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Chemistry and pharmacology of *Gynostemma pentaphyllum*

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Abstract

In traditional Chinese medicine, *Gynostemma pentaphyllum* (Thunb.) Makino is a herbal drug of extreme versatility and has been extensively researched in China. The dammarane saponins isolated from *Gynostemma pentaphyllum*, namely gypenosides or gynosaponins, are believed to be the active components responsible for its various biological activities and reported clinical effects. This review attempts to encompass the available literature on *Gynostemma pentaphyllum*, from its cultivation to the isolation of its chemical entities and a summary of its diverse pharmacological properties attributed to its gypenoside content. Other aspects such as toxicology and pharmacokinetics are also discussed. *In vitro* and *in vivo* evidence suggests that *Gynostemma pentaphyllum* may complement the popular herbal medicine, *Panax ginseng*, as it also contains a high ginsenoside content and exhibits similar biological activities.

Abbreviations: ara – arabinose; *G. pentaphyllum* – *Gynostemma pentaphyllum;* glu – glucose; i.g. – intragastric; i.m. – intramuscular; i.p. – intraperitoneal; i.v. – intravenous; LD_{50} – mean lethal dosage; lyx – lyxose; rha – rhamnose; s.c. – subcutaneous; xyl – xylose

Introduction

This review paper attempts to summarise the existing literature on *Gynostemma (G.) pentaphyllum* (Thunb.) Makino, with some reference made to the authors' own investigations.

G. pentaphyllum is a perennial creeping herb of the genus Gynostemma. The plant belongs to the Cucurbitaceae family which includes cucumber, gourd and melons (Blumert and Liu, 1999). Common names of *G. pentaphyllum* include Jiaogulan, Qi Ye Dan, Gong Luo Guo Di, Pian Di Sheng Gen, Xiao Ku Yao, Amachazuru, Dungkulcha, Baan Ja Kahn and Penta (Guo and Wang, 1993; China Pharmaceutical University, 1996). There are 21 species of *Gynostemma* mostly growing in southwestern China (southern Shaan Xi and areas south of the Yangtze River). The pentaphyllum species is the most prevalent and is dispersed throughout India, Nepal, Bangladesh, Sri Lanka, Laos, Myanmar, Korea and Japan (Blumert and Liu, 1999). *G. pentaphyllum* is distributed naturally in mountain forests, mountain valleys, wood, scrub, stream banks, roadsides, bushes, shaded and humid places at an elevation of 300–3200 m (China Pharmaceutical University, 1996).

The use of *G. pentaphyllum* has a history of about 500 years, with most of the reviewed material published in China. The book '*Herbs for Famine*' published in the Ming Dynasty (1368–1644 A.D.) describes the herb's usage as a vegetable, suitable as a food, or a dietary supplement

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during famine rather than as a medicinal herb (Cheng, 1990). The renowned herbalist Li Shi-Zhen (1578 A.D) later described *G. pentaphyllum* for treatment of haematuria, oedema and pain of the pharynx, heat and oedema of the neck, tumours and trauma (Wu, 1957; Li, 1985). According to traditional Chinese medicine (TCM) principles, the taste and nature of *G. pentaphyllum* is slightly bitter, neutral, warm, enhancing 'Yin' and supporting 'Yang' and suggested that the plant 'would be used to increase the resistance to infection and for anti-inflammation' (Blumert and Liu, 1999). Indications include hyperlipidaemia, palpitation and shortness of breath, chest congestion, tingling sensation in the limbs, dizziness, headache, forgetfulness, tinnitus, spontaneous perspiration, general weakness, swelling of abdomen, Qi deficiency of heart and spleen and stagnation of phlegm and blood (China Pharmaceutical University, 1996). Therefore, *G. pentaphyllum* has since been included in the most recent dictionary of Chinese Materia Medica, where the plant is prescribed in TCM for heat clearing, detoxification, antitussive, heart palpitation, fatigue syndrome, chronic bronchitis and expectorant for relieving cough (Wu, 1998; Blumert and Liu, 1999). In Japan, it is indicated as a diuretic, antipyretic, anti-inflammatory and tonic (Lin et al., 1993; Chen et al., 1996; Tanner et al., 1999).

