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Review

The genus *Epimedium*: An ethnopharmacological and phytochemical review

Huiping Ma[a], Xirui He[b,c], Yan Yang[d], Maoxing Li[a], Dingjun Hao[c], Zhengping Jia[a,*]

[a] *Department of Pharmacy, Lanzhou General Hospital of PLA, Lanzhou 730050, PR China*
[b] *Department of Pharmacy, Lanzhou University, Lanzhou 730000, PR China*
[c] *Xi'an Red Cross Hospital, Xi'an 710054, PR China*
[d] *Department of Agronomy, Gansu Agriculture University, Lanzhou 730070, PR China*

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ABSTRACT

Epimedium (Berberidaceae), is a genus of about 52 species in the family Berberidaceae, which also known as Rowdy Lamb Herb, Xianlinpi, Barrenwort, Bishop's Hat, Fairy Wings, Horny Goat Weed, and Yangheye or Yin Yang Huo (Chinese: 淫羊藿). Many plants have been proven to possess efficacy on sexual dysfunction and osteoporosis in traditional Chinese medicine (TCM). The paper reviews the ethnopharmacology, the biological activities and the correlated chemical compounds of *Epimedium* species. More than 260 compounds have been isolated; among them prenyl-flavonoids are the major constituents and also important chemotaxonomic markers. Modern pharmacology studies and clinical practice demonstrated that *Epimedium* and its active compounds possess wide pharmacological actions, especially in strengthening *yang*, hormone regulation, anti-osteoporosis, immunological function modulation, anti-oxidation and anti-tumor, anti-aging, anti-atherosclerosis and anti-depressant activities. Currently, effective monomeric compounds or active parts have been screened for pharmacological activity from *Epimedium in vivo* and *in vitro*.

Contents

* Corresponding author. Tel.: +86 931 899 4676.
E-mail address: limaox2005@yahoo.com.cn (Z. Jia).

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1. Introduction

Epimedium (Berberidaceae), also known as Rowdy Lamb Herb, Barrenwort, Bishop's Hat, Fairy Wings, Horny Goat Weed, Xianlinpi, Yangheye and Yin Yang Huo (Chinese: 淫羊藿), is a genus of about 52 species of herbaceous plants (Stearn, 2002). *Epimedium* is also named three branches-nine leaves grass, as there are three branches from the stem and three leaves in every branch. The leaves and stem can be used as a remedy. More than 15 species in this genus have a long history of use in traditional Chinese medicine (TCM) and are believed to "nourishing the kidney and reinforcing the *Yang*". Extracts of the aerial parts of this genus are used in a famous botanical supplement that has been widely used as a tonic, aphrodisiac and antirheumatic in China, Japan and Korea for more than 2000 years. This supplement has shown *in vivo* and *in vivo* activity against on sexual dysfunction, osteoporosis, cardiovascular diseases, menstrual irregularity, asthma, chronic nephritis and immunoregulation (Li, 1991; Wang et al., 2004; Meng et al., 2005).

In the last decades, the use of *Epimedium* plants in traditional Chinese medicine has led to a rapid increase in the information available on the active components of *Epimedium*, there chemical compounds and the pharmacological activities of these compounds. More than 260 compounds have been identified from different species of *Epimedium* (Wu et al., 2003a). Among them, prenyl-flavonoids are the major constituents and also important chemotaxonomic markers. At the same time, *in vivo* and/or *in vitro* experiments and clinical practice have demonstrated that *Epimedium* and its active compounds possess wide-reaching pharmacological actions, including strengthening *yang*, improving cardiovascular and cerebrovascular functions and modulating immunological function as well as having anti-osteoporosis, anti-oxidation, anti-tumor and anti-aging effects. In this review, we try to present and assess recent studies about the ethnopharmacology, phytochemistry, pharmacological activities, processing, cultivation and propagation of the genus *Epimedium*.

2. Botanical description and distribution

Epimedium is a low-growing, deciduous, perennial plant with leathery leaves that spreads by underground stems. The scale-like leaves are alternate, long-petiolate, ternately divided twice. The leaflets are ovate, acuminate, cordate, and up to 2.5–13.5 cm long and 1.5–7.5 cm wide, with setose margins. The flowers of this plant resemble a Bishop's hat (pendant-shaped), have long spurs and vary in color (purple, pink, rose, yellow or white) and are one to two inches wide. Flower of *Epimedium* has 8 piece of sepals, the outside 4 sepals are unequal, the inside 4 sepals are petaloid, reflexing at flowering time. The flower has 4 stamens and 1 ovary with several ovules. The *Epimedium* species is a tough, long-lived perennial. The unique, colorful flowers and leaves compose an attractive ground covers in the spring. Selected *Epimedium* species are shown in Fig. 1.

Epimedium grows mainly on cliffs under moist forests, near streams and wet lands at altitudes ranging from 200 to 3700 m (Ying and Chen, 2001). The overwhelming majority of *Epimedium* species are endemic to China, although some are found in eastern, southern and central Asia as well as Europe (Table 1). In China, there are 43 species that are mainly distributed in the southwest and cen-

Fig. 1. The aerial parts of *Epimedium koreanum*, *Epimedium brevicornum*, and *Epimedium sagittatum* (Sieb. & Zucc.) Maxim.

Table 1
The category and distribution of *Epimedium* plants in the whole world.

Distribution	Category
Chinese	*Epimedium davidii* Franch; *Epimedium baojingense* Q.L. Chen et B.M. Yang; *Epimedium dolichostemon* Stearn; *Epimedium koreanum* Nakai; *Epimedium fargesii* Franch; *Epimedium elongatum* Komarov; *Epimedium acuminatum* Franch; *Epimedium simplicifolium* Ying; *Epimedium brachyrrhizum* Stearn; *Epimedium multiflorum* Ying; *Epimedium enshiense* B.L. Guo et Hsiao; *Epimedium fangii* Stearn; *Epimedium reticulatum* C.Y. Wu; *Epimedium sagittatum* (Sieb. et Zucc.) Maxim. *var. glabratum* Ying; *Epimedium hunanense* (Hand.-Mazz.) Hand.-Mazz.; *Epimedium latisepalum* Stearn; *Epimedium ogisui* Stearn; *Epimedium chlorandrum* Stearn; *Epimedium platypetalum* K. Meyer; *Epimedium franchetii* Stearn; *Epimedium truncatum* H.R. Liang; *Epimedium boreali-guizhouense* S.Z. He et Y.K. Yang; *Epimedium leptorrhizum* Stearn; *Epimedium rhizomatosum* Stearn; *Epimedium pubescens* Maxim.; *Epimedium sagittatum* (Sieb. et Zucc.) Maxim.; *Epimedium sagittatum* (Sieb. et Zucc.) Maxim. *var. sagittatum*; *Epimedium pauciflorum* K.C. Yen; *Epimedium lishihchenii* Stearn; *Epimedium shuichengense* S.Z. He; *Epimedium sutchuenense* Franch.; *Epimedium myrianthum* Stearn; *Epimedium flavum* Stearn; *Epimedium wushanense* Ying, *Epimedium ecalcaratum* G.Y. Zhong; *Epimedium glandulosopilosum* H.R. Liang; *Epimedium parvifolium* S.Z. He et T.L. Zhang; *Epimedium stellulatum* Stearn; *Epimedium brevicornu* Maxim; *Epimedium ilicifolium* Stearn; *Epimedium mikinorii* Stearn; *Epimedium zhushanense* K.F. Wu et S.X. Qian; *Epimedium epsteinii* Stearn.
Japan	*Epimedium cremeum*, *Epimedium diphyllum*, *Epimedium grandiflorum*, *Epimedium grandiflorum var. thunbergianum*, *Epimedium grandiflorum var. higoense*, *Epimedium grandiflorum var. coelestre*, *Epimedium kitamuranum*, *Epimedium macranthum*, *Epimedium sempervirens. Epimedium sempervirens var. multifoliolatum*, *Epimedium setosum*, *Epimedium trifoliatobinatum.*
Europe	*Epimedium alpinum*, *Epimedium pubigerum*, *Epimedium pinnatum*, *Epimedium pinnatum subsp colchium*, *Epimedium canrabrigensis*, *Epimedium perralderianum.*
North Africa	*Epimedium perralderianum*, *Epimedium pinnatum.*
India	*Epimedium elatum.*
Korea	*Epimedium koreanum* Nakai.

tral regions (Table 2); 15 of these are circulated in the crude drug markets for use as Yin Yang Huo. Among them, *Epimedium sagittatum* (Sieb. & Zucc.) Maxim., *Epimedium koreanum* Nakai, *Epimedium pubescens* Maxim., *Epimedium wushanense* T.S. Ying and *Epimedium brevicornum* Maxim (EB) are wildly distributed and commonly used.

In the last 100–150 years, there is a wide array of new Chinese species is being cultivated in the west, many of these have

Table 2
The major medicinal plants and its specific distribution in China.

Chinese name	Latin name	Distribution
Dan ye yinyanghuo	*Epimedium simplicifolium* Ying	Guizhou
Xiao ye yinyanghuo	*Epimedium parvifolium* S.Z. He et T.L. Zhang	Guizhou
Shui cheng yinyanghuo	*Epimedium shuichengense* S.Z. He	Guizhou
Qian bei qinyanghuo	*Epimedium boreali-guizhouense* S.Z. He et Y.K. Yang	Guizhou
Duo hua yinyanghuo	*Epimedium multiflorum* Ying	Guizhou
Qian ling yinyanghuo	*Epimedium leptorrhizum* Stearn	Guizhou, Hunan, Hubei, Sichuan
Ni wu shan yinyanghuo	*Epimedium pimedium pseudowushanense* B.L. Guo	Guizhou
Zu shan yinyanghuo	*Epimedium zhushanense* K.F. Wu et S.X. Qian	Hubei
Pian xie yinyanghuo	*Epimedium truncatum* H.R. Liang	Hubei
En shi yinyanghuo	*Epimedium enshiense* B.L. Guo et Hsiao	Hubei
Mu yu ping yinyanghuo	*Epimedium franchetii* Stearn	Hubei, Guizhou
Zhi ju yinyanghuo	*Epimedium mikinorii* Stearn	Hubei
Xing hua yinyanghuo	*Epimedium stellulatum* Stearn	Hubei, Sichuan
Qiang jing yinyanghuo	*Epimedium rhizomatosum* Stearn	Sichuan
Si chuan yinyanghuo	*Epimedium sutchuenense* Franch	Sichuan, Guizhou, Hubei
Chuan xi yinyanghuo	*Epimedium elongatum* Komarov	Sichuan
Qing cheng shan yinyanghuo	*Epimedium qingchengshanense* G.Y. Zhong & B.L.Guo	Sichuan
Mao wen yinyanghuo	*Epimedium platypetalum* K. Meyer	Sichuan, Shanxi
Tian quan yanyanghuo	*Epimedium flavum* Stearn	Sichuan
Duan jing yinyanghuo	*Epimedium brachyrrhizum* Stearn	Sichuan
Shao hua yinyanghuo	*Epimedium pauciflorum* K.C. Yen	Sichuan
Fang shi yinyanghuo	*Epimedium fangii* Stearn	Sichuan
Kuan'e yinyanghuo	*Epimedium latisepalum* Stearn	Sichuan
Lu shan yinyanghuo	*Epimedium ogisui* Stearn	Sichuan
Chuan e yinyanghuo	*Epimedium fargesii* Franch	Sichuan, Hubei
Bao xing yinyanghuo	*Epimedium davidii* Franch	Sichuan, Yunnan
Chang rui yinyanghuo	*Epimedium dolichostemon* Stearn	Sichuang
Lv yao yinyanghuo	*Epimedium chlorandrum* Stearn	Sichuan
Wu shan yinyanghuo	*Epimedium wushanense* Ying	Sichuan, Guizhou, Hubei, Guangxi
Ge ye yinyanghuo	*Epimedium reticulatum* C.Y. Wu	Sichuan
Cu mao yinyanghuo	*Epimedium acuminatum* Franch	Sichuan, Guizhou, Yunnan, Hubei, Guangxi
Xian mao yinyanghuo	*Epimedium glandulosopilosum* H.R. Liang	Sichuan
Wu ju yinyanghuo	*Epimedium ecalcaratum* G.Y. Zhong	Sichuan
Zi ju yinyanghuo	*Epimedium epsteinii* Stearn	Hunan
Hu nan yinyanghuo	*Epimedium hunanense* Hand.-Mazz	Hunan, Hubei, Guangxi
Jian ye yinyanghuo	*Epimedium sagittatum* (Sieb & Zucc) Maxim	Hunan, Hubei, Guangdong, Zhejiang, An'hui, Jiangxi, Guagxi, Shanxi, Gansu, Sichuan
Tian ping shan yinyanghuo	*Epimedium myrianthum* Stearn	Hunan, Hubei
Chao xian yinyanghuo	*Epimedium koreanum* Nakai	Jilin, Liaoning, Zhejiang, An'hui
Shi zhen yinyanghuo	*Epimedium lishihchenii* Stearn	Jiangxi
Rou mao yinyanghuo	*Epimedium pubescens* Maxim	Shanxi, Gansu, Hubei, Sichuan, Henan, An'hui
Yinyanghuo	*Epimedium brevicornu* Maxim	Shanxi, Gansu, Shan·xi, Henan, Qinghai, Hubei, Sichuan
Zhen ping yinyanghuo	*Epimedium ilicifolium* Stearn	Shanxi

Table 3
The popular traditional food therapy or medicated diet of *Epimedium*.

