· Reviews ·

New Collection of Crude Drugs in *Chinese Pharmacopoeia 2010* III. *Kadsurae Caulis*

XU Li-jia, MA Pei, LI Li, WANG Wan-ying, XIAO Wei, PENG Yong, XIAO Pei-gen*

Key Laboratory of Bioactive Substances and Resources Utilization of Chinese Herbal Medicine, Ministry of Education, Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100193, China

Abstract: The dried cane of *Kadsura interior* (*Kadsurae Caulis*) is recorded in *Chinese Pharmacopoeia 2010* as Dian Jixueteng for the treatment of rheumatism, irregular menstruation, and deficiency of *Qi* and blood. In this paper, morphological characteristics, chemical constituents, and pharmacological activities in the cane of *K. interior* were summarized. Moreover, some suggestions about application and quality control of *Kadsurae Caulis* were proposed in order to provide a theoretical basis for further scientific use.

Key words: biological activities; chemical constituents; *Kadsurae Caulis*; *Kadsura interior*; morphological characteristics

DOI: 10.3969/j.issn.1674-6384.2012.03.001

Introduction

The dried cane of *Kadsura interior* A. C. Smith (Schisandraceae) is recorded in *Chinese Pharmacopoeia 2010* as *Kadsurae Caulis* (Dian Jixueteng) for the treatment of rheumatism, irregular menstruation, and deficiency of *Qi* and blood. It is a major raw material in the formula of Compound Dian Jixueteng Gao, which is mainly composed of the water extracts from *Kadsurae Caulis*, *Cyathulae Radix*, *Dipsaci Radix*, *Carthami Flos*, and black soybean as a traditional formula with the function of activating blood circulation and treating irregular menstruation (Chen *et al*, 1993).

Many Chinese herbal medicines exhibit their therapeutic effects via the synergy and integration of multi-components and multi-targets (Wu *et al*, 2010); And one disease/symptom could be treated via multi-targets by multi-components. Thus different herbs with similar effects for one disease may be a result of a variety of integrated components. Dian Jixueteng has very similar medical function with Jixueteng. Locally, different species including some plants of *Kadsura* A. L. Jussieu have the same name of Jixueteng due to their similarities in appearance or medicinal function. There are about fifteen species from six genera being used as Jixueteng in different areas of China, and the cane of *K. interior* is one of the substitutes. The real Jixueteng is botanically derived from the dried cane of *Spatholobus suberectus* Dunn, which possesses similar medicinal function with Dian Jixueteng, but quite different chemical components from the cane of *K. interior*. The compounds from Jixueteng mainly belong to the classes of flavonoid, steroid, and triterpenoid while the compounds from Dian Jixueteng mainly belong to the classes of lignan and triterpenoid.

In this review, we summarized the research progress in botany, phytochemistry, quality control, biological activities, and application in the cane of *K. interior* under the item of *Kadsurae Caulis* in *Chinese Pharmacopoeia 2010* (Pharmacopeia Committee of P. R. China, 2010) in order to provide scientific evidence for the better utilization of *Kadsurae Caulis*.

Brief history

The cane of *K. interior*, basically originated in Fengqing County, Yunnan Province, is accepted as *Kadsurae Caulis* independently in *Chinese Pharmacopoeia*

* Cooresponding author: Xiao PG Address: Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100193, China Tel: +86-10-6301 1294 Fax: +86-10-6303 8753 E-mail: xiaopg@ public.bta.net.cn

Received: August 26, 2011; Revised: December 12, 2011; Accepted: May 1, 2012

2010. In fact, the cane of *K. interior* has been used as the major raw materials of *Kadsurae Caulis* in the formula of Compound Dian Jixueteng Gao for a long history to enrich blood, dredge collaterals, promote blood circulation, and stimulate menstrual discharge.

Botanical identification and resources

K. interior distributes in the southwest of Fengqing County, Yunnan Province, China and the northeast of Burma, in the woods within 1200－2500 m elevation (Liu, Luo, and Wu, 1996).