The appearance of *G. pentaphyllum* consists of slender stems of thin, soft leaves arranged like fingers on a hand, bearing 3–9 leaves (usually 5–7 leaves). The leaflets are long and pliable, broadest below the middle and tapering to a point like a lance. They are rough to the touch on both sides, are coloured a deep green on the upper side and a light green underneath. *G. pentaphyllum* has male and female flowers on separate plants (Wang et al., 2004). The conical, multiple male flowers are 10–15 (up to 30) cm. The 5-cleft corolla of petals is pale green or white. The female flowers are similar but are much smaller than the male. The 2–3 cavity ovary is globe-shaped. The three styles and stigma are short and cleft into two parts. The fruit consists of a smooth, globular, small berry about 5–6 mm in diameter and black when ripe. The two ovo-heart shaped seeds inside (~4 mm in diameter) are coloured greyish brown or deep brown. The apex of the seed is obtuse and the base is heart-shaped. The flowering seasons in the northern hemisphere are March to November; the fruiting seasons are April to December (China Pharmaceutical University, 1996; Blumert and Liu, 1999).

The methods and optimal conditions for growing *G. pentaphyllum* are outlined in China Pharmaceutical University (1996), Wang et al. (1996) and Guo and Wang (1993). A soil (pH in the range 5.5–8.0, with an optimal pH of 6.5–7.0) more than 30 cm deep, rich in humus, nitrogen, phosphorus and moisture, is ideal for growing *G. pentaphyllum*. The optimal soil is well aerated and retains water, such as a fertile sandy loam. *G. pentaphyllum* prefers to grow in a warm and humid environment. The viable air temperature is −15–41.5 °C. The optimal air temperature is 15–30 °C. The light factor is important for growing *G. pentaphyllum* (Huang et al., 2004). The plant prefers shady areas, with a viable relative illumination of 40–80% and optimal relative illumination of 65–75%. Under these conditions, the output is the highest, the blossoming and bearing of fruit is increased and the total saponin content is the highest (Guo and Wang, 1993; Wang et al., 1996). Wind damage is common for this vine plant and can be reduced by introducing wooden sticks so that the plant can intertwine itself. An ideal chemical fertiliser is a nitrogen–phosphate–potassium compound (2–3 times) during the active growth period. Pests such as ants and snails can be controlled by various commercially available products. *G. pentaphyllum* may be collected when the vine reaches 2–3 m in length. In the subtropics and tropics, the herb is collected 4–5 times a year. With optimal growing conditions and luxuriance, collection may be every 20–30 days. In a high-yield plot, 4000–5000 kg of dried herb may be collected every hectare (Guo and Wang, 1993). In comparison, the cultivation of *Panax (P.) ginseng* (Araliaceae) is highly specialised, requiring a maturation period of up to seven years to attain optimal medicinal properties (Lee, 1992). Razmovski-Naumovski et al. (2005a) documents the cultivation of *Gynostemma pentaphyllum* outside its native China in Sydney, Australia. Some research has also been undertaken in cell culture of *G. pentaphyllum* (Zhang et al., 1989, 1995; Chang et al., 2005).

Isolation and identification methods

Gynostemma total saponins, namely gypenosides (or gynosaponins) exist mainly as dammarane

type-triterpene glycosides (Figure 1). Due to their structural similarity, gypenosides are subjected to a variety of isolation and identification methods. *G. pentaphyllum* (usually dried material) can be extracted with a variety of solvents, including water, methanol and ethanol for the more polar material; ethyl acetate, petroleum ether and chloroform for the less polar material, using an open system or under reflux. The separating methods include 1:1 partition with water and butanol, silica gel chromatography, alumina (Al_2O_3), sephadex (LH-20), ODS, XAD-2 and other styrene copolymers (Nagai et al., 1981; Takemoto et al., 1981, 1982; Kuwahara et al., 1989; Zhao et al., 1995; Wang and Li, 1997; Wang et al., 1997a).

Thin layer chromatography (TLC) provides the first identification profile of *G. pentaphyllum*. The recommended mobile phase systems for normal-phase silica gel plates include: chloroform/ethyl acetate/methanol/water (15:40:22:10) (Xie and Yan, 1987), chloroform/methanol/ethyl acetate (20:10:1) (Zheng and He, 2000) and chloroform/methanol/water (14:11:2) (Wang, 1994). For reversed-phase plates, the mobile phase system usually consists of methanol/water (75:25) (Kuwahara et al., 1989). To visualise the bands, spray reagents such as a solution of concentrated sulfuric acid and methanol (1:1) (Wang, 1994) or anisaldehyde/sulfuric acid/glacial acetic acid/methanol (1:10:20:170) (Jork et al., 1900) can be employed. Dipping the plate in sulfuric acid/methanol/water (20:10:175) can give greater colour uniformity of the bands.

