Virtual Evaluation on Activities of Flavonoids from *Scutellaria baicalensis*

SHANG Qian[1,2], LIU Wei[2], XU Wei-ren[2*], LIU Peng[2], HAN Ying-mei[2], CHEN Cheng-lung[3], TANG Li-da[2]

1. Basic Medical College, Tianjin Medical University, Tianjin 300070, China
2. Tianjin Key Laboratory of Molecular Design and Drug Discovery, Tianjin Institute of Pharmaceutical Research, Tianjin 300193, China
3. Department of Chemistry, National Sun Yat-sen University, Kaohsiung 80424, China

Abstract: **Objective** To explore the investigation method of complicated and profound traditional Chinese herbal medicine, the potential action mechanisms of flavonoids from *Scutellaria baicalensis* were studied by docking calculation. **Methods** In total, eight flavonoids (aglycones and their glicosides) from *S. baicalensis* were selected as ligands. The crystalline structures of targets related to common diseases were used as the receptors for calculation. The calculations were conducted with Schrödinger software package. The grading standard of selectivity was developed according to G-score between ligands and receptors. **Results** Twenty-six pharmacologic actions have been reported. Among all effects in literature, nine of them can be deduced from the docking calculation of aglycone. From glycosides with grade ++, 25 reported effects can be estimated by calculation. Apparently, the target selectivity of aglycones and their glycosides are different form the virtual evaluation. The virtual evaluation results of glycosides were closer to the reported effects. **Conclusion** Our proposed virtual evaluation method seems an effective way to investigate the complicated system of traditional Chinese herbal medicine. It suggests that aglycones may be effective as the form of glucoside *in vivo*, and metabolism is a very important factor for virtual evaluation.

Key words: aglycone; flavonoid glycoside; *Scutellaria baicalensis* Georgi; virtual evaluation
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Introduction

Scutellaria baicalensis Georgi (SBG) is one of the very common traditional Chinese herbal medicines. It is reported that SBG contains 113 components and the major components are flavonoid compounds (Pharmacopoeia Committee of P. R. China, 2005; Wang *et al*, 2002; Wang *et al*, 2007; Xiao *et al*, 2003; Li *et al*, 2002; Wen *et al*, 2004; Yang and Fu, 2004; Li and Tong, 2006; Zhou, Xie, and Yan, 2004). Among flavonoids, major is glycosides and minor is aglycone. Their biological activities are extensive (Mi and Cui, 2005; Guan and Yang, 2006; Zhang *et al*, 2000; Shang and Su, 2005; Xu *et al*, 2007; Song *et al*, 2007; Lu *et al*, 2009). The complexity of traditional Chinese medicine usually leads to very complicated action mechanism. Up to the present, there is no convenient way to analyze all the action mechanisms for traditional Chinese herbal medicine. This is the major obstacle to modernize the research of traditional Chinese herbal medicine. In our prior studies, we investigated the possible action mechanisms of several natural products including: phenylpropanoids, terpenoids, and volatile oils. The results form virtual evaluations provided good information (Xing *et al*, 2009; Fu *et al*, 2009; Liu *et al*, 2009). In the current research, we focused on the differences of aglycone and glycosides of flavonoids.

Methods

The eight components of SBG were selected for the current study (Zhou, Xie, and Yan, 2004). These component were divided into groups Ⅰ (flavones) and Ⅱ (flavanones). The basic structures of these two groups

* Corresponding author: Xu WR Address: Tianjin Institute of Pharmaceutical Research, 308 Anshanxidao, Nankai District, Tianjin 300193, China Tel: +86-22-2300 3529 E-mail: xwrtj@yahoo.com.cn
First author: Shang Q E-mail:dtsmalau@hotmail.com
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were given in Fig. 1. The generic names and substituent groups of these components were listed in Table 1. All molecules were optimized using OPLS_2005 force field (Friesner *et al*, 2004). After energy-minimized, the atomic charges were computed by MM94 software based on the optimized structures.

