it had PTP1B and alpha-glucosidase inhibitory activities. Moreover, schisandrols A and B, schisandrins A and B from *S. chinensis* were the ligands of pregnane X receptor, a xenobiotic receptor from nuclear receptor family.<sup>[23]</sup> Thus, it was speculated that the anti-diabetic effect of *S. chinensis* was through activating multiple targets except for PPAR $\gamma$ . Similar to *S. chinensis*, the anti-diabetic effects of *C. officinalis*, *A. plantago-aquatica* and the root of *T. kirilowii* were not through activating PPAR $\gamma$ .

*Momordica charantia* also named "bitter melon" had been found to be able to activate PPAR $\alpha$  and PPAR $\gamma$  *in vitro*.<sup>[52]</sup> In our study, we also found

it can activate PPAR $\gamma$ . Furthermore, extracts of *Panax ginseng*, *Salvia miltiorrhiza*, and *Gynostemma pentaphyllum* also can activate PPAR $\gamma$ .<sup>[23,53]</sup> The results were consistent with the previous study. However, among these chosen TCMs, only a few of them had been studied with regard to the PPAR $\gamma$  activation through a PPAR $\gamma$  transactivation assay *in vitro*. Our study firstly evaluated the PPAR $\gamma$  activation by different polarity extracts from 37 TCMs with a PPAR $\gamma$  transactivation assay, providing the basis of clarifying the specific mechanism, looking for other targets of activating extracts and screening the active compounds. Further studies will be focused on studying the specific mechanisms of active extracts on activating PPAR $\gamma$  and screening of the active compounds through bio-guided separation.

## CONCLUSION

In summary, we have established that petroleum ether extracts of *A. sroxburghii*, *P. hookeri*, *P. sibiricum*, *E. brevicornu*, ethyl acetate extracts of root bark of *L. barbarum*, rhizome of *P. saustralis* and fruit of *G. sinensis* can significantly activate PPAR $\gamma$  as shown by specific activation of a PPAR $\gamma$ -LBD luciferase receptor assay. Hence, the anti-diabetic activity of them could in part be mediated by this nuclear receptor. Additional research will be necessary to further identify the effects of active extracts such as ethyl acetate extract of root bark of *L. barbarum* on PPAR $\gamma$ -mediated gene expression and biological responses. Moreover, further studies also will be done to identify the active compounds of PPAR $\gamma$ -LBD.

## Financial support and sponsorship

Financial Support of this paper is provided by The National Natural Science Foundation of China (Grant No. 21175159, No. 21275169 and No. 81202886) and The International Cooperation Project of Ministry of Science and Technology of China (Grant No. 2010DFA32680).

## Conflicts of interest

There are no conflicts of interest.

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Zhining Xia

#### ABOUT AUTHOR

**Zhining Xia**, obtained his Ph. D, degree in University of Copenhagen. He is professor in the College of Chemistry and Chemical Engineering Chongqing University, Chongqing, China. His work mainly in: Medicinal plants, capillary electrophoresis, pharmaceutical analysis of Chinese medicines and nano-drug.