Kadsurae Caulis is mainly from the dried canes of *K. interior*, harvested in autumn with their branches and leaves removed, then sliced and sun-dried.

The product has a circle, elliptic or irregular inclined section with diameter of 1.8－6.5 cm. It is externally taupe, the outer cork is scaling off, and the exposed surface appears dark purple. The cork is thick, longitudinally furrowed or wrinkled, often accompanied by liverworts and lichens. The texture is too hard to broken. The odor is aromatic and the taste is bitter and astringent.

The characteristic of transverse section is described as follows: cortex narrow, red brown, and fibrous; The xylem is relatively broad, consisting of fine vessels scattered; The pith is small and taupe and shows vacancy.

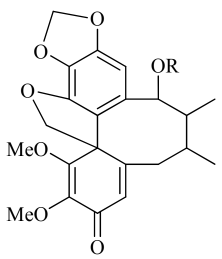
In some literatures, *Kadsurae Caulis* was usually the mixture of *K. heteroclita* (Roxb.) Craib and *K. interior* (Chen, 2007). The difference in the canes between *K. heteroclite* and *K. interio*r is the cork; The cork characteristic of *K. heteroclite* is yellowish-white, soft, and has rich flexibility, sometimes as thick as 7 mm, with longitude furrow and transverse crack.

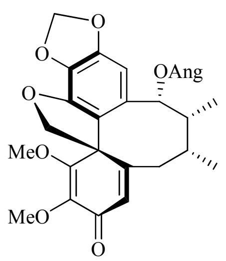
Chemical constituents

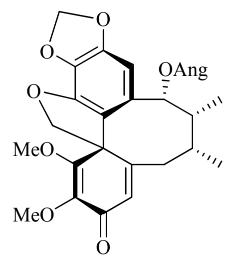
Lignans and triterpenoids are mainly bioactive components in the species, and lignans are usually considered as the characteristic components from the plants in the family of Schisandraceae. Main compounds are listed in Table 1 and their structures are demonstrated in Fig. 1.

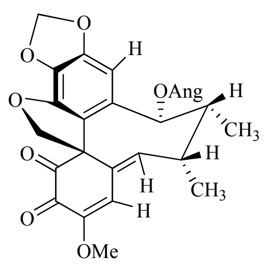
Table 1 Chemical constituents (1－34) from cane of *K. interior*

No.	Compounds	References	No.	Compounds	References
Lignans			**19**	gomisin A	Yu, Chen, and Situ, 1996
1	isointeriorin	Ding and Luo, 1990	**20**	schizandrin	Yu, Chen, and Situ, 1996
2	interiorin	Ding and Luo, 1990	**21**	(+)-deoxyschizandrin	Yu, Chen, and Situ, 1996
3	interiorin B	Ding and Luo, 1990	Triterpenoids		
4	interiorin C	Ding and Luo, 1990	**22**	ursolic acid	Zhou, Li, and Li, 2008
5	interiorin D	Ding and Luo, 1990	**23**	α-amyrin	Zhou, Li, and Li, 2008
6	interiotherin D	Chen *et al*, 2002	**24**	β-amyrin	Zhou, Li, and Li, 2008
7	heterolitin F	Chen *et al*, 1996	**25**	germanicol C	Zhou, Li, and Li, 2008
8	gomisin J	Peng *et al*, 1996	**26**	lupenol	Zhou, Li, and Li, 2008
9	schisandrin C	Chen *et al*, 2002	Others		
10	kadsurin	Ding and Luo, 1990	**27**	lupenone	Zhou, Li, and Li, 2008
11	schisantherin A	Zhou, Li, and Li, 2008	**28**	β-sitosterol	Zhou, Li, and Li, 2008
12	gomisin G	Yu, Chen, and Situ, 1996	**29**	7-oxositosterol	Zhou, Li, and Li, 2008
13	interiotherin B	Chen *et al*, 1996; Chen *et al*, 2002	**30**	isoflavonoids genisten	Zhou, Li, and Li, 2008
			31	formononetin	Zhou, Li, and Li, 2008
14	schisantherin D	Chen *et al*, 1996	**32**	7-hydroxy-4′,8-dimethoxyisoflavone	Zhou, Li, and Li, 2008
15	kadsuranin	Yu, Chen, and Situ, 1996			
16	interiotherin C	Chen *et al*, 2002	**33**	4′,7-dihydroxyflavone	Zhou, Li, and Li, 2008
17	interiotherin A	Chen *et al*, 1996	**34**	isoliquirtigenin	Zhou, Li, and Li, 2008
18	angeloylgomisin R	Chen *et al*, 1996			