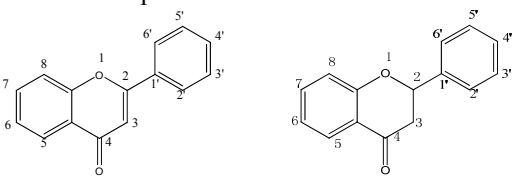

Fig. 1 Basic structures of flavonoids

Target proteins were obtained from Bioinformatics and Drug Design group (BIDD) Therapeutic Target Database (TTD). One hundred and sixty target proteins were collected. All these proteins are related to diseases and have corresponding pharmacologic actions. The crystalline structures of these proteins were obtained from RCSB Protein Data Bank (Wang *et al*, 2004). These target proteins can be sorted into groups according to their action mechanisms. Three types of target proteins: receptor, enzyme, and functional proteins are listed in Table 2.

All these proteins were pre-treated by removing the water molecules, subunits, and metal ions which are not related to active site. This was carried out by using Protein Preparation Wizard module in commercial Schrödinger software. The proteins were then saturated by adding hydrogen atoms and optimized by using OPLS_2005 force field (Wang *et al*, 2004).

Table 1 Denominations and substituent groups of flavonoids

Group	Code	Generic name	Substituent group
Ⅰ	I-1	Oroxylin	5,7-OH; 6-OCH_3
	I-2	Baicalein	5,6,7-OH
	I-3	Wogonin	5,7-OH; 8-OCH_3
	I-4	5,6-dihydroxy-7-*O*-glucoside-flavone	5,6-OH; 7-*O*-glu
	I-5	Wogonoside	5-OH; 8-OCH_3; 7-*O*-glucuronic acid
Ⅱ	Ⅱ-1	Dihydrooroxylin A	5,7-OH; 6-OCH_3
	Ⅱ-2	Eriodictyol	5,7,3',4'-OH
	Ⅱ-3	Dihydrobaicalin	5,6-OH; 7-*O*-glucuronic acid

Table 2 Targets used for docking calculation

Group	Type	PDB code
Receptor	enzyme-coupled receptor	PTK receptor: 1AGW, 1OEC, 1H9O, 1I44,1J91, 1PJK, 1N8Y, 1XKK, 2ITN, 1PKG, 1QSZ, 2P2H, 1RW8, 1SYO, 2OJ9, 2RFN
		cytokine and cytokine receptor superfamily: 1USM, 1HIB, 1RWK, 1IRA, 2ERJ, 1ALU, 3BPN, 1ILP, 1HE7
	ion-channel receptor	1MQG, 1MQH, 1VSO, 2F34, 2F3Z, 1JVM, 2BR7, 1KL8, 1PB7
	G Protein-coupled receptor	1ILP, 1ILQ, 2RH1, 2E4Y, 2E4Z, 1ISS, 2HLB, 1FF4, 1RSO
	intracellular receptor	1YTV, 2PJL, 1YJE, 1SOX, 3ERD, 1YY4, 1ERE, 1M2Z, 2AA5
Enzyme	Oxidoreductase	1DQ8, 1DQ9, 1JS3, 2Q7M, 1LRT, 1QYX, 1T4O, 1OG5, 1PQ2, 2F9Q, 2HI4, 2UOM, 1Z11, 1EGY, 1B1C, 2Z5Y, 1OJ9, 1CX2, 1GT8, 1TV5, 1CQE
	transferase	1CJW, 1EZF, 1HVY, 1IIC, 1RXY, 1STO, 2JGY, 1UOU, 1Z8D, 2OIO, 2NZT, 2YHX, 3B8A, 1OHW
	hydrolase	1KN6, 1R4L, 2OC2, 1MX9, 1ZD5, 1DX6, 1POQ, 1DX4, 1RO6, 1SO2, 1TAZ, 1XOM, 1Z1L, 2HD1, 2OUN, 2QYK, 2QYM, 1J1A, 1C25, 1YM9, 2OUD, 1BZC, 2GDD, 2JG4, 1GJC, 2QLY, 1GMY, 2NQD, 1GFW, 1NL6, 1NPZ, 2HBQ, 1F6W, 1D4H, 1HII
	synthetase	1W6K, 2CG5, 1FE2, 1YQ7, 1T4E, 1M9J
	kinase	1B38, 1OI9, 1CKP, 1IT6, 1S9I, 2H6D, 2F15, 2UV4, 2BAQ, 2GO1, 2GTM, 1TV0, 2B9F, 2EVA, 1A9U, 1PMN, 1S9J, 1PMQ, 1MP8, 3CC6, 1GXD, 2PEO, 1ROE, 1E2D
	other enzymes	1CJK, 1PKO, 1YKD, 2COL, 2FJT, 1Y5M, 2OVX, 1TWA, 1BGJ, 1P9D, 1TR4, 2O95, 1A7T, 1BMC, 1D3D, 1F8A, 1QZ9, 1A4G, 1ING, 2HU4, 1CAO, 1KOP, 2V5W, 1ZXM, 2O5C, 1GL9, 1S16, 1Z5A, 2B8V, 2HK2, 1DTQ
Functional proteins		1T1L, 2IQC, 1AAP, 1OWT, 1U3B, 2FK3, 2IDH, 1BZ4, 1CXV, 1FK6, 1IJQ, 1YPU, 2FCW, 1JV2, 1KDX, 1MF8, 1UHN, 1MOY, 1MQB, 2HEN, 2QO9, 1TOU, 1W98, 1XOX, 2I3I, 2UVL, 1YFQ, 1QMF, 1Z6F, 2C5W, 2J9P, 2UWY, 2AST, 2CBZ, 2FYL, 1ZLL, 3C4C, 2P1T, 1XAP, 1EXA, 2NPA, 1YOS, 1I7I, 1UPV, 3BN6, 2CJS, 2CJT, 2BBR, 1EJN, 2FW3, 2O63, 2IOI, 2JCR, 1QEW, 1PSK, 1SAO, 2QA6, 2J7X, 3BQD, 1T5Z, 1MR1, 1U7V, 1YF4, 2FFU, 2OCI, 3BIB, 1SRA, 1Z3S, 2NMN, 1H2M, 1USM, 1M7W, 1K3Z, 2DBF, 1BFS, 1EZQ, 1FOS, 1IQN