Due to the lack of a strong chromophore in gypenosides, high performance liquid chromatography (HPLC) conditions are usually restricted to the use of acetonitrile under UV (<203 nm) or refractive index. Identification has been achieved with liquid chromatography–mass spectrometry (LC-MS) using acetylated gypenosides and ^{1}H- and ^{13}C-NMR results via chemical degradation to aglycone and sugar moieties and comparison with compounds of closely related structures (Nagai et al., 1981). Characterisation of the aglycone has also been achieved with alkaline cleavage of the gypenosides and gas chromatography–MS (GC–MS) with trimethylsilated aglycones (Cui et al., 1998, 1999). Spectral methods such as ^{1}H–^{1}H two-dimensional ^{1}H correlation spectroscopy (COSY), ^{13}C distortionless enhancement by polarisation transfer (DEPT), homonuclear Hartmann–Hahn spectroscopy (HOHAHA), nuclear overhauser enhancement spectroscopy (NOESY), ^{13}C–^{1}H heteronuclear correlated spectroscopy (HETCOR) (Piacente et al., 1995), heteronuclear multiple-quantum correlation (HMQC), heteronuclear multiple bond correlation (HMBC) and total correlation spectroscopy (TOCSY) NMR spectra and fast atom bombardment (FAB)-MS have also been applied to identify the chemical structure of intact saponins, thus avoiding the use of degradation methods (Hu et al., 1996, 1997).

Saponin structures

The latest literature search on the Scifinder database found over 100 saponins isolated and identified from *G. pentaphyllum* by scientists in Japan

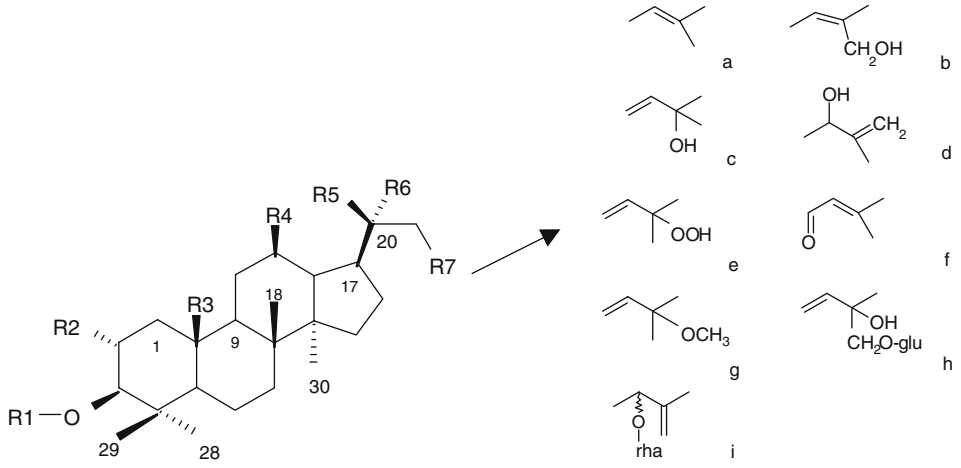

Figure 1. Dammarane skeleton of *G. pentaphyllum* with typical chains.