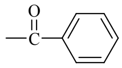






1 R＝Ang

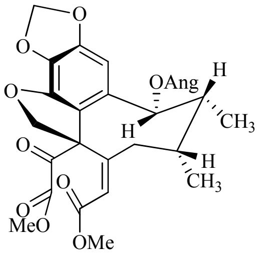
4 R＝$COCH_3$

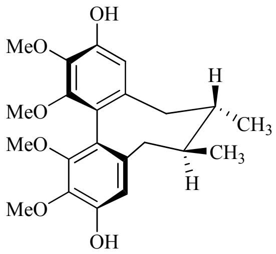
5 R＝ 

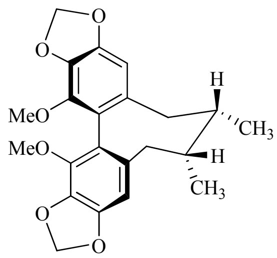
2

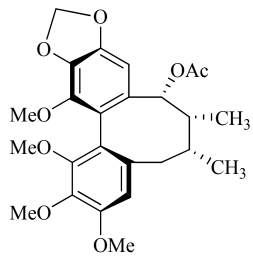
3

6

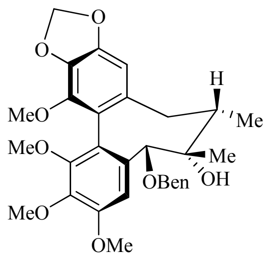


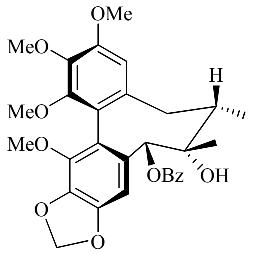


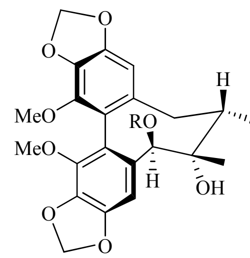


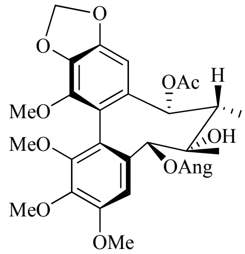


7 **8** **9** **10**

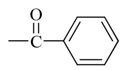




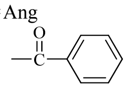




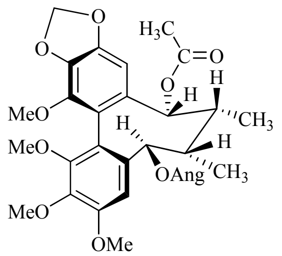
11

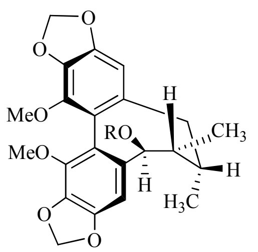
12 Bz= 

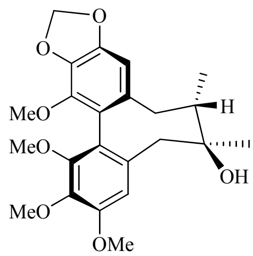
13 R ＝Ang

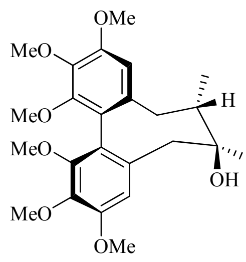
14 R ＝ 

15

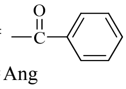






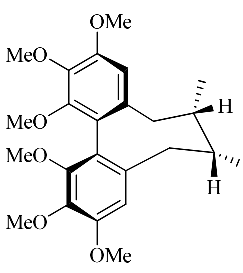


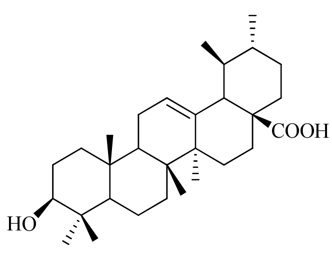
16

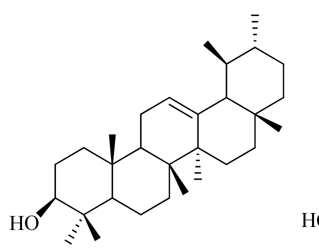
17 R＝ 

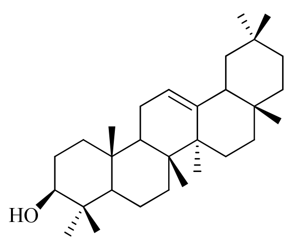
18 R＝Ang

19 **20**