Names	Prescription	Uses recorded	Formulation/mode of usage	Ref.
Yinyanghuo wine I	*Epimedium*, rice wine	Impotence, prospermia, rheumatic arthralgia, spasm of limbs,	Wines processing	Zhao (2004)
Yinyanghuo wine II	*Epimedium*, wine	Impotence, dysgenesia	Wines processing	Hu (2002)
Qiyang wine	Testis et Penis Callorhimi, *Epimedium*, Radix Morindae Officinalis, Ziziphus jujuba, Semen Cuscutae, Herba Cistanches Deserticolae, wine	Azoospermia, low motility of sperm	Wines processing	Hu (2002)
Bushenzhuangyang wine	*Epimedium*, Radix Morindae Officinalis, Herba Cistanches Deserticolae, Radix Codonopsis, Fructus Jujubae, Fructus Lycii, prepared rhizome of rehmannia, Fructus Rosae, rice wine	Impotence, prospermia, osteoporosis	Wines processing	Hu (2002)
Yinyanghuo gourou soup	*Epimedium*, dog meat	Impotence, prospermia, spermatorrhea	Decoctions	Hu (2002)
Gouqi eryang soup	Fructus Lycii, *Epimedium*, mutton	Impotence, prospermia, spermatorrhea	Decoctions	Hu (2002)
Shuangbu soup	*Epimedium*, Fructus Lycii, prepared Rhizome of Rehmannia, Radix Morindae Officinalis, Colla Comus Cervi, Radix Astragali Mongolici, Radix Codonopsis, Radix Angelicae Sinensis	Spermatorrhea, impotence, fatigue, prospermia, sterility, Menoxenia, uterine bleeding	Decoctions	Zhao (2004)
Yinyanghuo Yizhi soup	*Epimedium*, Fructus Alpiniae oxyphyllae, Cortex Cinnamomi Cassiae	Diuresis	Decoctions	Zhao (2004)
Yinyanghuo yangshen gruel	*Epimedium*, Goat kidney, rice	Excessive teratospermia syndrome	Gruel	Hu (2002)
Yinyanghuo gouqi noodles	*Epimedium*, Fructus Lycii, longan, noodles	Azoospermia	Medicated diet	Hu (2002)
Custard cream of Yinyanghuo	*Epimedium*, egg, Oleum Sesami	Impotence, prospermia, emaciation, osteoporosis, acratia, osteodynia, chilly	Medicated diet	Zhao (2004)
Erxian ointment	*Epimedium*, Rhizoma Curculiginis, Radix Morindae Officinalis, Rhizoma Anemarrhenae, Cortex Phellodendri Amurensis, Radix Angelicae Sinensis	Essential hypertension, chronic nephritis, urinary infection, acratia, neurasthenia, osteoporosis, dizziness and tinnitus, magersucht	Medicated diet	Zhao (2004)

only recently been discovered, and a number have yet to be named (Wikipedia, 2000, http://www.en.wikipedia.org/wiki/Epimedium; Flora of China). *Epimedium* species are commonly propagated by rhizome division both to preserve cultivar identity and because of low seed viability (Mihaljević and Vršek, 2009). *Epimedium* prefers to be planted in acidic soil sheltered from sunshine where humidity is relatively high. In its reproductive growth period (from early March to late May), it needs enough light to avoid unfavorable influence on the rapid re-growth of roots and shoots. On hot days and in the dry season, *Epimedium* must be watered. Growth conditions affected the contents of the major components present in *Epimedium* plants, so a proper habitat for the plant is needed (Zhang et al., 2003). However, the information on the conservation status of the species of *Epimedium* have not been well reported.

3. Ethnopharmacological use

Certain species of *Epimedium* have been used in traditional Asian medicine and have proven to have remarkably therapeutic activities (Zhang et al., 2008a,b,c,d). Many species of *Epimedium* have been believed to posses aphrodisiac qualities. According to legend, this property was discovered by a Chinese goat herder who noticed far more active sexual activity in his goats after they ate the plants (Ye, 2005). 400 years ago, *Epimedium* has been recorded in the Chinese medical classics *Shen Nong Ben Cao Jing* and it was considered as a "Middle grade" herb in the most famous Chinese medicine document *Ben Cao Gang Mu*. In China and Japan, *Epimedium sagittatum* (Sieb. & Zucc.) Maxim. and *Epimedium grandiflorum* have been used to treat impotence, prospermia, hyperdiuresis, osteoporosis, menopause syndrome, rheumatic arthritis, hypertension, and chronic tracheitis. In Korea, Sam-ji-goo-yeop-cho, the herb *Epimedium koreanum*, was traditionally used for impotence, spermatorrhoea and forgetfulness (Liu and Xu, 1984). Now, the major five *Epimedium* species, *Epimedium brevicornum* Maxim, *Epimedium sagittatum* (Sieb. and Zucc.) Maxim., *Epimedium pubescens* Maxim. *Epimedium wushanense* T.S. Ying and *Epimedium koreanum* Nakai are designated as the official sources of Herba Epimedii in the Chinese Pharmacopoeia (The State Committee of Pharmacopeia, 2005). The aerial parts of some other species, such as *Epimedium myrianthum*, *Epimedium acuminatum* and *Epimedium leptorrhizum*, are also used in particular localities (Xie et al., 2010). In addition to the aerial parts, the underground parts of *Epimedium* plants are widely used as anti-rheumatic medicine in Chinese folk medicines (China Herb Compilation, 1975).

In China, *Epimedium* is held in such high regard that it is not only used as a medicine to cure some diseases but also as a supplement to prevent disease and strengthen the body. To increase its effect, *Epimedium* was often used with other traditional medicines, such as Radix Morindae Officinalis, Fructus Jujubae, Semen Cuscutae, Herba Cistanches, Radix Morindae Officinalis, Herba Cistanches Deserticolae, Radix Codonopsis, Fructus Lycii, the prepared rhizome of rehmannia, Radix Astragali Mongolici, Radix Codonopsis and Radix Angelicae Sinensis and even with dog meat, mutton and testis and penis of Callorhimi. Generally, *Epimedium* is macerated in wine or decocted with water for oral consumption. However, recently, more convenient forms have been developed for consumption, such as tablets, capsules, ointments, gruel, noodles, and cream (Table 3) (The State Committee of Pharmacopeia, 2005).

4. Chemical constituents

The genus *Epimedium* is rich in flavonoids and lignans. Flavonoids constituted the majority of compounds isolated during the 1980s and 1990s. To date, 141 flavonoids, 31 lignins, 12 ionones, 9 phenol glycosides, 6 phenylethanoid glycosides, 5 sesquiterpenes (Table 4) and a number of other compounds representing a wide spectrum of secondary metabolite classes have been isolated and identified from the genus *Epimedium*. The most well-known and phytochemically characterized of these compounds are the flavonoids, and the most prominent components are the prenylated flavonol glycosides. These flavonoids displayed many bioactivities *in vivo* or *in vitro* (see in Supplemental Table, Fig. 2). Icariin,

Table 4
The compounds isolated from the genus *Epimedium* (the parent nucleus structure of the flavonoids illustrated in Fig. 2).

No.	Compounds	Species	References
Flavonoids			
8-Prenyl-flavonoids			
1	Icariin	*Epimedium koreanum*	Li et al. (1995a)
		Epimedium fargesii	Guo et al. (1996a)
		Epimedium leptorrhizum	Han et al. (2002a)
		Epimedium platyetalum	Zhu et al. (1993)
		Epimedium wushanense	Zhou et al. (2005)
		Epimedium breviconu	Liao et al. (1994)
		Epimedium acuminatum	Dong et al. (1994)
		Epimedium sagittatum	Mizuno et al. (1987)
		Epimedium grandiflorum	Tokuoka et al. (1975a)
2	Icariin I	*Epimedium koreanum*	Wang et al. (2010a,b)
		Epimedium hunanense	Liang et al. (1997)
3	Icariin II	*Epimedium koreanum*	Wang et al. (2010a,b)
4	Desme-O-methylicariine	*Epimedium sagittatum*	Zhao (2001)
5	Anhydroicaritin	*Epimedium koreanum*	Sun et al. (1998a)
		Epimedium wanshanense	Li et al. (1996a)
		Epimedium brevicornum	Guo et al. (1996b)
6	Anhydroicaritin 3-O-rhamnosylrhamnoside	*Epimedium koreanum*	Li et al. (1996b)
7	Anhydroicaritin-3-O-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranoside	*Epimedium wanshanense*	Li et al. (1996c)
8	Demethylanhydroicaritin	*Epimedium koreanum*	Zheng and Kong (2002)
		Epimedium wanshanense	Li et al. (1996a)
		Epimedium wanshanense	Li et al. (1996d)
9	Desmethylanhydroicaritin-3-O-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranoside	*Epimedium wanshanense*	Li et al. (1996c)
10	Icariside I	*Epimedium koreanum*	Li et al. (1995a)
		Epimedium leptorrhizum	Han et al. (2002a)
		Epimedium wanshanense	Li et al. (1996d)
		Epimedium wushanense	Zhou et al. (2005)
		Epimedium breviconu	Liao et al. (1994)
		Epimedium sagittatum	Mizuno et al. (1987)
11	2″-O-rhamnopyranosyl icariside I	*Epimedium koreanum*	Sun et al. (1995a)
12	Icariside II (Baohuoside I)	*Epimedium koreanum*	Sun et al. (1995a)
			Li et al. (1995a)
		Epimedium breviconu	Liao et al. (1994)
		Epimedium wanshanense	Fukai and Nomura (1988)
		Epimedium sempervirens	Mizuno et al. (1987)
		Epimedium sagittatum	Zhu et al. (1993)
		Epimedium platyetalum	Liang et al. (1997)
		Epimedium hunanense	Li and Liu (1988b)
		Epimedium davidii	
13	2″-O-rhamnosyl icarisid II	*Epimedium koreanum*	Kang et al. (1991)
		Epimedium leptorrhizum	Han et al. (2002b)
		Epimedium leptorrhizum	Jia et al. (1999)
		Epimedium wanshanense	Li et al. (1996d)
		Epimedium acuminatum	Jia et al. (1998)
		Epimedium brevicornum	Guo et al. (1996c)
14	3‴-Carbonyl-2″-β-L-quinovosyl icariside II	*Epimedium koreanum*	Zhang et al. (2007)
15	Epimedin A	*Epimedium koreanum*	Oshima et al. (1987)
		Epimedium sagittatum	Wang and Geng (2005)
		Epimedium breviconu	Wang et al. (2005b)
16	Epimedin B	*Epimedium koreanum*	Oshima et al. (1987)
		Epimedium fargesii	Guo et al. (1996a)
		Epimedium sagittatum	Wang and Geng (2005)
		Epimedium wanshanense	Li et al. (1996a)
		Epimedium breviconu	Guo et al. (1996b)
		Epimedium hunanense	Liang et al. (1997)
17	Epimedin C	*Epimedium koreanum*	Oshima et al. (1987)
		Epimedium fargesii	Guo et al. (1996a)
		Epimedium sagittatum	Wang and Geng (2005)
		Epimedium leptorrhizum	Han et al. (2002a)
		Epimedium wanshanense	Li et al. (1996a)
		Epimedium breviconu	Guo et al. (1996b)
		Epimedium acuminatum	Jia et al. (1998)
		Epimedium hunanense	Liang et al. (1997)
18	Epimedin I	*Epimedium koreanum*	Sun et al. (1998b)
19	Epimedin K	*Epimedium koreanum*	Sun et al. (1996a)
20	Epimedoside	*Epimedium koreanum*	Sun et al. (1995b)
21	Epimedoside A	*Epimedium koreanum*	Sun et al. (1995a)
		Epimedium fargesii	Guo et al. (1996a)
		Epimedium truncatum	Xu and Yang (2005)
		Epimedium acuminatum	Dong et al. (1994)
		Epimedium grandiflorum	Takemoto et al. (1975)
		Epimedium wushanense	Takemoto et al. (1975)

Table 4 (*Continued*)

No.	Compounds	Species	References
22	Epimedoside B	*Epimedium koreanum*	Ou and Ou (1997)
		Epimedium grandiflorum	Tokuoka et al. (1975b)
23	Epimedoside C	*Epimedium koreanum*	Li et al. (1995b)
		Epimedium truncatum	Xu and Yang (2005)
		Epimedium leptorrhiz um	Han et al. (2002a)
		Epimedium wanshanense	Li et al. (1997a, b)
		Epimedium grandiflorum	Tokuoka et al. (1975b)
24	Epimedoside D	*Epimedium koreanum*	Ou and Ou (1997)
		Epimedium grandiflorum	Tokuoka et al. (1975c)
25	Epimedoside E	*Epimedium koreanum*	Ou and Ou (1997)
		Epimedium grandiflorum	Tokuoka et al. (1975c)
26	Epimedikoreanin A	*Epimedium koreanum*	Li et al. (1995c)
27	Epimedikoreanin B	*Epimedium koreanum*	Li et al. (1996e)
28	Epimedikoreanin C	*Epimedium koreanum*	Li et al. (1996e)
29	Epimedikoreanin D	*Epimedium koreanum*	Li et al. (1996e)
30	Epimedokoreanoside I	*Epimedium koreanum*	Pachaly et al. (1990)
31	Epimedokoreanoside II	*Epimedium koreanum*	Pachaly et al. (1990)
32	Sagittatoside A	*Epimedium koreanum*	Li et al. (1994a)
		Epimedium leptorrhizum	Jia et al. (1999)
		Epimedium wanshanense	Li et al. (1996c)
		Epimedium sagittatum	Mizuno et al. (1988a)
33	Sagittatoside B	*Epimedium koreanum*	Li et al. (1994a)
		Epimedium wanshanense	Li et al. (1996c)
		Epimedium brevicornum	Guo et al. (1996c)
		Epimedium sagittatum	Mizuno et al. (1988a)
34	Sagittatoside C	*Epimedium sagittatum*	Mizuno et al. (1988a)
35	Sagittasine A	*Epimedium sagittatum*	Mizuno et al. (1988a)
			Wang et al. (2007)
36	Sagittasine B	*Epimedium sagittatum*	Mizuno et al. (1988a)
			Wang et al. (2007)
37	Sagittasine C	*Epimedium sagittatum*	Mizuno et al. (1988a)
			Wang et al. (2007)
38	Diphylloside A	*Epimedium koreanum*	Li et al. (1994a)
		Epimedium wanshanense	Li et al. (1996a)
39	Diphylloside B	*Epimedium diphyllum*	Mizuno et al. (1988b)
		Epimedium wanshanense	Li et al. (1996a)
		Epimedium acuminatum	Jia et al. (1998)
40	Diphylloside C (Ikarisosids C)	*Epimedium fargesii*	Guo et al. (1996a)
		Epimedium brevicornum	Guo et al. (1996c)
		Epimedium acuminatum	Jia et al. (1998)
		Epimedium grandiflorum	Fukai and Nomura (1988)
		Epimedium sempervirens	Mizuno et al. (1989)
		Epimedium diphyllum	
41	Ikarisoside A (Baohuoside II)	*Epimedium acuminatum*	Dong et al. (1994)
		Epimedium leptorrhizum	Han et al. (2002b)
		Epimedium wanshanense	Li et al. (1996d)
		Epimedium grandiflorum	Fukai and Nomura (1988)
		Epimedium sempervirens	Li et al. (1994b)
		Epimedium koreanum	Xu and Yang (2005)
		Epimedium truncatum	Guo et al. (1996c)
		Epimedium brevicornum	
42	2″-O-rhamnosy-likarisoside A	*Epimedium koreanum*	Kang et al. (1991)
		Epimedium wanshanense	Li et al. (1996d)
		Epimedium acuminatum	Jia et al. (1998)
43	Ikarisoside B	*Epimedium leptorrhizum*	Jia et al. (1999)
		Epimedium wanshanense	Li et al. (1996d)
		Epimedium acuminatum	Jia et al. (1998)
		Epimedium grandiflorum	Fukai and Nomura (1988)
44	Ikarisoside D	*Epimedium grandiflorum*	Fukai and Nomura (1988)
45	Ikarisoside E	*Epimedium grandiflorum*	Fukai and Nomura (1988)
		Epimedium sempervirens	
46	Ikarisoside F	*Epimedium koreanum*	Li et al. (1994a)
		Epimedium brevicornum	Guo et al. (1996c)
		Epimedium grandiflorum	Fukai and Nomura (1988)
47	Baohuosu	*Epimedium koreanum*	Li and Liu (1988b)
48	Baohuoside III	*Epimedium davidii*	Li and Liu (1988a)
		Epimedium truncatum	Xu and Yang (2005)
49	Baohuoside IV	*Epimedium koreanum*	Zhao (2001)
50	Baohuoside V	*Epimedium davidii*	Li and Liu (1988a)
		Epimedium truncatum	Xu and Yang (2005)
51	Baohuoside VI	*Epimedium davidii*	Li and Liu (1988b)
		Epimedium pubescens	Li (1992)
		Epimedium breviconu	Yan et al. (1998)
52	Baohoside VII	*Epimedium koreanum*	Li and Liu (1988b)
53	8-Isoprenylkaempferol	*Epimedium koreanum*	Sun et al. (1998b)
			Sun et al. (1998a)