and China since 1976, as shown in Table 1. Of these, eight saponins are the same as the protopanaxadiol-type ginsenosides Rb_1 (Gypenoside III) (Kuwahara et al., 1989; Takemoto et al., 1983a), Rc (Ma et al., 1995), Rb_3 (Gypenoside IV), Rd (Gypenoside VIII), F_2 (Ma et al., 1995), Rg_3 (Qin et al., 1992), malonyl-Rb_1 and malonyl-Rd (Kuwahara et al., 1989) found in *P. ginseng*. R_f, a protopanaxatriol has also been reported (Ma et al., 1995). These ginsenosides make up around 25% of the total gynosaponin in the plant and is the first example of ginseng saponins found outside of the Araliaceae family (Liu et al., 2004). The remainder of the total saponin content is mostly made up of gypenosides only known to occur in *G. pentaphyllum*. Gypenosides XXVIII, XXXVII, LV, LXII, LXIII are also found in *Gymnema sylvestra* (Yoshikawa et al., 1991). Gypenoside XVII (Yoshikawa et al., 1997), IX (notoginsenoside Fd) and XV (Wei et al., 1992) are also found in *P. notoginseng* and Gypenoside XVII and IX (Wang and Li, 1997) are found *P. quinquefolium*. Total saponin content is reported to be about 2.4% of the dried herb (Zhang et al., 1993). Studies show the total saponin content is highest before flowering. The content of the total saponins is different in different species, growing localities and time of collection (Ding and Zhu, 1992). The main sugar types (mostly in pyranose form) are β-D-glucose, β-D-xylose, α-L-arabinose and α-L-rhamnose found in positions C-3 (β) and C-20. Characteristic functional groups are hydroxyl, methyl, aldehyde, alcohol and the least common, ketone, found at position C-19. A hydroxyl group may also be found at C-2 (α) and C-12 (β) (Figure 1 and Table 1). New ocotillone-type saponins (Figure 2 and Table 2) bearing an epoxy ring at C-17 have also been isolated with structures $3\beta,12\beta,23S,24R$-tetrahydroxy-20*S*,25-epoxydammarane and (20*S*,24*S*)-20,24-epoxydammarane$-3\beta,12\beta,25$-triol (Liu et al., 2004). Crystal structures of gypenosides isolated include Gynoside A (Liu et al., 2004), Gynogenin II (Mackay et al., 1991) and Gynosaponin TN1 (Razmovski-Naumovski et al., 2005b).

Other components

Common sterols present in *G. pentaphyllum* in small amount (~0.0001%) include ergostanol, sitosterol and stigmasterol type (Marino et al., 1989). Cholestanols with 24,24-dimethyl substitution occur widely in the Cucurbitaceae family (Akihisa et al., 1988; 1989a, b). Chondrillasterol and its (24*S*)-epimer, spinasterol, are the most predominant sterol component. The usual configurations at C-24 are 24-alkyl-Δ^5-,Δ^7-,Δ^8-sterols and 24,24-dimethyl-Δ^7-sterols (Akihisa et al., 1986). The structures of the 24,24-dimethyl-Δ^7-sterols is unusual as they contain acyclic, quaternary carbon groups in the side chain (C-24) which is common in marine sponges (Akihisa et al., 1986). 4α-methylsterols (Akihisa et al., 1990), 14α-methylsterols (Akihisa et al., 1987), 24,24-dimethylsterols (Akihisa et al., 1988), ($24R/\alpha$)- and ($24S/\beta$) epimers of 14α, 24-dimethyl-5α-cholest-9(11)-en-3β-ol also occur (Akihisa et al., 1989a). The first acetylenic sterols from a non-marine organism were isolated from *G. pentaphyllum* (Akihisa et al., 1989b).

Other constituents reported are the flavonoids, ombuin, ombuoside (Fang and Zeng, 1989; Hu et al., 1997), rutin (Fang and Zeng, 1989), polysaccharides, vitamins (Deng et al., 1994), minerals (Zhang et al., 1993; Deng et al., 1994; Zhou et al., 1996a, b; Liang et al., 2002), carotenoids (Liu et al., 2004) and amino acids (Zhang et al., 1993; Deng et al., 1994). Allantoin and vitexin were also identified (Yin et al., 2004a). The absence of alkaloids has been reported (Arbain et al., 1989).

Biological activities

The medicinal properties of *G. pentaphyllum* have been mainly attributed to the saponins which have been the main focus of pharmacological studies in China (China Pharmaceutical University, 1996). The versatility of the plant has earned it the label 'the immortality herb' (Blumert and Liu, 1999).

Effects on lipid metabolism

The modulating effects of gypenosides on lipid metabolism *in vivo* have been extensively researched. In a study performed by la Cour et al. (1995), the lipid lowering effect of *Gynostemma* in a decoction with two other traditional Chinese herbs was investigated. The mixture significantly reduced the levels of serum triglyceride (TG) and cholesterol in rats and quails. Similarly in another

Table 1. Saponin structures of the dammarane type in *G. pentaphyllum* (from Scifinder Scholar, 2004).