The interaction between component molecule and target protein was investigated by carrying out the docking method (Friesner *et al*, 2004). The possible effectiveness of drug on protein was evaluated by the G-score difference (ΔG) between specific G-score (G_s) and non-specific G-score (G_{ns}). The more negative the score difference, the better the effectiveness of drug interacts with protein. In our virtual evaluation, the drug-to-protein interaction was assigned as specific and non-specific interaction. The specific interaction is the interaction between specific drugs and specific protein. The non-specific interactions are the interactions between randomly selected drugs and protein.

$$\Delta G = G_s - G_{ns}$$

Where G_s was obtained from Glide docking, and G_{ns} was obtained by the following equation (Xing *et al*, 2009):

$$G_{ns} = -6.323 + 0.260\ \text{chilv\_C} - 0.013\ \text{PEOE\_VSA-5} - 0.009\ \text{SlogP\_VSA3} + 0.007\ \text{SlogP\_VSA5}$$

Where chilv_C, PEOE_VSA-5, and SlogP_VSA3, SlogP_VSA5 are molecular descriptors form calculation methods as described in MOE

According to the previous studies (Xing *et al*, 2009), strong specific drugs have $\Delta G < -4.5$ and labeled by "+++"; Moderate specific drugs have $-4.5 \le \Delta G \le -3.0$ and labeled by "++"; Non-specific drugs have $\Delta G > -3.0$ and labeled by "+", respectively. This standard was also used to evaluate the possible effects of phenylpropanoids, terpenoids, and volatile oils virtually (Xing *et al*, 2009; Fu *et al*, 2009) and gave good results.

Results and discussion

The selectivity and interacted target proteins of the chosen drugs labeled by "+++" and "++" were given in Tables 3 and 4. The selectivity was evaluated based on the method mentioned above.

It has been reported that the flavonoids and their glycosides have the effects including antioxidant, protection of the immune system, antitumor, and so on (Mi and Cui, 2005; Guan and Yang, 2006; Zhang, 2000; Shang and Su, 2005; Xu *et al*, 2007; Song *et al*, 2007). However, there is no literature reported on the difference between flavonoids and their glycosides.

