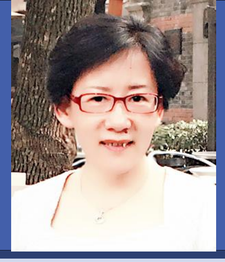

Function and structure of a novel anti-diabetes agent from *Ganoderma Lucidum*

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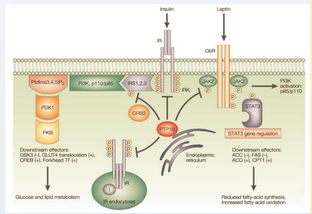
INTRODUCTION

Insulin signaling pathway and PTP1B



Morris F White. Insulin signaling in health and disease. Science, 2003, 302 (5651):1710-1711

- Inhibition of protein tyrosine phosphatase 1B (PTP1B) activity has been considered as a promising therapy approach to treat type 2 diabetes.
- Protein tyrosine phosphatase 1B (PTP1B) have been implicated in the regulation of insulin signal transduction process
- PTP1B dephosphorylate the insulin receptor as well as the substrate proteins, controlling the insulin signaling pathway
- Overactivation of PTP1B inhibits the insulin receptor signaling cascade. Therefore, PTP1B is an insulin-sensitive drug target for anti-diabetes.

OBJECTIVE

In this work, a novel PTP1B activity inhibitor, named FYGL (Fudan-Yueyang-G. lucidum), was screened from the fruiting bodies of Ganoderma lucidum. The efficient PTP1B inhibitory potency, plasma glucose level in vivo, toxicity of FYGL, and structure of FYGL were studied.

RESULTS

PTP1B inhibitor extracted from *G. lucidum*

Ganoderma lucidum

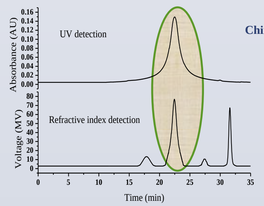
PTP1B inhibition

Extractions by alcohol, water, and then isolation

FYGL——
Fudan-Yueyang G. lucidum

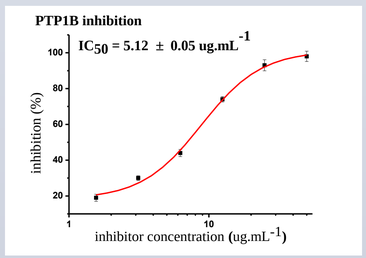
Chinese patent (ZL201110142167.8), PCT (WO 2012/019479 1)

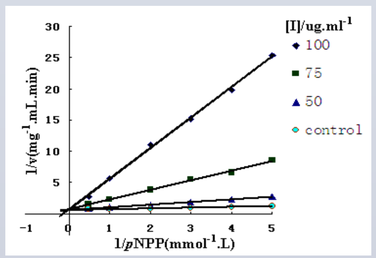
Incubation plant



- Both UV and refraction index in GPC analysis demonstrated the contents of 90%, molecular weight ~10^5, and both protein and sugar present in *FYGL*.
- *FYGL* is water soluble macromolecule

PTP1B inhibition of *FYGL* in vitro



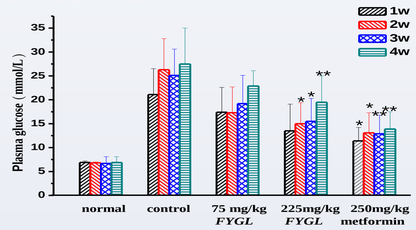


- PTP1B inhibition IC_{50} = 5.12 μg/mL
- Lineweaver--Burk plots indicated *FYGL* is a competitive inhibitor of PTP1B.

Bao-Song Teng, Ping Zhou,* et al. *J. Agric. Food Chem*. 2011, 59(12), 6492-6500.

RESULTS

Pharmacology Trials of *FYGL in vivo*



Plasma glucose level of db/db genetic type II diabetes mice

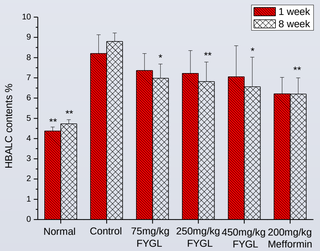
	group	Fasting plasma glucose level (mmol/L)
4 weeks	normal	6.9 ± 1.2**
	control)	28 ± 7
	FYGL 75 mg/kg	23 ± 3
	FYGL 225 mg/kg	18 ± 5**
	metformin 250mg/kg	14 ± 4**

N = 7, *p <0.05 vs. control，p <0.01 vs. control**

- **Taking *FYGL* orally for 4 weeks，the plasma glucose level was significantly decreased dose-dependently, compared with that of control.**

Chendong Wang, Ping Zhou,* et al. *Brit J Nutr*, 2012, 108, 2014-2025.