Gypenoside	Formula	R1	R2	R3	R4	R5	R6	R7	References
I	$C_{60}H_{102}O_{27}$	glu(6 → 1)rha | (2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)glu	CH_3	a	Takemoto et al. (1983a)
II	$C_{60}H_{102}O_{26}$	glu(6 → 1)rha | (2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)rha	CH_3	a	Takemoto et al. (1983a)
V (Gynos E)	$C_{54}H_{92}O_{22}$	glu(2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)rha	CH_3	a	Takemoto et al. (1983a)
V 6″-malonyl	$C_{57}H_{94}O_{25}$	glu(2 → 1)glu(6 → 1)mal	H	CH_3	OH	O-glu(6 → 1)rha	CH_3	a	Kuwahara et al. (1989)
VI	$C_{54}H_{92}O_{21}$	glu(6 → 1)rha | (2 → 1)glu	H	CH_3	OH	O-glu	CH_3	a	Takemoto et al. (1983a)
VII(Gynos G)	$C_{54}H_{92}O_{21}$	glu(6 → 1)rha	H	CH_3	OH	O-glu(6 → 1)rha	CH_3	a	Takemoto et al. (1983a)
IX (Gynos I; Notog Fd)	$C_{47}H_{80}O_{17}$	glu	H	CH_3	OH	O-glu(6 → 1)xyl	CH_3	a	Takemoto et al. (1983a)
X (Gynos J)	$C_{48}H_{82}O_{17}$	glu	H	CH_3	OH	O-glu(6 → 1)rha	CH_3	a	Takemoto et al. (1983a)
XI (Gynos K)	$C_{48}H_{82}O_{17}$	glu(6 → 1)rha	H	CH_3	OH	O-glu	CH_3	a	Takemoto et al. (1983a)
XIII (Gynos M)	$C_{41}H_{70}O_{12}$	H	H	CH_3	OH	O-glu(6 → 1)xyl	CH_3	a	Takemoto et al. (1983a)
XIV (Gynos N)	$C_{42}H_{72}O_{12}$	H	H	CH_3	OH	O-glu(6 → 1)rha	CH_3	a	Takemoto et al. (1983a)
XV	$C_{52}H_{88}O_{21}$	xyl(2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)xyl	CH_3	a	Takemoto et al. (1983b)
XVI	$C_{53}H_{90}O_{21}$	xyl(2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)rha	CH_3	a	Takemoto et al. (1983b)
XVII (Gynos S)	$C_{48}H_{82}O_{18}$	glu	H	CH_3	OH	O-glu(6 → 1)glu	CH_3	a	Takemoto et al. (1983b)
XVIII	$C_{60}H_{102}O_{27}$	glu(6 → 1)rha | (2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)rha	CH_3	b	Takemoto et al. (1983b)
XIX (Gynos P)	$C_{54}H_{92}O_{23}$	glu(2 → 1)glu glu(6 → 1)rha	H	CH_3	OH	O-glu(6 → 1)rha	CH_3	b	Takemoto et al. (1983b)
XX	$C_{60}H_{102}O_{28}$	| (2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)glu	CH_3	b	Takemoto et al. (1983b)
XXI	$C_{41}H_{70}O_{13}$	H	H	CH_3	OH	O-glu(6 → 1)xyl	CH_3	b	Takemoto et al. (1983b)
XXII[b]	$C_{53}H_{90}O_{23}$	glu(2 → 1)glu	H	CH_2OH	H	O-glu(6 → 1)xyl	CH_2OH	a	Takemoto et al. (1984a)
XXIII[b]	$C_{48}H_{82}O_{19}$	glu(2 → 1)glu	H	CH_2OH	H	OH	CH_2-O-glu	a	Takemoto et al. (1984a)
XXIV[b]	$C_{48}H_{80}O_{19}$	glu(2 → 1)glu	H	CHO	H	OH	CH_2-O-glu	a	Takemoto et al. (1984a)
XXV[b]	$C_{47}H_{78}O_{18}$	ara(2 → 1)glu	H	CHO	H	OH	CH_2-O-glu	a	Takemoto et al. (1984b)
XXVI[b]	$C_{47}H_{78}O_{18}$	ara(2 → 1)glu	H	CHO	H	O-glu	CH_2OH	a	Takemoto et al. (1984b)
XXVII	$C_{42}H_{72}O_{13}$	glu(2 → 1)glu	H	CH_2OH	H	OH	CH_3	a	Takemoto et al. (1984c)
XXVIII	$C_{42}H_{70}O_{13}$	glu(2 → 1)glu	H	CHO	H	OH	CH_3	a	Takemoto et al. (1984c)
XXIX	$C_{41}H_{68}O_{12}$	ara(2 → 1)glu	H	CHO	H	OH	CH_3	a	Takemoto et al. (1984b)
XXX[b]	$C_{42}H_{72}O_{14}$	glu	H	CH_2OH	H	O-glu	CH_2OH	a	Takemoto et al. (1984a)
XXXI[b]	$C_{42}H_{72}O_{14}$	glu(2 → 1)glu	H	CH_2OH	H	OH	CH_2OH	a	Takemoto et al. (1984a)

Table 1. Continued.