Table 4 (*Continued*)

No.	Compounds	Species	References
54	8-Prenylkaempferol-4′-methylether-3-[xylpsyl(1–4)rhamnoside]-7-glucoside	*Epimedium wushanense*	Li and Liu (1990a)
55	Breviflavone A	*Epimedium brevicornu*	Yap et al. (2005) Shen et al. (2007)
56	Breviflavone B	*Epimedium brevicornu*	Yap et al. (2005) Shen et al. (2007)
57	Rouhuoside	*Epimedium wushanense* *Epimedium pubescens*	Zhou et al. (2005) Li and Liu (1990b)
58	Korepimedoside A	*Epimedium koreanum*	Sun et al. (1995a)
59	Korepimedoside B	*Epimedium koreanum*	Sun et al. (1996b)
60	Korepimedoside C	*Epimedium koreanum*	Sun et al. (1998a) Sun et al. (1998c)
61	Sempervirenoside A	*Epimedium sempervirens*	Mizuno et al. (1988c)
62	Sempervirenoside B	*Epimedium sempervirens*	Mizuno et al. (1990)
63	Cuhuoside	*Epimedium acuminatu*	Liang et al. (1993)
64	Caohuoside A (Epimedin L)	*Epimedium koreanum*	Li et al. (1996f) Wang et al. (2010a,b)
65	Caohuoside B	*Epimedium koreanum*	Li et al. (1995d)
66	Caohuoside C	*Epimedium koreanum*	Li (1995)
67	Caohuoside E	*Epimedium koreanum*	Li et al. (1995e)
68	Hexandraside E	*Epimedium koreanum* *Epimedium breviconu*	Zheng and Kong (2002) Yan et al. (1998)
69	Hexandraside F	*Epimedium sagittatum*	Wang and Geng (2005)
70	Maohuosides A	*Epimedium platyetalum*	Wang et al. (2002a,b)
71	Maohuosides B	*Epimedium platyetalum*	Wang et al. (2002a,b)
72	Acuminatoside	*Epimedium acuminatum*	Hu et al. (1992a)
73	Platypetaloside A	*Epimedium platyetalum*	Zhu et al. (1993)
74	3,5,7-Trihydroxyl-4′methoxyl-8-prenylflavone-3-O-α-L-rhamnopyranosyl-(1–2)-α-L-rhamnopyranoside	*Epimedium koreanum*	Li et al. (1994a)
6-Prenyl-flavonoids			
75	Wushanicariin	*Epimedium breviconu*	Liang et al. (1988) Yan et al. (1998)
8-(2,3-Substituent group)-butyl flavonoids			
76	Caohuoside D	*Epimedium koreanum*	Li et al. (1995f)
77	Caohuoside F	*Epimedium koreanum*	Li and Song (2006)
78	Icaritin	*Epimedium koreanum*	Li et al. (1995a)
79	Icaritin-3-O-rhamnopyranoside	*Epimedium koreanum*	Li et al. (1994a)
80	Icaritin-3-O-rhamnoside	*Epimedium breviconu*	Wang et al. (2005b)
81	Wanepimedoside A	*Epimedium wanshanense*	Li et al. (1996d)
82	Brevicornin	*Epimedium brevicornum.*	Guo et al. (1996b)
7,8-Prenyl-lactone flavonoids(y-dimethyl-chromene flavonoids)			
83	Ikarisoside	*Epimedium koreanum*	Zhao (2001)
84	Acuminatin	*Epimedium koreanum* *Epimedium acuminatum*	Sun et al. (1998d) Hu et al. (1992b)
85	Acumination	*Epimedium acuminatum*	Zhao (2001)
86	Sutchuenmedin A	*Epimedium sutchuenense*	Mizuno et al. (1991) Yu et al. (2009)
87	Sutchuenmedin B	*Epimedium sutchuenense*	Yu et al. (2009)
88	Sutchuenoside A	*Epimedium sutchuenense*	Song et al. (2009)
89	Sutchuenoside B	*Epimedium sutchuenense*	Song et al. (2009)
Biflavone			
90	Ginkgetin	*Epimedium koreanum*	Sun et al. (1998b) Sun et al. (1998a)
91	Isoginkgetin	*Epimedium koreanum*	Sun et al. (1998b) Sun et al. (1998a)
92	Bilobetin	*Epimedium koreanum*	Sun et al. (1998b) Sun et al. (1998a)
Other flavonoids			
93	Neoicariin	*Epimedium sagittatum*	Yao et al. (2004)
94	Yinyanghuo A	*Epimedium sagittatum*	Chen et al. (1996)
95	Yinyanghuo B	*Epimedium sagittatum*	Chen et al. (1996)
96	Yinyanghuo C	*Epimedium sagittatum*	Chen et al. (1996)
97	Yinyanghuo D	*Epimedium sagittatum*	Chen et al. (1996)
98	Yinyanghuo E	*Epimedium sagittatum*	Chen et al. (1996)
99	Yinyanghuo F	*Epimedium sagittatum*	Huang et al. (1993)
100	Yinyanghuo G	*Epimedium sagittatum*	Huang et al. (1993)
101	Yinyanghuo H	*Epimedium sagittatum*	Huang et al. (1993)
102	Sutchuenoside	*Epimedium sutchuenense*	Zhao (2001)
103	Kaempferol-3-dirhamnoside	*Epimedium truncatum* *Epimedium breviconu*	Xu and Yang (2005) Yang et al. (2009a)
104	Kaempferol-3-O-β-D-gatactoside	*Epimedium koreanum*	Li et al. (1994b)
105	Kaempferol-3,7-O-α-L-dirhamnoside	*Epimedium breviconu*	Yan et al. (1998)
106	Kaempferol-3-O-alpha-L-rhamnopyranoside	*Epimedium acuminatum*	Hu et al. (1992a)
107	Kaempferol-3-O-(2″-E-p-coumaroyl,4″-Z-p-coumaroyl)-a-L-rhamnopyranoside	*Epimedium sagittatum*	Wang et al. (2007)
108	Kaempferol-3-O-(3″-Z-p-coumaroyl,4″-E-p-coumaroyl)-a-L-rhamnopyranoside	*Epimedium sagittatum*	Wang et al. (2007)

Table 4 (*Continued*)

No.	Compounds	Species	References
109	Kaempferol-3-O-(2″,4″-di-Ep-coumaroyl)-a-L-rhamnopyranoside	*Epimedium sagittatum*	Wang et al. (2007)
110	Kaempferol-3-O-(2″-Z-p-coumaroyl,4″-E-p-coumaroyl)-a-L-rhamnopyranoside	*Epimedium sagittatum*	Wang et al. (2007)
111	Kaempferol-3-O-(3″,4″-di-E-p-coumaroyl)-a-L-rhamnopyranoside	*Epimedium sagittatum*	Wang et al. (2007)
112	(2R,3R)-dihydrokaempferol-4′-O-b-D-glucopyranoside	*Epimedium sagittatum*	Wang et al. (2007)
113	Quercetin	*Epimedium koreanum*	Li et al. (1995a)
		Epimedium wanshanense	Li et al. (1996d)
114	Isoquercetin	*Epimedium sagittatum*	Wang et al. (2007)
115	Quercetin-3-O-a-L-rhamnoside	*Epimedium sagittatum*	Wang et al. (2007)
116	Quercetin-3-O-b-D-galactoside	*Epimedium sagittatum*	Wang et al. (2007)
117	Quercetin-3-O-a-L-rhamnopyranosyl(1–2)-a-L-rhamnopyranoside	*Epimedium sagittatum*	Wang et al. (2007)
118	Hyperin	*Epimedium fargesii*	Guo et al. (1996a)
		Epimedium truncatum	Xu and Yang (2005)
		Epimedium koreanum	Sun et al. (1995a)
119	Hyperoside	*Epimedium koreanum*	Li et al. (1995a)
		Epimedium brevicornu	Li et al. (2005a,b)
120	Tricin	*Epimedium koreanum*	Li et al. (1995g)
		Epimedium brevicornu	Guo et al. (1996b)
121	Tricetin-3′,5′-dimethyl ether	*Epimedium sagittatum*	Wang et al. (2007)
122	Tricetin-3′-methyl ether	*Epimedium sagittatum*	Wang et al. (2007)
123	5,7,4′-Trihydroxy-30-(2-hydroxy-3-methylbut-4-enyl)flavone	*Epimedium sagittatum*	Wang et al. (2007)
124	5-Hydroxy-6,7-dimethoxy-3′,4′-methylene-dioxyflavone	*Epimedium sagittatum*	Li et al. (1995d)
125	3,5,7,4′-Tetrahydroxyl-8-isopentene-flavonoids-3-O-α-L-rhamnopyranoside	*Epimedium breviconu*	Yang et al. (2009b)
126	5,7,4′-Trihydroxy-8,3′-diprenylflavone	*Epimedium breviconu*	Yang et al. (2009a)
127	Luteolin	*Epimedium koreanum*	Li et al. (1994b)
128	Astragalin	*Epimedium koreanum*	Li et al. (1994a)
129	Liquiritigenin	*Epimedium koreanum*	Li et al. (1995g)
130	Hydnocarpin	*Epimedium sagittatum*	Wang et al. (2007)
131	5″-Methoxyhydnocarpin	*Epimedium sagittatum*	Wang et al. (2007)
132	Hydnocarpin-D	*Epimedium sagittatum*	Wang et al. (2007)
133	Methoxyhydnocarpin-D	*Epimedium sagittatum*	Wang et al. (2007)
134	5′,5″-Dimethoxyhydnocarpin-D	*Epimedium sagittatum*	Wang et al. (2007)
135	2-(β-Hydroxyphenoxy)-5,7-dihydroxy-6-prenylchromone	*Epimedium koreanum*	Sun et al. (1998a)
136	Sagittin	*Epimedium sagittatum*	Wu et al. (1995)
137	Anthocyanin	*Epimedium grandiflorum*	Yoshitama (1984)
138	Cayratinin	*Epimedium grandiflorum*	Yoshitama (1984)
139	Eyanidin 3-p-coumaroylsophoroside	*Epimedium grandiflorum*	Yoshitama (1984)
140	Apigenin	*Epimedium sagittatum*	Wang et al. (2007)
141	Daidzein	*Epimedium sutchuenense*	Song et al. (2009)
Lignins			
142	Icariside E1	*Epimedium grandiflorum*	Miyaes et al. (1987a)
143	Icariside E2	*Epimedium grandiflorum*	Miyaes et al. (1987a)
144	Icariside E3	*Epimedium grandiflorum*	Miyaes et al. (1988)
145	Icariside E4	*Epimedium diphyllum*	Miyase and Ueno (1991)
146	Icariside E5	*Epimedium diphyllum*	Miyase and Ueno (1991)
147	Icariside E6	*Epimedium sagittatum*	Matsushita et al. (1991)
148	Icariside E7	*Epimedium sagittatum*	Matsushita et al. (1991)
149	Icariols A1	*Epimedium sagittatum*	Matsushita et al. (1991)
150	Icariols A2	*Epimedium sagittatum*	Matsushita et al. (1991)
151	Icariresinol-4′-β-D-glucopyranoside	*Epimedium leptorrhizum*	Han et al. (2002a)
		Epimedium grandiflorum	Tokuoka et al. (1975d)
152	(+)Syringaresinol-O-β-D-glucoside	*Epimedium grandiflorum*	Miyaes et al. (1987a)
153	3,5-Demethoxy-syringaresinol-glucoside	*Epimedium sagittatum*	Matsushita et al. (1991)
154	Liriodendrin	*Epimedium grandiflorum*	Miyaes et al. (1987a)
155	(−)-Olivil	*Epimedium sagittatum*	Matsushita et al. (1991)
		Epimedium grandiflorum	Tokuoka et al. (1975d)
156	(−)-Olivil-4″-O-β-D-glucopyranoside	*Epimedium grandiflorum*	Miyaes et al. (1987a)
157	Dihydrodehdrodiconiferyl alcohol-4′glucoside	*Epimedium diphyllum*	Miyase and Ueno (1991)
158	(+)-Cycloolivil	*Epimedium diphyllum*	Miyase and Ueno (1991)
		Epimedium koreanum	Zheng and Kong (2002)
		Epimedium breviconu	Yang et al. (2009b)
159	(+)-Lyoniresinol-3-O-xyloside	*Epimedium diphyllum*	Miyase and Ueno (1991)
160	(−)-Lyoniresinol-3-O-xyloside	*Epimedium diphyllum*	Miyase and Ueno (1991)
161	EL1	*Epimedium sagittatum*	Matsushita et al. (1991)
162	EL2	*Epimedium sagittatum*	Matsushita et al. (1991)
163	EL3	*Epimedium grandiflorum*	Miyaes et al. (1987a)
164	EL4	*Epimedium grandiflorum*	Miyaes et al. (1987a)
165	EL5	*Epimedium grandiflorum*	Miyaes et al. (1987a)
166	EL6	*Epimedium diphyllum*	Miyase and Ueno (1991)
167	EL7	*Epimedium grandiflorum*	Miyaes et al. (1987a)
168	EL8	*Epimedium diphyllum*	Miyase and Ueno (1991)