Table 3 The grading results of aglycone selectivity and interacted target proteins

Code	++
Ⅰ-1	PDE, estrogen receptor
Ⅰ-2	mitogen-activated protein kinase 8, acetylcholinesterase, PDE, and estrogen receptor
Ⅰ-3	mitogen-activated protein kinase 8, acetylcholinesterase, and PDE
Ⅱ-1	mitogen-activated protein kinase 14, PDE, and estrogen receptor
Ⅱ-2	lanosterol synthase, mitogen-activated protein kinase 14, acetylcholinesterase, PDE, aldose reductase, tumor necrosis factor-α-converting enzyme, PTK, transforming growth factor receptor, vasopressin receptor, estrogen receptor, and retinoic acid receptor

Based on our results, due to high specific interaction (grade +++) glycosides may strongly work on erectile dysfunction, cancers, Chagas' disease, hypercholesterolemia, Leishmania infections, unspecified osteoporosis, Toxoplasma infections, skeletal disorders, unspecified cardiovascular disease, unspecified viral infection, tuberculosis, heart failure, asthma, inflammation, diabetes mellitus, autoimmune diseases, depression, Alzheimer's disease, hypoxic-ischemic encephalopathy, motor neurone disease, and its complications.

Corresponding to selectivity grade ++, glycosides may have a certain effects on hypercholesterolemia, cancers, unspecified cardiovascular disease, unspecified viral infection, hearing loss, unspecified inflammatory disorders, obesity, diabetes mellitus and its complications, tuberculosis, fungal diseases, kinetoplastida parasite infection, angiogenesis, unspecified dysmenorrheal, hypertension, liver cirrhosis, nephrotic syndrome, restenosis, asthma, heart failure, atherosclerosis, guillain-barre syndrome, unspecified chronic obstructive pulmonary disease, hypoxic-ischemic encephalopathy, chronic experimental allergic encephalomyelitis, dysregulation of apoptosis, neurodegenerative diseases, brain inflammation, cerebral ischemia, inflammation, unspecified anxiety disorder, convulsions, drug dependence, inflammatory pain, neuronal injury, bacterial infections, hyper-insulinemia, insulin resistance, coronary heart disease, dyslipidemia, myocardial infarction, ischemic stroke, neurological diseases, proliferative diseases, skin diseases, thrombosis, coagulative disorders, multiple organ failure, erectile dysfunction, hypocholesterolemia, autoimmune

diseases, embolic focal cerebral ischemia, ischemic renal injury, migraine, myocardial hypertrophy, neutrophil-mediated disorders, pulmonary fibrosis, and shock (endotoxin).

Table 4 The grading results of glycosides selectivity and interacted target proteins

Code	++	+++
Ⅰ-4	lanosterol synthase, cell division protein kinase2, mitogen-activated potein kinase, 3-phosphoinositide dependent protein kinase-1, thymidylate kinase, glycylpeptide *N*-tetradecanoyltransferase, FGFR2, insulin receptor, epidermal growth factor receptor, PTK, hepatocyte growth factor receptor, vasopressin receptor, nuclear receptor ROR-alpha, myc proto-oncogene protein, stathmin-like domain complex, and PDE	mitogen-activated protein kinase kinase 1, and PDE
Ⅰ-5	lanosterol synthase, mitogen-activated protein kinase 8, 3-phosphoinositide dependent protein kinase-1, adenylate cyclase, 92 kDa type IV collagenase, beta-secretase, diphosphomevalonate decarboxylase, angiotensin-converting enzyme, epoxide hydrolase 2, acetylcholinesterase, M-phase inducer phosphatase 1, caspase-1-3, glycylpeptide *N*-tetradecanoyltransferase, casein kinase II, alpha chain, epidermal growth factor receptor, transforming growth factor receptor, hepatocyte growth factor receptor, glutamate receptor 5, vasopressin receptor, nuclear receptor ROR-alpha, penicillin binding protein, peroxisome proliferator activated receptor (PPARs) 3-hydroxy-3-methylglutaryl-coenzyme A reductase, stathmin-like domain complex, nuclear receptor coactivator 1, and mucin	farnesyl pyrophosphate synthetase, cell division protein kinase2, serine threonine protein phosphatase, dual specificity mitogen-activated protein kinase kinase, mitogen-activated protein kinase kinase kinase 4, thymidylate kinase, adenylate cyclase, DNA topoisomerase, PDE, phospholipase A2, glycogen phosphory-lase, muscle form, insulin receptor, epidermal growth factor receptor, PTK, ephrin receptor, and multidrug resistance protein
Ⅱ-3	serine threonine protein phosphatase, mitogen-activated protein kinase kinase kinase 14, 92 kDa type IV collagenase, beta-secretase, diphosphomevalonate decarboxylase, angiotensin-converting enzyme, PDE, phospholipase A2, M-phase inducer phosphatase 1, cytochrome P450, insulin-like growth factor receptor, hepatocyte growth factor receptor, glutamate receptor, fatty acid binding protein, PPARs 3-hydroxy-3-methylglutaryl- coenzyme A reductase, mothers against decapentaplegic homolog 9, and mucin	farnesyl pyrophosphate synthetase, cell division protein kinase2, dual specificity mitogen-activated protein kinase kinase, mitogen-activated protein kinase, thymidylate kinase, adenylate cyclase, beta-secretase, DNA topoisomerase, PDE, insulin receptor, epidermal growth factor receptor, PTK, ephrin receptor, and multidrug resistance protein