Glycosylated hemoglobin (HbAlc) level of db/db mice



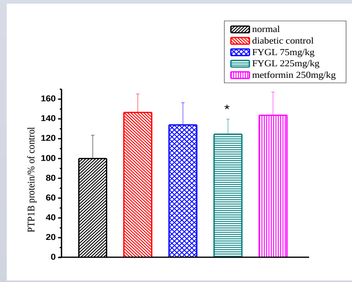
	group	HbA1C %
8 weeks	normal	4.4 ± 0.2**
	control	8.4 ± 0.8
	FYGL (L) 75 mg/kg	7.2 ± 0.8*
	FYGL(M) 250 mg/kg	6.9 ± 0.8 **
	FYGL (H) 450 mg/kg	6.7 ± 1.4*
	metformin 200mg/kg	6.4 ± 0.3 **

n = 8, *p < 0.05 *vs.* control，p < 0.01 *vs.* control.**

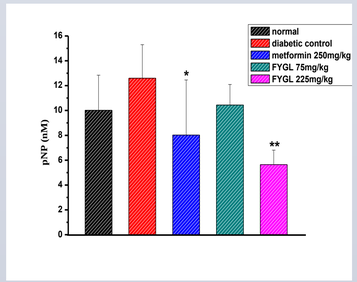
- **HbAlc is considered a "golden index" indicating the plasma glucose level. After 8 weeks，HbA1c level was significantly decreased dose-dependently for the mice treated by *FYGL* and metformin.**

Deng Pan, Ping Zhou,* et al. *PLoS One,* 2013, 8(7), e68332.

Mechanism of PTP1B target *in vivo*



PTP1B expression in skeletal muscle



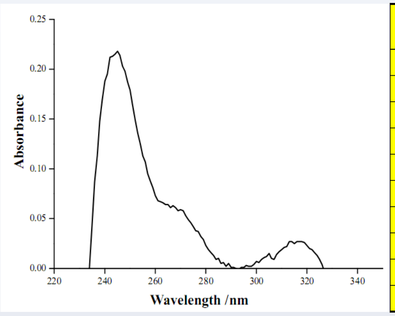
PTP1B activity in skeletal muscle

- Compared with control group, PTP1B expression and activity were inhibited dose-dependently in *FYGL* group, also indicating that the target of *FYGL* is PTP1B *in vivo*.

Chendong Wang, Ping Zhou,* et al. *Brit J Nutr,* 2012, 108, 2014-2025.

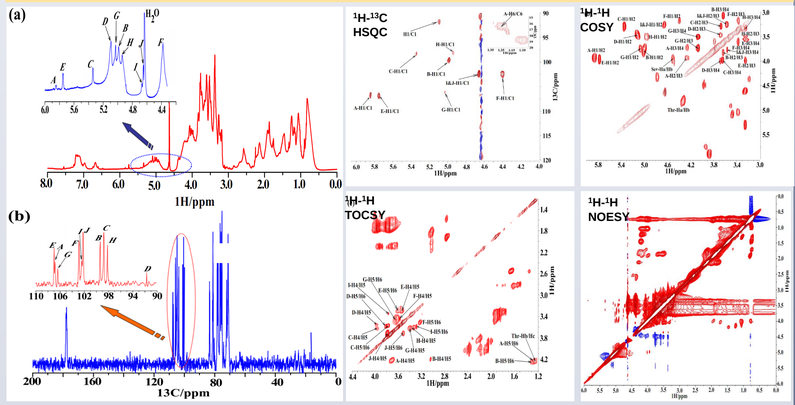
RESULTS

Structure characteristic of *FYGL*



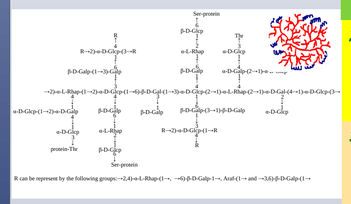
	Content (%) (before elimination)	Content (%) (after elimination)
Asp	14.4	14.2
Thr	8.98	5.00
Ser	10.2	6.40
Glu	9.04	9.51
Gly	12.8	12.3
Ala	9.88	12.14
Val	7.81	7.90
Ile	5.00	5.30
Phe	3.58	3.71
Pro	5.84	6.12

- Figure is β-elimination reaction probed by UV, which indicates that protein is bound with saccharide by O-glycosidic linkage.
- Table is amino acid contents before and after β-elimination reaction, which shows that after β-elimination reaction, both Thr and Ser contents were decreased, while Ala increased, indicating that protein bind covalently with saccharide by Thr and Ser residues.



- NMR analysis suggest *FYGL* being a heteropolysaccharide with α and β linkages, the peaks within 170 - 175 ppm in ^{13}C NMR indicates protein present. The backbone is hyperbranced polysaccharide and proteins are grafted. (**Deng Pan, Ping Zhou,* *et al. Carbohydrate Polymer,* 2015, 117, 106–114.**)

CONCLUSION



1. ***FYGL*, screened from *G. lucidum*, is an efficient PTP1B inhibitor *in vivo***
2. ***FYGL* can decrease the plasma glucose level through inhibiting the PTP1B expression and activity, consequently, regulating the tyrosine phosphorylation level of the IR β-subunit.**
3. ***FYGL* contain hyperbranched proteoglycan, which may play special roles for its bioactivities of PTP1B inhibition and antihyperglycemic potency.**

ACKNOWLEDGEMENT and CONTACT

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