Table 4 (*Continued*)

No.	Compounds	Species	References
169	EL9	*Epimedium sagittatum*	Matsushita et al. (1991)
EL1–EL6: 1-(4-hydroxy-3-methoxyphenyl-2-[4-(3-hydroxypropyl)-2-methoxyphenoxyl]-1,3-propan-ediol and its rhamnoside or glucoside			
EL7–EL8: 1-(4-hydroxy-3-methoxyphenyl-2-[4-(3-rahmnopyranoxypropyl)-2-hydroxrphenoxyl]-1,3-pr-opanediol			
EL9: 1-(4-hydroxy-3,5-dimethoxyphenyl-2-[4-(3-hydroxrphenoxyl)-2,6-dimethoxyphenyl]-1,3-propanediol			
170	(+)-Dihydro-dehydrodiconiferyl alcohol-4-O-β-D-glucopyranoside	*Epimedium sagittatum*	Wang et al. (2007)
171	(7R, 8S)-4,9-dihydroxyl-3,3′-dimethyoxyl-7,8-dihydrobenzofunan-1′-propanolneolignan-9′-O-α-L-rhamnopyranoside	*Epimedium breviconu*	Yang et al. (2009b)
172	(7R, 8S, 8′R)-4,4′,8′,9-tetrahydroxyl-3,3′-dimethyoxyl-7,9′-monoepoxylignan	*Epimedium breviconu*	Yang et al. (2009b)
Ionones			
173	Icariside B_1	*Epimedium grandiflorum*	Miyaes et al. (1987b)
		Epimedium diphyllum	Miyase and Ueno (1991)
174	Icariside B_2	*Epimedium grandiflorum*	Miyaes et al. (1987b)
		Epimedium sagittatum	Matsushita et al. (1991)
		Epimedium diphyllum	Miyase and Ueno (1991)
175	Icariside B_3	*Epimedium grandiflorum*	Miyaes et al. (1987a)
176	Icariside B_4	*Epimedium grandiflorum*	Miyaes et al. (1987a)
177	Icariside B_5	*Epimedium grandiflorum*	Miyaes et al. (1988)
178	Icariside B_6	*Epimedium grandiflorum*	Miyaes et al. (1988)
179	Icariside B_7	*Epimedium grandiflorum*	Miyaes et al. (1988)
180	Icariside B_8	*Epimedium sagittatum*	Matsushita et al. (1991)
		Epimedium diphyllum	Miyase et al. (1989)
181	Icariside B_9	*Epimedium sagittatum*	Matsushita et al. (1991)
182	Icariside B_{10}	*Epimedium grandiflorum*	Miyase and Ueno (1991)
183	Blumenol C glucoside	*Epimedium grandiflorum*	Miyaes et al. (1988)
184	Roseside	*Epimedium grandiflorum*	Miyaes et al. (1987a)
Phenols glycosides			
185	Icariside A_1	*Epimedium grandiflorum*	Miyaes et al. (1987b)
		Epimedium sagittatum	Matsushita et al. (1991)
186	Icariside A_2	*Epimedium grandiflorum*	Miyaes et al. (1988)
187	Icariside A_3	*Epimedium grandiflorum*	Miyaes et al. (1988)
188	Icariside A_4	*Epimedium grandiflorum*	Miyase et al. (1989)
189	Icariside A_5	*Epimedium grandiflorum*	Miyase and Ueno (1991)
190	Icariside A_6	*Epimedium grandiflorum*	Miyase et al. (1989)
191	Icariside A_7	*Epimedium koreanum*	Sun et al. (1998b)
192	Epimedoicarisoside A	*Epimedium koreanum*	Li et al. (1995b)
193	Icarisoside A	*Epimedium wushanense*	Xie et al. (2007)
Phenylethanoid glycosides			
194	Phenethyl glucoside	*Epimedium grandiflorum*	Miyaes et al. (1988)
		Epimedium sagittatum	Matsushita et al. (1991)
195	Ikarisoside D_1	*Epimedium grandiflorum*	Miyaes et al. (1987a)
		Epimedium diphyllum	Miyase and Ueno (1991)
196	Ikarisoside D_2	*Epimedium diphyllum*	Miyase and Ueno (1991)
197	Ikarisoside D_3	*Epimedium sagittatum*	Matsushita et al. (1991)
198	Salidroside	*Epimedium grandiflorum*	Miyaes et al. (1987b)
		Epimedium diphyllum	Miyase and Ueno (1991)
		Epimedium koreanum	Sun et al. (1998d)
		Epimedium breviconu	Yang et al. (2009a)
199	Thalictoside	*Epimedium grandiflorum*	Miyaes et al. (1987b)
		Epimedium diphyllum	Miyase and Ueno (1991)
		Epimedium leptorrhizum	Jia et al. (1999)
		Epimedium hunanense	Liang et al. (1997)
Sesquiterpenes			
200	Icariside C_1	*Epimedium grandiflorurn*	Miyaes et al. (1987b)
		Epimedium koreanum	Chen and Zhang (2005)
201	Icariside C_2	*Epimedium grandiflorum*	Miyaes et al. (1987b)
202	Icariside C_3	*Epimedium grandiflorum*	Miyaes et al. (1987b)
203	Icariside C_4	*Epimedium grandiflorum*	Miyaes et al. (1987b)
204	Icariside F	*Epimedium koreanum*	Chen and Zhang (2005)
Others compounds			
205	Icariside A_1	*Epimedium koreanum*	Sun et al. (1995a)
206	Ikarisoside F_1	*Epimedium grandiflorum*	Miyaes et al. (1988)
207	Ikarisoside F_2	*Epimedium grandiflorum*	Miyaes et al. (1988)
		Epimedium diphyllum	Miyase and Ueno (1991)
208	Ikarisoside G_1	*Epimedium grandiflorum*	Miyaes et al. (1988)
209	Icariside H_1	*Epimedium grandiflorum*	Matsushita et al. (1991)
210	6-Demethoxy-7-methylcapillarisin	*Epimedium sagittatum*	Huang et al. (1993)
211	6-Demethoxy-4′-methyl-8-isopentenylcapillarisin	*Epimedium sagittatum*	Huang et al. (1993)
212	6-Demethoxy-7-isopentenylcapillarisin	*Epimedium sagittatum*	Huang et al. (1993)
213	Syringin	*Epimedium diphyllum*	Miyase and Ueno (1991)
214	Isoliquiritigenin	*Epimedium koreanum*	Li et al. (1994b)
215	Emodin	*Epimedium koreanum*	Li et al. (1995g)
216	(Z)-3-hexenyl glucoside	*Epimedium grandiflorum*	Miyaes et al. (1988)
		Epimedium diphyllum	Miyase and Ueno (1991)

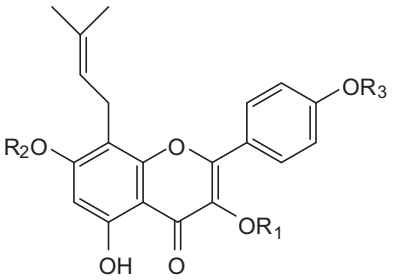
Table 4 (*Continued*)

No.	Compounds	Species	References
217	3,7,11-Trimethyl-2,6-dodecadien-1,10,11-trihydroxyl-10 (S)-O-β-D-glucopyranoside	*Epimedium koreanum*	Chen and Zhang (2005)
218	1,2-Bis-(4-hydroxy-3-methoxyphenyl)-propane-1,3-diol	*Epimedium grandiflorum*	Matsushita et al. (1991)
219	Maltol	*Epimedium koreanum*	Sun et al. (1995a) Sun et al. (1998d)
220	Daucosterol	*Epimedium koreanum*	Li et al. (1995a)
221	Inositol	*Epimedium koreanum* *Epimedium brevicornu*	Zheng and Kong (2002) Li et al. (2005a,b)
222	β-Methoxyphenol	*Epimedium breviconu*	Wang et al. (2005b)
223	1,2,3,4-Tetrahydro-3,7-dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-6-methoxy-2,3-naphthalenedimethanol	*Epimedium koreanum*	Chen et al. (2006)
224	Aseicosanol	*Epimedium dewuense*	Yang et al. (2006)
225	β-Sitosterol	*Epimedium dewuense* *Epimedium sagittatum* *Epimedium leptorrhizum* *Epimedium breviconu*	Yang et al. (2006) Wu et al. (1995) Han et al. (2002b) Wang et al. (2005b) Yang et al. (2009b)
226	γ-Sitosterol	*Epimedium dewuense*	Yang et al. (2006)
227	Daucosterol	*Epimedium platyetalum* *Epimedium wanshanense* *Epimedium dewuense* *Epimedium breviconu* *Epimedium koreanum*	Wang et al. (2002a,b) Li et al. (1997a,b) Yang et al. (2006) Wang et al. (2005b) Li et al. (1995a)
228	6,22-Hopanediol	*Epimedium leptorrhizum*	Han et al. (2002b)
229	6-Hydroxy-11,12-dimethoxy-2,2-dimethyl-1,8-dioxo-1,3,4,8-tetrahydro-2H-7-oxa-2-azonia-benzo [c]phenanthrene	*Epimedium koreanum*	Liu et al. (2003)
230	Magnoflorine	*Epimedium koreanum*	Tomita and Ishii (1957a,b)
231	20-Hydroxydammar-24-en-3-one	*Epimedium dewuense*	Yang et al. (2006)
232	Artonin U	*Epimedium dewuense*	Yang et al. (2006)
233	Tritriacontane	*Epimedium leptorrhizum*	Han et al. (2002b)
234	β-Hydroxybenzaldehyde	*Epimedium breviconu*	Yang et al. (2009b)
235	Phydroxyphenethyl	*Epimedium breviconu*	Yang et al. (2009b)
236	Epimedokoreanone A	*Epimedium koreanum*	Li et al. (1996e)
237	1,3,5,8-Tetrahydroxy xanthone	*Epimedium breviconu*	Wang et al. (2005b)
238	1-Hydroxy-1,3,5,8-tetrahydroxy xanthone	*Epimedium breviconu*	Wang et al. (2005b)
239	5,7-Dihydroxy-2-(β-hydroxyphenoxy)-6-prenylchromone	*Epimedium koreanum*	Sun et al. (1998b)
240	2-Phenoxychromones	*Epimedium sagittatum*	Wang et al. (2007)
241	Chlorogenic	*Epimedium sagittatum*	Wang et al. (2007)
242	β-Coumaric	*Epimedium sagittatum*	Wang et al. (2007)
243	β-Hydroxy benzoic acid	*Epimedium koreanum*	Li et al. (1994b)
244	2,4-Dihydroxy benzoic acid	*Epimedium koreanum*	Li et al. (1994b)
245	Octadecylic acid	*Epimedium dewuense*	Yang et al. (2006)
246	Oleanolic acid	*Epimedium truncatum*	Xu and Yang (2005)
247	Succinic acid	*Epimedium breviconu*	Yang et al. (2009b)
248	Behenic acid	*Epimedium breviconu*	Wang et al. (2005b)
249	Caffeoyl-hexaric acid	*Epimedium koreanum*	Wang et al. (2010a,b)
250	Cis-3-O-caffeoylquinic acid	*Epimedium koreanum*	Wang et al. (2010a,b)
251	Trans-3-O-caffeoylquinic acid	*Epimedium koreanum*	Wang et al. (2010a,b)
252	Cis-3-O-p-coumaroylquinic acid	*Epimedium koreanum*	Wang et al. (2010a,b)
253	Cis-4-O-caffeoylquinic acid	*Epimedium koreanum*	Wang et al. (2010a,b)
254	Dimer of 5-O-caffeoylquinic acid	*Epimedium koreanum*	Wang et al. (2010a,b)
255	Trans-5-O-caffeoylquinic acid	*Epimedium koreanum*	Wang et al. (2010a,b)
256	Cis-5-O-caffeoylquinic acid	*Epimedium koreanum*	Wang et al. (2010a,b)
257	Trans-4-O-p-coumaroylquinic acid	*Epimedium koreanum*	Wang et al. (2010a,b)
258	Cis-5-O-p-coumaroylquinic acid	*Epimedium koreanum*	Wang et al. (2010a,b)
259	5-O-feruloylquinic acid	*Epimedium koreanum*	Wang et al. (2010a,b)
260	1-*O*-β-Glucopyransosyl-1,4-dihydroxy-2-(3′-hydroxy-3′-methyl butyl)benzene	*Epimedium breviconu*	Yang et al. (2009a)

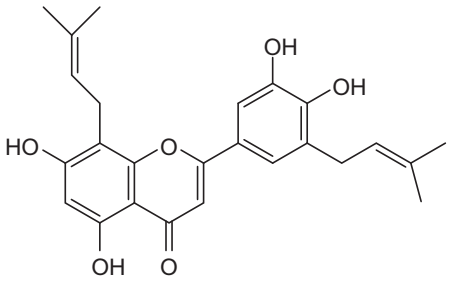
icaritin, desmethylicaritin, des-methylanhydroicaritin, icariside II, ikarisoside A, baohuoside-1, baohuoside II, epimedokoreanin B, breviflavone B, luteolin, hyperoside, epimedin B and epimedin C have been confirmed to possess *yang*-strengthening, estrogenic, antitumor, antioxidant, antiradiation, anti-inflammatory, anti-microbial, anti-hepatotoxic, cardiovascular, neuroprotective, anti-aging, anti-depressant, anxiolytic and other activities.