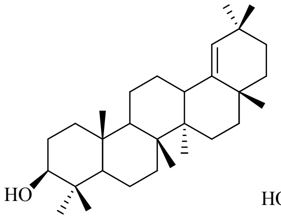




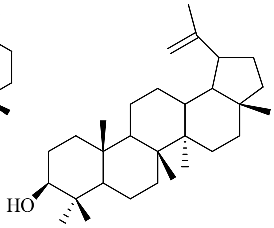




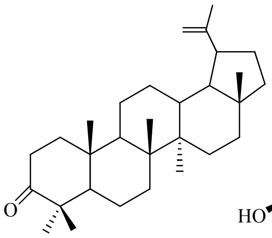
21 **22** **23** **24**



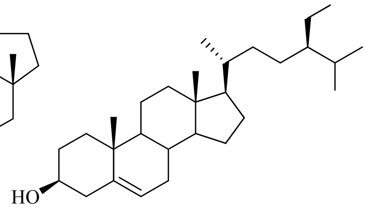
25



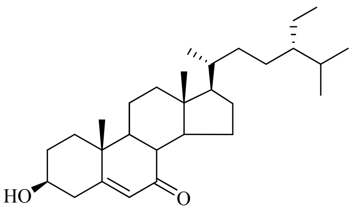
26



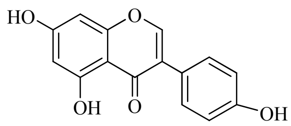
27



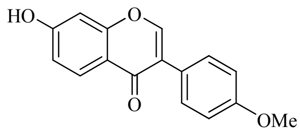
28



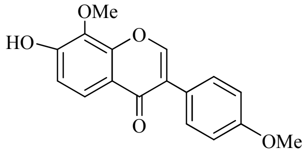
29



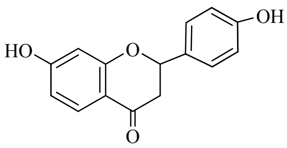
30



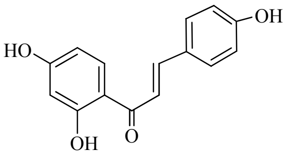
31



32



33



34

Fig. 1 Chemical structures of compounds 1－34

Lignans

Lignan is an important type of components in this species. Totally, 21 lignans (**1－21**) were isolated from the cane of *K. interior*. Among them, seven compounds (**1－7**) contained special tetrahydrofuran ring spanning the biphenyl linkage. Those are spirobenzofuranoid dibenzocyclooctadienes mostly presented in the plants of *Kadsura* A. L. Jussieu, which could be considered as marker compounds in the plants of *Kadsura* A. L. Jussieu.