According to our results, the selectivity of aglycone compounds are grade ++. The ΔG between flavones and flavanones is very little. In comparison with glycosides, the number of related targets for aglycone is rather small. The aglycone may be useful to treat brain injury, cancer, unspecified cardiovascular disease, neurodegenerative diseases, unspecified osteoporosis, postmenopausal symptoms, hypoxic-ischemic encephalopathy, erectile dysfunction, unspecified Crohn's disease, hearing loss, unspecified inflammatory disorders, insulin resistance, obesity, vascular injury response, neuropathic pain, diabetes mellitus and its complications, unspecified dysmenorrhea, liver cirrhosis, and nephrotic syndrome.

Twenty-six pharmacologic actions are reported. Among all effects in literature, nine of them can be deduced from the docking calculation of aglycone. Form glycosides with grade ++, 25 reported effects can be estimated from calculation. Apparently, the target selectivity of flavonoids and their glycosides is different from the virtual evaluation. The virtual evaluation results of glycosides are closer to the reported effects.

It is well known that there are transformation and balance between aglycones and their glycosides in body. Since the effects of aglycones in clinic are the same as those of their glucosides. It suggests that aglycones may be effective in the form of glucoside *in vivo*, and metabolism is a very important factor for virtual evaluation.

We also found that the aglycone selectively interacted proteins are related to other diseases including hearing loss, liver cirrhosis, obesity, erectile dysfunction, unspecified osteoporosis, unspecified dysmenorrhea, nephrotic syndrome. In addition to those effects, glycosides related to more diseases, such as angiogenesis, epilepsy, glaucoma, ischemic renal injury, vascular injury response, Alzheimer's disease, motor neurone disease and its cpmplications, asthma, skin diseases, tuberculosis, parasitic diseases, and multiple organ failure. Therefore, it can be inferred that flavonoids may also be used as medical treatment for

these diseases. However, this must be confirmed by future experiments.

Conclusion

In this study, an experiment was performed by docking method. Based on the ΔG of ligand, we can obtain the selectivity of components. According to grading method investigated by Xing *et al* (2009; Chen, Xu, and Tang, 2007; Krovat, Steindl, and Langer, 2005), evaluated results were determined.

Flavonoids have multi-component and multi-function. They are often used in traditional Chinese herbal medicine. Their action mechanisms to specific diseases are not understood well at present. In the current research, we chose some components and studied their possible usage as medical treatment to diseases. The result indicates that a single component may interact effectively with different proteins, and also many components may be effective to interact with single protein. This feature is typical for traditional Chinese herbal medicines. Among total 26 effects, 25 reported effects can be estimated from virtual evaluation for glucoside but not aglycone. It suggests that aglycones may be effective in the form of glucoside *in vivo*. It also suggests that metabolism of drug is a very important factor to be considered for virtual evaluation in future.

Up to now, we have investigated several kinds of natural products with virtual evaluation method. Although our method can only provide qualitative results, it seems a beneficial way to treat the complicated system of traditional Chinese herbal medicine. There is a long way before people can realize the complex mechanisms of traditional Chinese herbal medicine. Many virtual evaluations and experiments should be performed in future, and their results should be compared again and again. With the development of structural biology and theoretical chemistry, the mechanisms of complicated natural products will be predicted more and more accurately.

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