4.1. Flavonoids

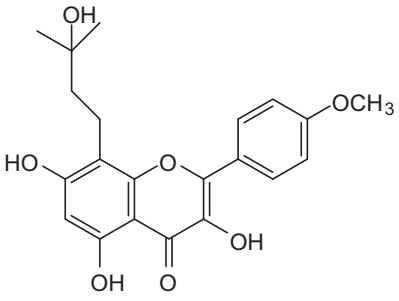
Flavonoids and their derivatives are important chemical components of the genus *Epimedium*; more than 141 flavonoids, including flavonol, flavone, chalcone, flavanone, and flavonol glycoside, have been found from 17 *Epimedium* species (Table 4, Fig. 3). Of these flavonoids, 74 (1–74) were substituted with a pentenyl group at C-8, and the major active compounds were flavonol glycosides, in particular, 3-O-, 7-O- or 3,7-di-O-glycosides. The sugar moieties of the glycosides are usually glucose, rhamnose, xylose or their corresponding mono- or di-acetyl sugars (Wu et al., 2003a; Zhao et al., 2008b). The best-known and most thoroughly phytochemically characterized *Epimedium* species are *Epimedium koreanum*, *Epimedium sagittatum*, *Epimedium brevicornum* and *Epimedium grandiflorum*. The chemical constituents of *Epimedium dewuense*, *Epimedium leptorrhizum*, *Epimedium*



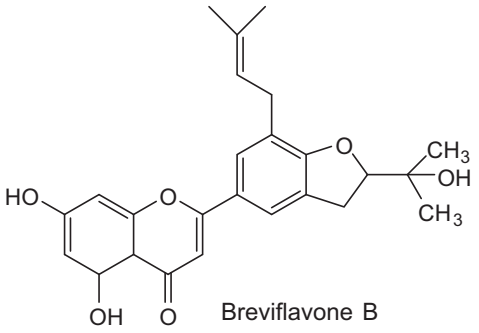
Name	R_1	R_2	R_3
Icariin	Rha	Glc-Glc	Me
Epimedin B	Rha-Xyl	Glc	Me
Epimedin C	Rha-Rha	Glc	Me
Diphylloside A	Rha-Glc	Glc	H
Desmethylicaritin	Rha	Glc	H
Desmethylanhydro-icaritin	H	H	H
Baohuoside II (Icariside II)	H	Glc	Me
Baohuoside II (Ikarisoside A)	Rha	H	H



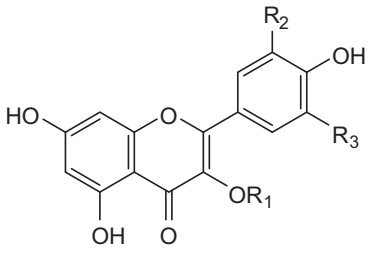
Epimedokoreanin B



icaritin



Breviflavone B



Name	R_1	R_2	R_3
Luteolin	Rha-Glc	H	OH
Hyperoside	Glc	OH	H

Fig. 2. The chemical structure of some activities compounds from the genus *Epimedium*.

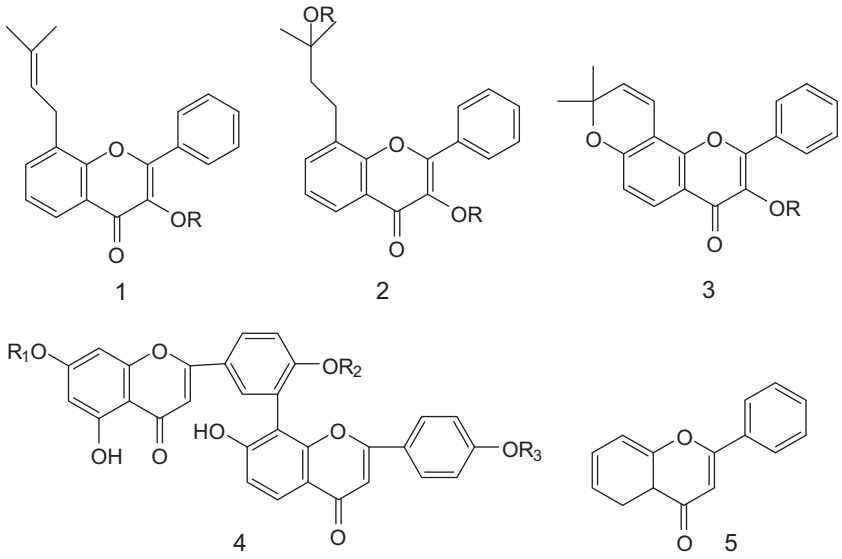


Fig. 3. The parent nucleus structure of the flavonoids.

wanshanense, *Epimedium platyetalum*, *Epimedium diphyllum*, *Epimedium hunanense*, *Epimedium wushanense*, *Epimedium sutchuenense*, *Epimedium acuminatum*, *Epimedium truncatum*, *Epimedium pubescens*, *Epimedium davidii* and *Epimedium fargesii* have also been determined. However, the phytochemical knowledge about *Epimedium myrianthum*, *Epimedium dewuense*, *Epimedium platyetalum*, *Epimedium hunanense* and *Epimedium davidii* is far from adequate, even though these species are frequently used in the practice of TCM.

4.2. Lignans

Lignans are a class of secondary metabolites, consisting of two phenyl-propanoid molecules connected by 8–8′ carbon atoms. Thirty-one lignans and their glycosides have been identified from the genus *Epimedium*. Ikarisoside E_1, ikarisoside E_2, ikarisoside E_3, (+)syringaresinol-O-β-D-glucoside, (−)-olivil-4″-O-β-D-glucopyranoside, EL3, EL4, EL5 and EL7 were obtained and identified from *Epimedium grandiflorum* (Miyaes et al., 1987a, 1988). In 1991, ikarisoside E_4, ikarisoside E_5, dihydrodehydrodiconiferyl alcohol-4′glucoside, (+)-lyoniresinol-3-O-xyloside, (−)-lyoniresinol-3-O-xyloside, EL6 and EL8 were isolated from *Epimedium diphyllum* (Miyase and Ueno, 1991). Ikarisoside E_6, ikarisoside E_7, icariol A_1, icariol A_2, 3, 5-demethoxy-syringaresinol-glucoside, (−)-olivil, EL1, EL2, EL9 and (+)-dihydro-dehydrodiconiferyl alcohol-4-O-β-D-glucopyranoside were isolated from *Epimedium sagittatum* (Sieb. & Zucc.) Maxim. (Matsushita et al., 1991; Wang et al., 2007). In addition, (+)-cycloolivil was isolated from *Epimedium diphyllum*, *Epimedium koreanum* and *Epimedium brevicornum* (Miyase and Ueno, 1991; Zheng and Kong, 2002; Yang et al., 2009b).

4.3. Ionones

Twelve ionones and their derivatives were isolated and identified from the genus *Epimedium*. Ikarisoside B_1, an amorphous powder, was obtained from an extract of the aerial parts of *Epimedium grandiflorum* and *Epimedium diphyllum* and identified by chemical and spectroscopic evidence (Miyaes et al., 1987b; Miyase and Ueno, 1991). Ikarisoside B_2, which forms colorless needles (mp 172.5–174.0 °C), was isolated from aerial parts of *Epimedium grandiflorum*, *Epimedium sagittatum* and *Epimedium diphyllum* (Miyaes et al., 1987b; Matsushita et al., 1991; Miyase and Ueno, 1991); ikarisoside B_3 (colorless needles), ikarisoside B_4 (amorphous powder), ikarisoside B_5 (amorphous powder), ikarisoside B_6 (colorless needles, mp 143–144 °C), ikarisoside B_7 (colorless needles, mp 202–203 °C), ikarisoside B_{10}, blumenol C glucoside and roseside were obtained from aerial parts of *Epimedium grandiflorum* (Miyaes et al., 1987a; Miyaes et al., 1988; Miyase and Ueno, 1991). Ikarisoside B_8 and ikarisoside B_9 were isolated from aerial parts of *Epimedium sagittatum* (Hiroyuki et al., 1991), and ikarisoside B_8 was also obtained from *Epimedium diphyllum* (Miyase and Ueno, 1991).

4.4. Phenol glycosides

In 1987, Miyaes et al. first isolated a phenol glycoside, ikarisoside A_1 (colorless needles, mp 220–222 °C), from *Epimedium grandiflorum* (Miyaes et al., 1987b). In 1988, 1989 and 1991, Miyaes et al. obtained five more of these compounds, ikarisoside A_2 (amorphous powder), ikarisoside A_3 (amorphous powder), ikarisoside A_4, ikarisoside A_5 and ikarisoside A_6, from *Epimedium grandiflorum* (Miyaes et al., 1988; Miyase et al., 1989; Miyase and Ueno, 1991). In addition, icariside A_7 and epimedoicarisoside A were isolated from *Epimedium koreanum* (Sun et al., 1995b; Li et al., 1995b).

4.5. Phenethyl alcohol glycosides

So far, only six phenethyl alcohol glycosides have been identified from the genus *Epimedium*. Phenethyl glucoside was obtained from *Epimedium grandiflorum* and *Epimedium sagittatum* (Sieb. & Zucc.) Maxim. (Miyaes et al., 1988; Matsushita et al., 1991), ikarisoside D_1 was obtained from *Epimedium grandiflorum* and *Epimedium diphyllum*, and ikarisoside D_2 and ikarisoside D_3 were obtained from *Epimedium diphyllum* and *Epimedium sagittatum* (Sieb. & Zucc.) Maxim., respectively (Miyase and Ueno, 1991; Matsushita et al., 1991). In addition, salidroside and thalictoside were isolated from several *Epimedium* plants.

4.6. Sesquiterpenes

Sesquiterpenoids, a class of terpenes, are defined as the group of 15-carbon compounds derived from the assembly of three isoprenoid units and having the molecular formula $C_{15}H_{24}$. So far, five of these compounds have been purified and characterized from *Epimedium grandiflorum*, comprising ikarisoside C_1 (amorphous powder), ikarisoside C_2 (amorphous powder), ikarisoside C_3 (amorphous powder) and ikarisoside C_4 (amorphous powder) and icariside F (Miyaes et al., 1987b).

4.7. Other compounds

A range of other compounds has also been isolated from *Epimedium* plants along with the above-mentioned constituents, including acids, alkaloids, xanthones and aldehydes. In 1988, Miyaes et al. isolated three new glycosides, ikarisoside F_1, ikarisoside F_2 and ikarisoside G_1, together with two known glycosides, (*Z*)-3-hexenyl glucoside and phenethyl glucoside, from the water extract of *Epimedium grandiflorum*. Icariside H_1 and 1,2-bis-(4-hydroxy-3-methoxyphenyl)-propane-1,3 diol were also isolated from *Epimedium grandiflorum* in the following year (Hiroyuki et al., 1991). β-Hydroxy benzoic acid, 2,4-dihydroxy benzoic acid, maltol, emodin, daucosterol, insistol, icariside A_1, magnoflorine and 1,2,3,4-tetrahydro-3,7-dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-6-methoxy-2,3-naphthalenedimethanol were obtained from *Epimedium koreanum* Nakai. In 2006, seven compounds, aseicosanol, octadecylic acid, 20-hydroxydammar-24-en-3-one, artonin U, β-sitosterol, daucosterol and γ-sitosterol, were isolated from *Epimedium dewuense*. β-Sitosterol was also isolated from *Epimedium sagittatum* (Sieb. & Zucc.) Maxim., *Epimedium leptorrhizum* and *Epimedium brevicornum*. (7R, 8S)-4, 9-dihydroxyl-3,3′-dimethyoxyl-7,8-dihydrobenzofunan-1′-propanolneo-lignan-9′-O-α-L-rhamnopyranoside, (7R,8S,8′R)4, 4′,8′,9tetrahydroxyl3,3′-dimethyoxyl7,9′-monoepoxylignan, p-hydroxybenzaldehyde, succinic acid, p-hydroxyphenethyl, 1,3,5,8-tetrahydroxy xanthone, 1-hydroxy-1,3,5,8-tetrahydroxy xanthone, β-methoxyphenol and behenic acid were isolated from *Epimedium brevicornum*. In addition, 2-phenoxychromones, p-coumaric acid and chlorogenic acid were purified and characterized from *Epimedium sagittatum* (Sieb. & Zucc.) Maxim.

5. Methods of quality control

Flavonoids are thought to be the major active components in *Epimedium*. The major flavonoid compounds icariin, epimedin A, epimedin B, and epimedin C are frequently used as quality control markers for *Epimedium* and its medicinal extracts (Table 5) (Liu et al., 2006a). In 2003, icariin and epimedin C from four samples of *Epimedium brevicornum* Maxim., *Epimedium sagittatum* (Sieb. & Zucc.) Maxim., *Epimedium pubescens* Maxim and *Epimedium koreanum* Nakai were analyzed by high-performance liquid chromatography (HPLC) to determine the differences between the

Table 5
Main compound content in some Chinese *Epimedium* species.

Plant	Icariin	Epimedin B	Epimedin C	Sagittatoside B	Baohuoside I	Totally
Epimedium sagittatum	Trace–1.34	Trace–0.78	0.07–4.02	0.05–0.80	0.06–0.33	0.67–7.07
Epimedium brevicornu	0.63–1.18	0.17–2.01	1.09–1.19	0.09–0.11	0.08–0.09	2.76–4.58
Epimedium acuntinatum	0.44–0.86	0.32–1.16	1.65–2.34	0.19–0.93	Trace–0.24	2.89–4.77
Epimedium koreanum	1.55–3.69	0.85–1.24	0.49–0.89	0.25–0.51	0.90–1.04	4.59–7.37
Epimedium pubescens	0.41–1.40	0.74–1.28	1.14–1.76	0.06–0.68	0.12–0.65	3.47–4.77
Epimedium leptorrhizum	Trace		Trace–0.14	Trace	Trace	Trace
Epimedium wushanense	0.46–0.64	0.30–0.40	2.88–3.34	0.10–0.28	0.06–0.13	3.80–4.79

Mdideanetph (2010), http://www.mdidea.net/products/herbextract/icariin/data10.html.

official source herbs listed in the Chinese Pharmacopoeia. In this study, icariin and epimedin C were measured with a Hypersil BDS-C18 column and gradient elution (acetonitrile and water containing 0.05% phosphoric acid) at a flow rate of 1.0 ml/min. The detection wavelength was 272 nm. The icariin contents of *Epimedium brevicornum*, *Epimedium sagittatum* (Sieb. & Zucc.) Maxim., *Epimedium pubescens* and *Epimedium koreanum* were 1.71%, 2.24%, 0.73% and 0.83%, respectively. The contents of epimedin C were 1.52%, 0.58%, 0.19%, 1.36% and 2.27%, respectively (Wang et al., 2003a). Thus, the determination of the major flavonoids is required for the evaluation of the quality of each species and the control of dosage during clinical studies. So far, a variety of methods, including UV spectrophotometry, thin-layer chromatography (TLC), HPLC (Ito et al., 1986), micellar electrokinetic chromatography (MEKC) (Liang et al., 1996), capillary zone electrophoresis (CZE) (Liu et al., 2006a), high-performance liquid chromatography-diode-array detector fingerprinting (HPLC-DAD) (Xie et al., 2010), high-performance liquid chromatography-mass spectrometer/mass spectrometer (HPLC-MS/MS) (Ying et al., 2004), high-performance liquid chromatography-electrospray ionization-mass spectrometer/mass spectrometer (HPLC-ESI-MS/MS) (Zhao et al., 2008a), pressurized liquid extraction (PLE) and ultra-performance liquid chromatography (UPLC) method (Chen et al., 2008), have been used to further study the flavonoids in *Epimedium*.