Triterpenoids

Five triterpenoids (**22－26**) have been isolated from the cane of *K. interior.* They are ursolic acid, α-amyrin, β-amyrin, germanicol C, and lupenol. Up to now, there were no reports show that the cane of *K. interior* contains those typical triterpenoids as other species in *Kadsura* A. L. Jussieu.

Other compounds

Eight compounds including steroides (**27** and **28**) and flavonoids (**29－34**) were isolated and identified.

Pharmacological research

Anti-oxidant

The EtOH extract from the cane of *K. interior* resulted in decreasing the active products of CCl_4-induced lipid peroxidation (LP), such as thiobarbituric acid reactive substances (TBA-RS), conjugated dienes, and fluorescent products in the liver of mice (Yang *et al*, 1992a). Dibenzocyclooctadiene- type lignans isolated from the cane of *K. interior* potently inhibited LP in rat liver homogenate stimulated by Fe^{2+}-ascorbic acid, the CCl_4-reduced form of nicotinamide adenine dinucleotide phosphate (NADP), and adenosine diphosphate-reduced form of nicotinamide adenine dinucleotide phosphate (ADP-NADPH) (Yang *et al*, 1992b). Gomisin J could inhibit lipid peroxide (LPO) induced by hydroxy free radical in rat liver mitochondria scavenge the superoxide anion radical, and also protect the cultured myocardial cells from injury during the development of the calcium paradox (Jin *et al*, 2000; Peng *et al*, 1996).

Antitumor

Some neolignans were screened as potential antitumor promoters by examing their ability to inhibit Epstein-Barr virus early antigen (EBV-EA) activation (induced by 12-*O*-tetradecanoylphorbol-13-acetate) in Raji cells. Neokadsuranin and schisandrin C were the most potent compounds. The results suggested that some neolignans might be valuable antitumor promoters or chemopreventors (Chen *et al*, 2002).

Anti-HIV

Compound **15** was weakly active as an anti-HIV agent (Pu *et al*, 2008). Interiotherins A (I) and schisantherin D inhibited HIV replication with EC_{50} of 3.1 and 0.5 μg/mL, respectively (Chen *et al*, 1996).

Gomisin G exhibited the most potent anti-HIV activity with EC_{50} and therapeutic index (TI) of 0.006 μg/mL and 300, respectively. Schisantherin D, kadsuranin, and schisandrin C showed good activities with EC_{50} values of 0.5, 0.8, and 1.2 μg/mL, and TI of 110, 56, and 33.3, respectively. The anti-HIV data indicated that the relative position and types of substituents on the phenolic hydroxy groups of either natural lignans or synthetic biphenyl compounds, rather than the numbers of bromine(s) on aromatic rings are of primary importance. In the cyclooctane ring of natural lignans, the position and substitution of hydroxy groups are also important to enhance the anti-HIV activity (Chen *et al*, 1997).

Platelet activating factor (PAF) receptor antagonistic and other activities

Using [3H] PAF binding to human platelet membrane assay, tigloylgomisin B, angeloylgomisin P, and *R*-(+)-gomisin M1 showed the antagonistic activities of PAF receptor (Han *et al*, 1992). Schisanhenol (SAL) and (+)-anwulignan (AN) have the inhibitory effects on platelets aggregation induced by ADP and PAF *in vitro*. The inhibitory effect of heteroclitin D is the most potent and could be one of the important active components from the medicinal plants of *Kadsura* A. L. Jussieu (Jiang, Zhang, and Chen, 2005). This study suggested that the extract from the cane of *K. interior* at proper doses could promote the growth and development of hippocampal neurons (Xiao *et al*, 2002). Gomisin J could inhibit *L*-type calcium channels (Zhang *et al*, 2000).