The interactions of multiple chemical compounds may contribute to the therapeutic effects of Chinese medicine. Therefore, the analysis of multiple components is necessary to control the quality of medicines. In 2007, a reliable PLE and HPLC method mentioned above was developed for the simultaneous determination of 15 flavonoids, namely icariin, epimedin A, epimedin B, epimedin C, hexandraside E, hexandraside F, epimedoside C, baohuoside I, baohuoside II, baohuoside VII, caohuoside C, sagittatoside A, sagittatoside B, 2″-*O*-rhamnosyl icariside II and kaempferol-3-*O*-rhamnoside, in different species of *Epimedium*. The analysis was performed with a Zorbax SB-C18 analytical column (250 mm × 4.6 mm, 5 μm) with a gradient elution of water and acetonitrile and diode-array detection (270 nm). All of the calibration curves showed good linearity ($r^2 > 0.9997$) within the test ranges (Chen et al., 2007a,b). In 2008, a rapid ultra-performance liquid chromatography (UPLC) method was developed for the simultaneous determination of the above 15 flavonoids in 17 species of *Epimedium*. The analysis was performed on Waters Acquity UPLC system with an acquity UPLC BEH C18 column (50 mm × 2.1 mm, 1.7 μm) and gradient elution of 50 mM acetic acid aqueous solution and acetonitrile within 12 min (Chen et al., 2008). In 2010, an efficient and new method was developed to enrich and identify the prenyl flavonoid glycosides and phenolic acids of *Epimedium* using UPLC combined with quadrupole time-of-flight mass spectrometry (UPLC–Q-TOF-MS) and a "click oligo (ethylene glycol)" (Click OEG) column. In this method, MS combined with selective enrichment provided a powerful means for analyzing prenyl flavonoid glycosides and phenolic acids in natural products (Wang et al., 2010a,b).

6. Biological activity

Epimedium pharmacological actions have attracted extensive attention. Orally, *Epimedium* has traditionally been used to treat impotence, involuntary ejaculation, sexual dysfunction, weak backs and knees, osteoarthritis, postmenopausal bone loss, osteoporosis, arthralgia, mental and physical fatigue, memory loss, hypertension, coronary heart disease, bronchitis, chronic hepatitis, HIV/AIDS, polio, chronic leukopenia and viral myocarditis. It is also used to arouse sexual desire.

In clinics, *Epimedium* is used to treat osteoporosis, climacteric period syndrome, breast lumps, hyperpiesia and coronary heart disease. *Epimedium* also has immunity-enhancing, anti-aging, anti-tumor and anti-AIDS pharmacological activities. Consequently, *Epimedium* has enormous potential for research and exploitation.

The major active constituents of Herba Epimedii are flavonoids, and among them, epimedin A, B, C and icariin are considered major bioactive components that make up more than 52% of the total flavonoids in Herba Epimedii (Zhang et al., 2008a,b,c,d). An overview on the current status of modern pharmacological evaluations is summarized in supplemental Table.

6.1. Treatment of sexual dysfunction (aphrodisiac, kidney tonic)

Epimedium plants are able to boost sexual activity by enhancing sexual arousal, increasing vitality and improving sperm counts *in vitro* and *in vivo*. For a long time, this remedy has been used to cure erectile dysfunction and other impotence conditions. The plants are also able to increase a man's power and sexual desire as well.

Many extracts of *Epimedium* plants have traditionally to reinforce the Kidney *Yang*, to treat "coldness" and male impotence (Li, 1991). For example, *Epimedium sagittatum* has been used to treat erectile dysfunction since the Han dynasty (202 BC–AD 220). Modern pharmacological studies have shown that phosphodiesterase-5 (PDE-5) is the target protein for inhibition to treat erectile dysfunction, and the major compounds of the herbs exhibited an inhibiting effect on PDE-5, based on the ligand–protein interaction observed a reliable multiple linear regression model (Chen, 2009). Intracavernous administration of 300–10,000 μg *Epimedium brevicornum* extract induced a penile erection in the rat, as measured by a significant increase in the intracavernous pressure (ICP) to 99.7 ± 0.3 mm Hg. Nitric oxide may be involved in this penile erection-inducing effect. No central nervous system effect of the extract appears to be present in the elicitation of penile erections in the rat (Chen and Chiu, 2006).

Epimedium extracts possess a male-hormone-like effect. Intragastric administration of an *Epimedium* decoction to rats, at a dose of 2.0 mg/kg body weight (bw) for 14 days, markedly improved sexual function, increased the weight of attached genitals and raised the content of testosterone in the plasma (Wang et al., 2001). The effect of glycosides from *Epimedium grandiflorum* on the growth of guinea pigs was investigated *in vivo*. The glycosides from *Epimedium grandiflorum* (5 g/kg) were fed to Netherlands guinea pigs for eight weeks, and the body weight and testicular

growth of the animals as well as the sperm density and viability in the epididymis and vice-testis viability were observed and measured. The administration of glycosidic fraction from *Epimedium grandiflorum*, at dosage of 5 g/kg for 8 weeks strongly increased the weights of the whole animal as well as those of the testicles, epididymis, adenohypophysis and seminal vesicles. The administration of this glycosides fraction stimulated the sensory nerves and generated specific physiological signs of sexual arousal (Luo, 1998). Intragastric administration of the total flavonoids from *Epimedium brevicornum*, at a dose of 150.0 mg/kg bw for 7 days, significantly increased the weight of the anterior pituitary gland, epididymis and seminal vesicles in juvenile rats, raised the testosterone, estradiol and luteinizing hormone levels and promoted testosterone secretion in rat stromal cells. These results indicated that the total flavonoids of *Epimedium brevicornum* promote the male reproductive system and reproductive endocrine activities (She et al., 2003). The aqueous extract (250 and 500 mg/ml) of *Epimedium brevicornum* improved the superoxide dismutase (SOD) vitality of sperm suspensions, reduced the malondialdehyde (MDA) content of sperm suspensions, ameliorated the injury of sperm membranes by reactive oxygen species to some extent and protected the function of sperm membranes. Thus, *Epimedium brevicornum* significantly protected the structure and function of sperm membranes by improving their SOD vitality and intervening in lipid peroxidation (Yang et al., 2007). *Epimedium* significantly improved the symptoms of "*Yang*-deficiency syndrome" induced by glucocorticoid and increased testosterone levels and oestradiol levels and reduced the level of luteinizing hormone. The results suggest that *Epimedium* facilitates the pituitary gland(s)-glandular system (Xu, 1996). The processed product of *Epimedium* significantly increased the level of testosterone in the plasma of mice and promoted the proliferation and secretion of testicular tissues. This action is similar to that of intramuscular testosterone, but no weight reduction of testicular tissue was observed (Niu, 1995). However, *Epimedium acuminatum*, *Epimedium stelluatum*, *Epimedium fargesii*, *Epimedium franchetii*, *Epimedium zhushanense* and *Epimedium leishanense* exhibited higher activities than estradiol on the estrogen receptors ERa (mean relative efficacy: 1.58 ± 0.25) and ERb (mean relative efficacy: 0.55 ± 0.20) (Shen et al., 2007).

In young mice, icariin has gonadotropin-like and male hormone-like effects; it significantly promotes the growth of the epididymis and seminal vesicles. This finding provides a prospect for the treatment of male infertility caused by low testosterone levels. In addition, researchers also found that icariin increased the weight of the seminal vesicles in mouse testes as well as promoted basal testosterone secretion and cAMP production in rat Leydig cells. This result provides a medical basis for the treatment of male infertility induced by a low level of testosterone (Tian and Yang, 2004). The penile erection-inducing effects of icariin (5 mg/kg) were assessed in rat arteriogenic erectile dysfunction; endothelial nitric oxide synthase (eNOS) expression and the cGMP concentration were used as the index of activity. Icariin significantly increased the expression of eNOS (Tian et al., 2004b) and the concentration of cGMP within the corpus cavernosum smooth muscle. These two signaling molecules induced the relaxation of corpus cavernosum smooth muscle and lead to the penile erection-inducing effect (Qiao et al., 2002). Icariin at a dose of 30–1000 μg/l also directly stimulated the granulosa cells to secrete estradiol and, at high doses, promoted the secretion of corticosterone by adrenal cortex cells to at high doses, suggesting that the reinforcing kidney and strengthening *yang* activities of *Epimedium* are related the direct stimulation of the target gland to secrete hormones (Li et al., 1997a,b). The inhibitory effects of icariin on PDE5 and PDE4 activities were investigated by a two-step radioisotope procedure with [(3)H]-cGMP/[(3)H]-cAMP, and the results indicated that icariin showed dose-dependent inhibitory effects on PDE5 and PDE4 activities. The IC_{50} of icariin on PDE5 was 0.432 μmol/l and on PDE4 was 73.50 μmol/l. *Epimedium* also contains essential trace elements, such as zinc, manganese and iron. These elements are implicated in male reproductive function and the development of human genitals (Song et al., 1993).

Like the drugs Viagra and Cialis, *Epimedium* may increase libido and improve erectile function through a variety of mechanisms, such as increased energy and increased production of testosterone and sexual hormones.

6.2. Effect on bone metabolism

Epimedium has been one of the most frequently used herbs in the prevention and treatment of osteoporosis in TCM. Experimental studies have shown systematic activities of *Epimedium* and its metabolites on bone metabolism, such as preventing calcium loss, stimulating the proliferation of osteoblasts, inhibiting bone resorption and promoting bone formation.

6.2.1. In vivo tests

The oral administration of total flavonoid extracts of *Epimedium* (50–200 mg/kg/day, for one month) to rats with osteoporosis can dramatically improve the femur dry weight, femoral ash weight and the calcium and phosphorus contents of bone, increase trabecular bone area and the thickness of the proximal tibia as well as increase the cortical bone area percentage in the middle section of the tibia (Ji et al., 2000; Ma et al., 2002a). The active ingredient of *Epimedium*, icariin, has been shown to activate the Na-K-ATP enzyme, reduce erythrocyte aggregation and whole-blood viscosity, inhibit vascular smooth-muscle extracellular Ca^{2+} influx and peripheral vascular expansion, increase blood flow and improve the structure and function of bone tissue.

Intragastric administration of 10 ml/kg/day water extract of *Epimedium* to rats with degenerated cervical vertebrae improved the calcium and phosphorus contents, increased the activity of the serum alkaline phosphatase, inhibited the formation of osteophytes, delayed cervical bone degeneration and prevented the degeneration of cervical bone (Zhao and Xu, 2008). Administration of a lyophilized aqueous extract of *Epimedium* at a dose of 500.0 mg/kg body weight (bw) to castrated male rats for 12 weeks significantly increased the bone mineral density ($P < 0.05$), osteoprotegerin level ($P < 0.05$) and decreased the microcrack percentage per unit trabecular area. *Epimedium* prevented the loss of bone mass and improve bone structure in castrated male rats (Wang and Liu, 2008). Intragastric administration of 5 g/(kg day) *Epimedium* to male rats with Kidney-*Yang* insufficiency induced by prednisone induced bone formation and helped rebuild the injured bone by increasing the serum BMP-7 content and up-regulating renal and femoral BMP-7 expression (Zhou et al., 2008).

In addition, *Epimedium* promoted the absorption of fracture hematomas, cartilage calcification, external callus bridging, callus conversion and growth, lamellar bone emergence, marrow recanalization and bone matrix calcification (Hong and Shi, 1999).

6.2.2. Effect on the multiplication and differentiation of the osteoblasts

Osteoblasts originate from bone marrow stromal cells, which have the potential to differentiate into several different lineages, including osteoblasts, chondroblasts, adipocytes and myoblasts. Scleroblast is the important functioning cell type in bone formation and bone re-construction. Currently, alkaline phosphatase (ALP) activity is considered to be the main index of osteoblast function and differentiation and can reflect the maturity of osteoblasts. Higher ALP activity correlates with greater maturity. When the ALP activity increased, cells tended to proliferate. Type I collagen protein is another osteoblast differentiation marker and is also the

main component of bone organic matrix (Rodan and Noda, 1991; Lynch et al., 1995; Scutt et al., 1996).

Studies have shown that the crude extract, total flavonoids and main flavonoid constituents from Herba Epimedii stimulate the proliferation of primary osteoblasts (Wang et al., 2002a,b; Han et al., 2003) and osteoblast-like UMR106 cells (Meng et al., 2005; Xie et al., 2005).

At concentrations of 1–10 mg/l, the total flavonoids of *Epimedium pubescens* significantly promoted the proliferation of osteoblasts and enhanced the extent of mineralized tuberculation *in vitro* (Li et al., 2002a). Further studies have shown the flavonoids of Herba Epimedii (50 μg/ml) promote the osteogenic differentiation of human bone marrow-derived mesenchymal stem cells. These compounds enhanced the mRNA expression of BMP-2, BMP-4, Runx2, β-catenin and cyclin D_1 (Zhang et al., 2010).

Polysaccharides from *Epimedium* significantly increased the rates of cell proliferation and DNA synthesis in cultured mouse bone-marrow cells (Liu et al., 1991). The serum from old male rats that were continuously fed the water extract of *Epimedium* (1, 2 g/ml) for one month promoted the proliferation and differentiation of newborn rat calvarial osteoblasts. These results suggest that the promotion of proliferation and differentiation by the water extract of *Epimedium* may contribute to the generation of a relatively large number of specific factors, such as BMP and leptin (Ma et al., 2002b). In addition, *Epimedium* promoted gonadal secretion and generated a male hormone-like effect on the proliferation and differentiation of osteoblasts.

The EtOH extract and the n-butanol fraction (1×10^{-3} mg/ml) from the crude extract of *Epimedium brevicornum* were found to show proliferation-stimulating activity in the osteoblast-like UMR106 cells. Furthermore, three flavonoid compounds (icariin, epimedin B and C) isolated from this fraction by an activity-guided assay also significantly promoted the proliferation of osteoblast-like UMR106 cells. These results suggested that *Epimedium brevicornum* extracts might have activity against osteoporosis and that flavonoids such as icariin might be the active substances that stimulate osteoblasts (Meng et al., 2005). In fact, further studies showed that various doses of icariin improved the proliferation and activity of cultured osteoblasts. Especially at a dose of 10 ng/ml, icariin depressed ALP activity ($P < 0.05$) in the early stage and improve ALP activity in the later stage of osteoblast proliferation (Wang et al., 2002a,b). Several trace elements, particularly, manganese (Mn) and zinc (Zn), are essential in bone metabolism as cofactors for specific enzymes. It has been reported that there is a relationship between osteoporosis and trace-element deficiency and the efficacy of Ca, Mn and Zn supplementation on spinal bone mineral density in postmenopausal women. Interesting, the mineral elements, manganese (Mn), zinc (Zn) and iron (Fe), were abundant in Herba Epimedii. The combination of 10 μmol/l Zn, Ca and Mn with icariin and total flavonoids greatly improved cell viability and, meanwhile, dramatically enhanced alkaline phosphatase activity compared to each agent alone. An increased cell growth inhibition was also observed by combining 0.1 μmol/l, 1 μmol/l Zn with 10 μmol/l icariin and 10 μmol/l Mn with 0.06 μg/ml total flavonoids. Meanwhile, decreased alkaline phosphatase activity was also found with several icariin–Zn/Mn and total flavonoids–Zn/Ca/Mn combinations. These results suggested that mineral elements greatly enhanced the efficacy of icariin and total flavonoids from Herba Epimedii on the viability and differentiation of primary osteoblasts in certain combinations (Zhang et al., 2008a,b,c,d).

6.2.3. Effect on osteoclastic cells

Osteoclasts are bone-resorbing cells derived from multipotent myeloid progenitor cells. They play a crucial homeostatic role in skeletal modeling and remodeling and destroy bone in many pathologic conditions. Parenteral administration of an *Epimedium* solution induced osteoclast apoptosis and inhibited bone resorption in a dose-dependent manner. Further study showed that the *Epimedium*-treated cells showed shrinkage of cytosol, condensation of nuclei, breakage of nuclei, dark-stained nuclei and light-stained cytosol (Li et al., 2002b). Total flavonoids (10^{-4} mol/l) of Herba Epimedii decreased the numbers of the osteoclasts and directly inhibited osteoclast resorption activity *in vitro* (Zhang et al., 2004). Further study showed the inhibition effects of flavonoids on the proliferation of the RAW 264.7 cell line are bidirectional, depending on their concentrations and chemical structures. Ikarisoside A is a potent inhibitor of osteoclastogenesis in NF-κB ligand-stimulated RAW 264.7 cells as well as in bone marrow-derived macrophages. Ikarisoside A (2.5–20 μM) decreased the expression of osteoclast-specific genes, such as matrix metalloproteinase 9, tartrate-resistant acid phosphatase, receptor activator of NF-κB (RANK) and cathepsin K. These data indicate that ikarisoside A has potential use in the treatment of diseases involving abnormal bone lysis, such as osteoporosis, rheumatoid arthritis and periodontal bone erosion (Choi et al., 2010). Icariin at the concentrations of 100 and 50 μmol/l significantly inhibited the formation of osteoclast-like cells in rabbit bone-marrow cells induced by 1,25-$(OH)_2D_3$. Icariin at concentrations of 100, 50 and 10 μmol/l also significantly inhibited the bone-resorbing activity and greatly suppressed the number and surface area of resorption lacuna. So, icariin not only suppressed the bone-resorbing activity of mature osteoclasts but also inhibited the formation of osteoclast-like multinucleated cells, showing that it should be considered as a candidate drug for the treatment of bone loss (Zhang et al., 2007c).

6.2.4. Effect on bone marrow-derived stroma cells

Icariin (0.1 μmol/l) improved the proliferation of goat bone marrow-derived stroma cells (BMSCs) by increasing the proportion of cells in the S and G2/M phases. However, 100 μmol/l icariin depressed the proliferation of BMSCs, but icariin promoted alkaline phosphatase activity and osteocalcin expression in goat BMSCs in a dose-dependent manner (Wu et al., 2009).

6.2.5. Effect on cartilage growth in vitro

A crude extract *Epimedium brevicornum* (0.05–10.00 mg/l) increased the weight of cartilage ($P < 0.01$) in a time-dependent manner. The length as well as the wet and dry weights of femurs cultured with 1.00 mg/l total flavonoids from *Epimedium brevicornum* for seven days was significantly improved. This finding demonstrated that *Epimedium brevicornum Maxim* can accelerate cartilage growth as well as cell proliferation (Feng et al., 2009).

In conclusion of the effect on bone metabolism, the mechanism by which *Epimedium* can act in the prevention and treatment of osteoporosis includes the following three points: (1) the promotion of osteoblast proliferation and increase in bone formation; (2) the inhibition of osteoclast-raising activities and decrease in the bone absorption level; and (3) the promotion of collagen synthesis and matrix mineralization in bone stromal cells. In TCM, the kidney is believed to be in charge of the bone, and *Epimedium* was thought to invigorate the kidney and strengthen bones and muscles; now, its efficacy in the prevention and treatment of osteoporosis has been confirmed by clinical studies.

6.3. Effect on the immune system

Epimedium has effects on humoral immunity, cellular immunity and nonspecific immunity. *Epimedium* and its extracts or ingredients had a considerable effect on the immune organs, immune cells and immune factors.

6.3.1. Effect on the thymus

The thymus, a central immune organ, plays an important role in modulating immune system function. Polysaccharides, icariin and related compounds from *Epimedium* were shown to activate the thymus. A methanolic extract of roots and rhizomes of *Epimedium alpinum* at low concentrations (0.1 μg/ml and 1 μg/ml) significantly enhanced the concanavalin A induced proliferation of splenocytes and thymocytes, whereas higher concentrations of the extract (50–500 μg/ml) showed inhibition of this process. Further data showed that this effect was correlated with the up-regulation of the expression of interleukin-2 receptor α (IL-2Rα) and the increased production of IL-2. *Epimedium* polysaccharide (10–50 mg/kg) activated the thymus and decreased the intrathymic count of $L3T4^+$ and Lyt_2 cells in mice. At the same time, it enhanced cellular immune function by promoting the release of mature cells and increasing the production of IL-2 in the thymus (Ding et al., 1992).

6.3.2. Effect on macrophages

Epimedium and its crude extract also affect the secretion of macrophage cytokines and regulate immune function. Subcutaneous injection of 0.2 and 0.4 ml of an *Epimedium*-Propolis adjuvant (*Epimedium* total flavonoids and crude propolis) into 3-day-old chicks significantly enhanced the phagocytic activities of chicken peritoneal macrophages. In mice, 0.4 ml of this preparation significantly enhanced the cytotoxic effects on peritoneal macrophages and antagonized the immune inhibition of cyclophosphamide (Hu et al., 1999). The total flavonoids of *Epimedium* (400 mg/kg) significantly strengthened the phagocytosing function of the monocyte–macrophage system in normal mice, raised the level of serum hemolysin antibody formation, antagonized the inhibition of monocyte–macrophage phagocytic capacity induced by cyclophosphamide and reduced serum hemolysin antibody levels as well as the intensity of delayed-type hypersensitivity (Zhang and Yu, 1999). *Epimedium* polysaccharide, icariin and related compounds significantly increased the phagocytosis of macrophages, improved the lymphocyte transformation rate, and promoted the production of interleukin-1 and tumor necrosis factor.

6.3.3. Effect on T and B lymphocytes

In vitro, the methanolic extract of the leaf of *Epimedium pubescens* markedly inhibited the proliferation of mouse lymphocytes induced by mitogens and the mixed lymphocyte reaction (Wang and He, 1986). In patients with vital energy deficiency, the methanolic extract of the leaf of *Epimedium sagittatum* (Sieb. & Zucc.) Maxim. significantly enhanced the leukocyte count and the lymphocyte transformation rate (Liu et al., 1985). In maintenance hemodialysis patients, *Epimedium koreanum* significantly increased the CD^{4+} counts and CD^{4+}/CD^{8+} ratio ($P < 0.05$) and improved the T_H levels. In the delayed-type hypersensitivity mouse model, the total flavonoids of *Epimedium koreanum* increased the CD^{4+} level of T-lymphocyte subpopulations (Yang et al., 1998).

Studies showed that the total flavonoids of *Epimedium koreanum* reduced the T-cell apoptosis rate, down-regulated the apoptosis gene FasL and the mRNA expression of TNFR1, up-regulated the apoptosis gene Bcl-2 at the level of mRNA expression and reduced the abnormally high levels of caspase 8 and caspase 3 activity in corticosterone rat T cells (Shen and Chen, 2002). *Epimedium* polysaccharides (50 mg/kg) promoted the proliferation and differentiation of T and B mouse lymphocytes *in vitro* and *in vivo* and significantly increased the activity of these lymphocytes (Zhang et al., 1996).

6.3.4. Effects on NK and LAK cells

The oral administration of the total flavones and polysaccharides of *Epimedium* at doses of 240 mg/kg for 30 days significantly enhanced the activities of NK cells in aged rats; similarly, it enhanced the activity of LAK cells and acted synergistically with IL-2 (Meng et al., 1996). At the same time, icariin (10–100 ug/ml) enhanced NK-cell activity and provided a high cytotoxic activity of LAK cells *in vitro*.

6.3.5. Antibody responses

The n-butanol fraction of the aerial parts of *Epimedium hunanense* and the compound epimedin C significantly enhanced the response of spleen antibody-forming cells (SAFCs) to normal levels in mice treated with hydrocortisone acetate. They also caused a significant recovery of interleukin-2 (IL-2) production in these mice. In conclusion, these substances are active components with immuno-enhancing effects (Liang et al., 1997). An aqueous extract of *Epimedium koreanum* at therapeutic concentrations (40 and 120 mg/kg) enhanced the production of antibodies and cytokines in mice, and this effect was more marked when the mice were immunized with ovalbumin. This result suggests that the extract is effective on Th-cell functions and protects the host from immune diseases (Kim et al., 2001).

6.4. Effect on the cardiovascular system

Experiments showed that *Epimedium* and the non-amino-acid components of its alcohol-based extract affected the heart, blood pressure, blood rheology, and arrhythmia and that they were used to improve the subjects' myocardial ischemia, increase coronary blood flow, decrease the heart rate, improve myocardial ischemia tolerance and cure hypotension and arrhythmia (Mdidea, 2010, http://www.mdidea.com/products/herb extract/icariin/data06.html).

6.4.1. Effect on vessels, blood and heart

Icariin expands the coronary blood vessels, the femoral artery and cerebral blood vessels. It has a direct effect on relaxing vascular smooth muscle in a non-competitive inhibition manner, significantly reduces noradrenaline-promoting extracellular Ca^{2+} influx, and reduces the contraction of the basilar artery. Studies have shown that icariin increases the cerebral blood flow through the expansion of vascular smooth muscle and lowers cerebral vascular resistance to protect the brain from ischemic injury and improve cerebral ischemia and cerebral hypoxia in laboratory animals (Hou et al., 2004).

The water extract of *Epimedium sagittatum* (Sieb. & Zucc.) Maxim. leaf had a significantly preventive effect on the ventricular fibrillation induced by chloroform in mice and the ventricular fibrillation induced by calcium chloride in rats. It also had obvious therapeutic effect on the aconitine-induced arrhythmia in rats. An extract of herba Epimedii, at doses of 0.25 and 0.50 mg/ml slowed down the heart rate of isolated rat hearts and reduced myocardial contraction while increasing the irrigation flow; thus, the *Epimedium* extract showed a protective effect on myocardial ischemia (Guo et al., 2005). Total flavones from Herba Epimedii (24, 12, and 6 mg/kg) improved the abnormal electrocardiogram J-point of the acute myocardial ischemia model and effectively prevented the increase of blood viscosity. At doses of 34 and 17 mg/kg, the total flavones lengthened the coagulation time in mice. These results suggest that the total flavones from Herba Epimedii have protective effects on ischemic myocardium and improve circulation through the coronary artery (Wang et al., 2007d).

6.4.2. Anti-hypertensive activity

The aqueous extract of *Epimedium grandiflorum* showed significant hypotensive activity in normal and spontaneously hypertensive rabbits (Inokuchi et al., 1984; Inokuchi et al., 1985), and efficacy in the treatment of hypertension-complicated coronary disease (Yu et al., 1992). The flavonoid glycosides of *Epimedium*

glandiflorum, at a concentration of 0.13 g/l, reduced blood pressure by expanding the coronary blood vessels, the femoral artery and the cerebral vasculature as well as reducing peripheral resistance in isolated organs and animal models (Xu and Chen, 1994). In addition, injection of the total flavonoids of Herba Epimedii into the lateral ventricles at a dose of 26 mg/kg promoted the secretion of an amino acid neurotransmitter (r-aminobutyric acid) in the encephalocele periventricular system and enhanced the affinity of GABA for the $GABA_A$ receptors; at the same time, it strengthened the inhibition of the central sympathetic cardiovascular system and decreased blood pressure (Fu et al., 2007).

6.4.3. Anti-arrhythmia effect

A water extract of *Epimedium brevicornum* was found to be markedly effective in preventing ventricular fibrillation induced by chloroform in mice and ventricular fibrillation induced by calcium chloride in rats. At the same time, intraperitoneal injection of the water extract of *Epimedium brevicornum*, at a dose of 5.0 ml/kg bw, markedly inhibited the arrhythmia induced by aconitine in rats and obviously inhibited the action potential amplitude of isolated sciatic nerves in toads, but it did not antagonize the arrhythmia induced by adrenaline in rabbits. The results showed that the crude extract has obviously protective effect on drug-induced arrhythmia, which may be related to its inhibition of Na^+ or Ca^{2+} influx (Zeng et al., 2002). Administration of the total flavone glycoside of *Epimedium koreanum* by vena jugularis injection at the dosages of 60 mg/kg and 120 mg/kg significantly counteracted barium chloride-induced arrhythmia in hamsters and adrenaline-induced arrhythmia in guinea pigs.