Chemical constituents proposed for quality control

By now, no quality control method for *Kadsurae Caulis* has been reported yet. The lignan heteroclitn D with notable activities was considered as the standard compound of *Kadsurae Caulis* in HPLC analysis (Lu, 2006), although the compound was isolated from the cane of *K. heteroclite*. The characteristic lignans, especially spirobenzofuranoid dibenzocyclooctadienes, could be recommended as the standard components for the quality control of *Kadsurae Caulis* and related formula in further study.

Application

The canes of *K. interior* were used as the major raw material of *Kadsurae Caulis* in the formula of Compound Dian Jixueteng Gao for a long history (Wu, Lu, and Chen, 2010).

Compound Dian Jixueteng Gao, a traditional Chinese patent medicine, is made of the water extract of *Kadsurae Caulis*, *Cyathulae Radix*, *Dipsaci Radix*, and *Carthami Flos*. It is mainly used for the treatment of blood deficiency, numbness of hands and feet, painful aching of the joints, and irregular menstruation.

Conclusion

The cane of *K. interior* is one of the new crude drugs collected in *Chinese Pharmacopoeia 2010*. It is one of the main components of Compound Dian Jixueteng Gao. Modern researches indicates that cane of *K. interior* with plentiful spirobenzofuranoid dibenzocyclooctadienes has obvious pharmacological activities on anti-oxidant, antitumor, anti-HIV, and so on. Researchers are providing more findings from the cane of *K. interior*, which will be helpful for the improvement of national regulations of traditional Chinese herbs. It also should be emphasized that the canes of both *K. interor* and *K. heteroclite* are used as the major raw materials of *Kadsurae Caulis* for a long history. Although the cane of *K. heteroclite* has not been included in *Chinese Pharmacopoeia 2010*, its application is also extensive locally. Thus, the resources and the original plants about *Kadsurae Caulis* should be deeply investigated in future.

References

Chen DF, 2007. Bioactive constituents of *Kadsura* medicinal plants. *Chin J Nat Med* 5: 15-19.

Chen DF, Xu GJ, Xu LS, Jin RY, 1993. A resource investigation and commodity identification of *Spatholobus suberectus*. *Chin Tradit Herb Drugs* 24: 34-37.

Chen DF, Zhang SX, Chen K, Zhou BN, Wang P, Cosentino LM, Lee KH, 1996. Two new lignans, interiotherins A and B, as anti-HIV principles from *Kadsura interior*. *China J Nat Prod* 59: 1066-1068.

Chen DF, Zhang SX, Kozuka M, Sun QZ, Feng J, Wang Q, Mukainaka T, Nobukuni Y, Tokuda H, Nishino H, Wang HK, Morris-Natschke SL, Lee KH, 2002. Interiotherins C and D, two new lignans from *Kadsura interior* and antitumor-promoting effects of related neolignans on Epstein-Barr virus activation. *J Nat Prod* 65: 1242-1245.

Chen DF, Zhang SX, Xie L, Xie JX, Chen K, Kashiwada Y, Zhou BN, Wang P, Cosentino LM, Lee KH, 1997. Anti-AIDS agents-XXVI. Structure-activity correlations of gomisin-G-related anti-HIV lignans from *Kadsura interior* and of related synthetic analogs. *Bioorg Med Chem* 5: 1715-1723.

Editorial board of *Chinese Materia Medica*. *Chinese Materia Medica*, 1999. Shanghai Science & Technology Press: Shanghai.

Ding ZH, Luo S, 1990. Study on new lignans from *Kadsura interior* A. C. Sm. *Acta Chim Sin* 48: 1075-1079.

Han GQ, Dai P, Xue R, Arison BH, Lankin DC, Hwang SB, 1992. Dibenzocyclooctadiene lignans with platelet-activating factor (PAF) antagonist activity from *Kadsura heteroclite*. *J Chin Pharm Sci* 1: 20-27.

Jiang SL, Zhang YY, Chen DF, 2005. Effects of heteroclitin D, schisanhenol and (+)-anwulignan on platelet aggregation. *Fudan Univ J Med Sci* 32: 467-470.