6.4.4. Effect on blood system

Experiments on rabbits showed that the total flavonoids of *Epimedium* reduced the aggregation response of platelets and erythrocytes, extending the prothrombin time, lowering whole-blood viscosity and inhibiting thrombosis (Gao, 1992a,b). Icariin promoted blood-cell proliferation, differentiation and maturation and plays an important role in hematopoietic function in the body.

6.4.5. Angiogenesis effect

Studies have found that *Epimedium sagittatum* (Sieb. & Zucc.) Maxim. has an angiogenic effect. Extracts of *Epimedium sagittatum* (Sieb. & Zucc.) Maxim. stems and leaves at a dose of 1 g herb D.W./ml stimulated tiny blood vessels and showed a strong promotion of angiogenesis activity both *in vitro* and *in vivo* (Wang et al., 2004).

6.5. Anti-tumor effects

6.5.1. Induction of tumor-cell differentiation

Icariin (62.5,125, 250 mg/l) showed inhibitory effects on the human promyelocytic leukemia cell line HL-60 after a 12-h incubation. At the same time, at dosage of 100 mg/l, it increased the reduction of Nitro Blue Tetrazolium Chloride (NBT) and the mean optical density (MOD) after a 48-h incubation. The nuclei of HL-60 cells became rod-shaped or lobulate, and the nuclear volume decreased. Further studies showed that the induction of differentiation in HL-60 cells might be related to an elevated cAMP/cGMP ratio (Zhao et al., 1996a,b; Zhao et al., 1997).

6.5.2. Inhibition of tumor-cell proliferation

Different alcohol extracts of Herba Epimedii had antiproliferative activities in human breast cancer cells *in vitro*. The 95% EtOH extract of Herba Epimedii significantly inhibited the proliferation of the MCF-7 human breast cancer cell line at doses of 100–800 μg/ml; the 70% alcohol extract showed a certain antiproliferative activity, whereas the 20% and 40% alcohol extracts showed no significant antiproliferative activity (Cheng et al., 2007). Studies also showed that icariin at a concentration of 100 ug/ml inhibited the proliferation of HL-60, a human hepatoma cell line (H7402) and mouse bone marrow mononuclear cell leukemia cells (WEH I-3) *in vitro* (Zhao et al., 1995).

6.5.3. Anti-tumor diffusion

Icariin at a concentration of 0.3 uM decreased the adhesion of high metastatic human lung tumor cell lines (PG) to laminin and decreased the cells' ability to invade or migrate. It reduced the expression of CD44V6, LN2R and CK18 in the highly metastatic human lung tumor cell line. At the same time, icariin decreased the expression of c-myc and Tiam-1 mRNA and enhanced the expression of Nm-3-H1 mRNA at a dose of 0.3 uM. These results suggest that icariin may play multiple anti-metastatic roles (Mao et al., 2001).

6.5.4. Induction of apoptosis

Icariin (0.15, 0.3 and 0.6 uM) induced apoptosis in a time- and dose-dependent manner in HL-60. It down-regulated the mRNA and protein expression of the apoptosis-associated genes bcl-2 and c-myc (Li et al., 1999).

6.6. Anti-aging and anti-oxidation effects

Epimedium had obvious anti-oxidation and free radical scavenging activities; it also affects aging through different mechanisms, in particular by regulating the immune and endocrine systems and improving metabolism and organ function.

Human embryonic lung diploid fibroblasts of the 2BS national standard strain were used as an aging model. The effects of *Epimedium* on DNA synthesis of 2BS fusion cells were observed by cell denucleation and cell fusion techniques. In the 0.025 (v/v) *Epimedium* water extract-containing media, 2BS cells could be continuously cultured for 56.0 ± 2.6 passages, while in the control group, only 49.0 ± 2.6 passages could be achieved ($P < 0.01$). After treatment with *Epimedium* water extract for 2 h, the aging 2BS cells were denucleated and fused with young 2BS cells. The [3H]TdR incorporation percentage in these treated cells was significantly higher than that in the untreated control cells ($P < 0.01$) (Wu et al., 2003b). With the increase in age, the mean level of phosphorylation of p65, IκBα and IκBε in rat spleen lymphocytes decreased obviously, while intragastric administration (0.06 g/kg) of *Epimedium koreanum* flavonoids activated the Rel/NF-κB family and the increase the phosphorylation of p65, IκBα and IκBε. The results showed that *Epimedium* flavonoids had strongly up-regulated the expression of these proteins during aging (Liu et al., 2008). In addition, intragastric administration of a mixture of polysaccharide and total flavonoids from *Epimedium* to rats for 60 days at doses of 30, 60, 120 mg/kg day significantly raised the levels of the monoamine neurotransmitter NE, DA and 5-hydroxyindoleacetic acid in the hypothalamus of aging rats and also inhibited the activities of AchE in both brain tissues and whole blood in mice. Noradrenergic (NE), dopamine (DA) and 5-hydroxyindoleacetic acid promoted the ability to learn and remember. The experiments showed that *Epimedium* delayed natural senescence in animals (Meng et al., 1996).

Intragastric administration of fats infused by *Epimedium brevicornum* at a dose of 0.5 g/kg/day for 8 weeks reduced mitochondrial DNA deletion in heart, brain and skeletal muscles in the aged rat; the same treatment increased adenosine triphosphate (ATP) synthesis in the mitochondria of brain, heart and skeletal muscles as well as enhanced mitochondrial respiratory chain complex enzyme I and II activities in skeletal muscle, brain and heart. These results indicated that *Epimedium* protected mitochondrial DNA from oxidative damage in aged rats (Wang et al., 1996). The polysaccharide liposomes of *Epimedium wushanense* at a dose of 30 mg/kg

bw significantly increased super oxide dismutase (SOD) enzyme complex and glutathione peroxidase (GSH-Px) activity in organs and blood, reduced the LPO content in the serum and liver tissues of aging animals and reduced lipofuscin in the myocardium of aging animals (Zeng et al., 1997). In an isolated culture of hepatic tissue, the total flavonoids from *Epimedium* were able to restrain the oxygen level of liver homogenate and mitochondria oxidated spontaneously or inductively by VitC-Fe^{2+} with an IC_{50} of 34.87 μg/ml, 70.34 μg/ml, 198.45 μg/ml, and 332.65 μg/ml, respectively. Moreover, this effect was predominant in eliminating free radicals, including DPPH, •OH and $•O^{2-}$ with an IC_{50} 4.67 μg/ml, 598.17 μg/ml and 413.21 μg/ml, respectively. So the total flavonoids from *Epimedium* were effective against oxidation *in vitro* (Zhao et al., 2009). In addition, the N^+ of magnoflorine magnoflarine from *Epimedium* attracted the hydroxyl radical and reduced the reactivity of •OH, so it had a protective effect on the normal function of the cell membrane (Niu et al., 2000).

6.7. Anti-hypoxia and anti-fatigue effects

The total flavonoids from *Epimedium* have shown significant anti-hypoxia activity in normobaric hypoxia models. Intragastric administration of the total flavonoids from *Epimedium* (300, 600, 900 mg/kg) to mice prolonged the survival time of the normobaric hypoxic mice, lessened encephaledema and pneumonedema and raised the contents of hemoglobin and leukocytes (Zhang et al., 2009). Oral administration of the total flavonoids of *Epimedium*, at a dose of 500 mg/kg bw for 14 days, significantly prolonged the time of weight-bearing swimming and decreased the creatinine and urea nitrogen levels in mice sera (Ma et al., 2009).

6.8. Anti-inflammatory, anti-virus and anti-bacterial activities

The total flavonoids of *Epimedium* significantly reduced the PGE and MDA levels, increased the vitality of erythrocyte catalase in mice, inhibited the ear swelling and granulation tissue hyperblastosis induced by croton oil and induced the capillary permeability induced by intraperitoneal injection of acetic acid (Palmer, 1914). So we thought the anti-inflammatory properties of *Epimedium* plants may contribute to their local and traditional use in rheumatism.

The total flavonoids of *Epimedium* significantly inhibited poliovirus and enterovirus. In addition, the flavonoids had inhibitory effects on *Micrococcus pyogenes* var. *albus*, *Staphylococcus aureus*, *Diplococcus pharyngis communis*, *Micrococcus catarrhalis* and *Haemophilus influenzae*. Clinical studies showed that the compound preparation made from *Epimedium* and radix *Morindae officinalis* at the dose of 0.5 ml/kg could lower the level of viremia and had a positive effect on asthma in young children, especially for asthma caused by viral infections (Fang et al., 2003). Icariin, a major 8-isoamyleneflavonol glycoside in the genus *Epimedium*, notably inhibited the activities of food pollutant bacteria, with MICs of 0.23% for *Aspergillus* sp, 0.12% for *Escherichia coli* and *Staphylococcus aureus*, and 0.05% for *Bacillus subtilis*, *Penicillium* sp and *Hansenula* sp (Yan and Qiu, 2005). The anti-inflammatory, antiviral and antibacterial effects of this commonly used plant might be new hot spots for pharmacological studies in the following years.

6.9. Hepatoprotective

The anti-hepatotoxic activity of Icariside II was evaluated by measuring the activity of glutamic pyruvic transaminase in CCl_4-intoxicated primary cultured rat hepatocytes, and a concentration of 200 μM resulted in a 78% reduction of the toxicity (Cho et al., 1995). Icariin, another major flavonol glycoside in *Epimedium*, significantly reduced the levels of glutamic pyruvic transaminase and sorbitol dehydrogenase and resulted in a 76% protection from toxicity at concentrations ranging from 1 μM to 20 μM (Lee et al., 1995).

7. Clinical studies

The clinical effects of preparation from *Epimedium* for ED (Liu, 1990), high blood pressure, coronary heart disease (Yu et al., 1989) have been studied. The useful and anthoritatively clinical studies were very limited and most of these preparations were made of the rude extraction from *Epimedium* alone or with other herbals and most of these studies were designed very simple. Recently, we are very interesting to see some reports in Internet. A double-blind clinical trial relating to the effect of *Epimedium* Herbal Complex Supplement on sexual satisfaction in healthy men was compared with Viagra. In the study, 25 healthy men and 13 men who used Viagra were assigned to initially receive daily therapy for 45 days, and it is said daily use of this herbal complex for a minimum of 45 days resulted in a more enhancement of sexual satisfaction than Viagra (Mdideanet, 2010, http://www.mdidea.net/products/herbextract/icariin/data07.html).

8. Processing

In China, *Epimedium* was traditionally prepared by stir-frying in oil or suet. This method was claimed to produce a synergistic effect on promoting sexual function (Xu et al., 1985). In Cui et al. (1996) designed a new technology to preserve the ingredients of *Epimedium* and induce the synergistic effect of suet. In this method, 20 g suet was melted to 60 °C, and then 100 g *Epimedium* leaf was added and stir-fried for 10 min at 60 °C. The finished product was light yellow-green, and the oil was light. The product processed by this method had a higher icariin content and greater efficacy for improving sexual desire and performance.

9. Side effects and acute toxicity

Epimedium, as a traditional Chinese herbal medicine, has been used for 2000 years as a aphrodisiac in China. Although it is listed as a food and a medicine, investigation of its relative systematic toxicity and safety evaluations have been lacking, and no major side effects have yet been discovered. In 2006, the safety of the water extract of Herba Epimedii was evaluated in terms of its acute toxicity and cellular toxicity. Experiments including the mice bone marrow micro-nuclear test, the Ames test and the *TK* gene mutation experiment were performed. It was found that Herba Epimedii did not have mutagenic effects and that its LD_{50} was higher than 80 g/kg. Its IC_{50} in Chinese hamster ovary cells and Chinese hamster lung cells was 55.4 and 19.53 mg/ml, respectively, and all toxicity tests were negative (Sui et al., 2006). In 2007, the acute toxicity of the total flavonoids of *Epimedium* were measured by intragastric administration to NIH mice at a dose of 36 g/kg/day for 7 days. This dosage was equal to 1440 times the normal human dosage, and no mouse deaths were observed (Li et al., 2007b). The long-term toxicity of the total flavonoids of *Epimedium* was investigated in a normal Wistar rat model by intragastric administration of the extract, at the dosage of 410 g/kg/day for 12 weeks. No significant differences were found in treated rats for any blood parameter analyzed (including aspartate aminotransferase and the antioxidant enzymes glutathione peroxidase and superoxide dismutase), and no major pathology changes were seen (Li et al., 2008).

In short, there are no known warnings or contraindications for the use of *Epimedium* plants, and the ideal dosage is not known. Capsules or tablets are sold in various doses, ranging from

250 to 500 mg. In very high doses, they may have a stimulatory effect and may cause sweating or feeling hot. In animal studies, prolonged use of excessive amounts of *Epimedium* was associated with decreased thyroid activity (Mdideanetp, 2010, http://www.mdidea.net/products/herbextract/icariin/data08.html). Regretfully, many products are standardized by their active icariin content, and the chronic, acute and long-term toxicity of this flavonoid have not been assessed *in vivo* or *in vitro*.

10. Conclusion

In CTM, the kidney is alleged to be crucial for sexual and bone health. In clinical practice, *Epimedium* has successfully been used to tonify the kidneys and invigorate the *yang*. Modern *in vitro* and *in vivo* pharmacological studies have increasingly confirmed the traditional use of *Epimedium* plants. The crude extracts and compounds from the aerial parts or roots possess many kinds of biological functions, especially in the improvement of sexual dysfunction, regulation of hormones and modulation of immunological functions as well as anti-osteoporosis, anti-tumor, anti-aging and anti-atherosclerosis activities. According to the literature, most of the pharmacological activities of *Epimedium* plants can be explained by the high content of flavonoids and polysaccharide present in the genus, especially 8-prenylflavonoids.

Phytochemical and pharmacological studies of the compounds isolated from the genus *Epimedium* have received much interest in recent years, but the pharmacological studies so far have mostly been performed *in vitro* and *in vivo* with animals. Therefore, clinical studies in humans are urgently needed to confirm this traditional phytotherapy. The constituents of this genus as well as their pharmacological and toxicity profiles should be further investigated with both *in vitro* and *in vivo* studies. In addition, taking into account their therapeutic efficiency and economical considerations, the total flavonoids and/or active ingredients might be developed into new drugs for the treatment of various diseases, especially sexual dysfunction, osteoporosis and immunity-related diseases.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jep.2011.01.001.

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