Jin XL, Gu Z, Hu TX, Wang MH, Chen DF, 2000. Effects of lignan gomisin J from *Kadsura interior* on liver mitochondria lipid peroxidation and on the superoxide anion radical. *Chin Pharmacol Bull* 16: 26-28.

Liu YH, Luo XR, Wu RF, 1996. *Flora of China* (*Vol. 30*). Science Press: Beijing.

Lu Y, 2006. Study on the chemical constituents of *Kadsurae Caulis* and quality control for *Fufang Dianjixueteng Gao*. Fudan University: Shanghai.

Luo YP, Wang SJ, Zhao JF, Yang XD, Li L, 2009. Study on the chemical constituents of *Kadsura heteroclita*. *J Yunnan Univ*: *Nat Sci Ed* 31: 406-409.

Peng HL, Chen DF, Lan HX, Zhang XM, Gu Z, Jiang MH, 1996. Anti-lipid peroxidation of gomisin J on liver mitochondria and cultured myocardial cells. *Acta Pharmacol Sin* 17: 538-541.

Pharmacopeia Committee of P. R. China, 2010. *Pharmacopoeia of People's Republic of China*. China Medical Science and Technology Press: Beijing.

Pu JX ,Yang LM, Xiao WL, Li RT, Lei C, Gao XM, Huang SX, Zheng YT, Sun HD, 2008. Compounds from *Kadsura heteroclita* and related anti-HIV activity. *State Key Lab Phytochem Plant Resour West China* 69: 1266-1272.

Wang W, Ma XC, Liu P, Liu Rx, Guan SH, Guo D, 2006. Two new dibenzylbutyrolactone type lignans from the stems of *Kadsura heteroclita*. *Nat Prod Commun* 1: 109-112.

Wu R, Lu Y, Chen DF, 2010. The quality standards of *Fu Fang Ji Xue Teng Gao*. *Chin Tradit Pat Med* 9.

Wu SS, Guo GG, Li CW, Wu HH, HH, Chen CY, 2010. The hypothesis of "Cutting-down-effect of Diseases" concerning Chinese herbs and its experimental testing via integration and synergistic actions of multicomponents and multi-targets in the anti-peptic ulcer effects of Lizong Pill. *World Sci Technol*－*Mod Tradit Chin Med Mater Medica* 12: 580-584.

Xiao F, Luo HM, Li XG, Gu F, 2002. The effect of *Kadsura heteroclita* on the cultured hippocampal neurons. *J Chin Med Mater* 25: 800-802.

Yang XW, Hattori M, Namba T, Chen DF, Xu GJ, 1992a. Antilipid peroxidative effect of an extract of the stems of *Kadsura heteroclita* and its major constituent, kadsurin, in mice. *Chem Pharm Bull* 40: 406-409.

Yang XW, Miyashiro H, Hattori M, Namba T, Tezuka Y, Kikuchi T, Chen DF, Xu GJ, Hori T, 1992b. Isolation of novel lignans, heteroclitins F and G, from the stems of *Kadsura heteroclita*, and anti-lipid peroxidative actions of heteroclitins A－G and related compounds in the *in vitro* rat liver homogenate system. *Chem Pharm Bull* 40: 1510-1516.

Yu YQ, Chen DF, Situ B, 1996. Determination of lignans of *Kadsura interior* A. C. Smith by HPLC. *Chin J Pharm Anal* 16: 313-316.

Zhang XM, Chen DF, He XJ, Yang S, Zheng P, Jiang MH, 2000. Blocking effects of heteroclitin D and gomisin J on *L*-type calcium channels in ventricular cells of guinea pig. *Acta Pharmacol Sin* 21: 373-376.

Zhou SY, Li RT, Li HM, 2008. Study on chemical constituents of *Kadsura interior*. *J Kunming Univ Sci Technol*: *Sci Tech* 33: 81-85.