Gypenoside	Formula	R1	R2	R3	R4	R5	R6	R7	References
XXXII[b]	$C_{42}H_{72}O_{14}$	glu	H	CH_2OH	H	OH	CH_2-O-glu	a	Takemoto et al. (1984a)
XXXIII[b]	$C_{42}H_{70}O_{14}$	glu(2 → 1)glu	H	CHO	H	OH	CH_2OH	a	Takemoto et al. (1984a)
XXXIV[b]	$C_{54}H_{90}O_{23}$	glu(2 → 1)glu	H	CHO	OH	O-glu(6 → 1)rha	CH_2OH	a	Takemoto et al. (1984b)
XXXV[b]	$C_{53}H_{88}O_{23}$	glu(2 → 1)glu	H	CHO	H	O-glu(6 → 1)xyl	CH_2OH	a	Takemoto et al. (1984b)
XXXVI	$C_{53}H_{88}O_{21}$	ara(2 → 1)glu	H	CHO	H	O-glu(6 → 1)rha	CH_3	a	Takemoto et al. (1984d)
XXXVII	$C_{52}H_{86}O_{21}$	ara(2 → 1)glu	H	CHO	H	O-glu(6 → 1)xyl	CH_3	a	Takemoto et al. (1984d)
XXXVIII	$C_{42}H_{72}O_{14}$	glu(2 → 1)glu	H	CH_2OH	OH	OH	CH_3	a	Takemoto et al. (1984c)
XXXIX(20*R*)	$C_{42}H_{72}O_{14}$	glu(2 → 1)glu	H	CH_2OH	OH	CH_3	OH	a	Takemoto et al. (1984c)
XL(20*R*)	$C_{42}H_{70}O_{14}$	glu(2 → 1)glu	H	CHO	OH	CH_3	OH	a	Takemoto et al. (1984c)
XLI(20*R*)	$C_{42}H_{72}O_{13}$	glu(2 → 1)glu	H	CH_2OH	H	CH_3	OH	a	Takemoto et al. (1984c)
XLII	$C_{54}H_{92}O_{24}$	glu(2 → 1)glu	OH	CH_3	OH	O-glu(6 → 1)glu	CH_3	a	Takemoto et al. (1984e)
XLIII[c]	$C_{54}H_{92}O_{23}$	glu(2 → 1)glu	OH	CH_3	OH	O-glu(6 → 1)rha	CH_3	a	Takemoto et al. (1984e)
XLIV	$C_{48}H_{82}O_{19}$	glu	OH	CH_3	OH	O-glu(6 → 1)glu	CH_3	a	Takemoto et al. (1984e)
XLV	$C_{48}H_{82}O_{18}$	glu	OH	CH_3	OH	O-glu(6 → 1)rha	CH_3	a	Takemoto et al. (1984e)
XLVI	$C_{48}H_{82}O_{19}$	glu(2 → 1)glu	OH	CH_3	OH	O-glu	CH_3	a	Takemoto et al. (1984e)
XLVII	$C_{54}H_{92}O_{24}$	glu(2 → 1)glu	OH	CH_3	OH	O-glu(6 → 1)rha	CH_3	b	Takemoto et al. (1984f)
XLVIII	$C_{53}H_{88}O_{22}$	ara(2 → 1)rha | (3 → 1)glu	H	CHO	H	OH	CH_2-O-glu	a	Takemoto et al. (1984f)
XLIX	$C_{52}H_{86}O_{21}$	ara(2 → 1)rha | (3 → 1)xyl	H	CHO	H	OH	CH_2-O-glu	a	Takemoto et al. (1984f)
L	$C_{42}H_{72}O_{14}$	glu(2 → 1)glu	OH	CH_3	OH	OH	CH_3	a	Takemoto et al. (1984f)
LI	$C_{42}H_{72}O_{14}$	glu(2 → 1)glu	OH	CH_3	OH	CH_3	OH	a	Takemoto et al. (1984f)
LII[a]	$C_{47}H_{78}O_{18}$	ara(2 → 1)rha	H	CHO	H	OH	CH_2-O-glu	a	Guo et al. (1987) and Zhou (1988)
LIII	$C_{41}H_{68}O_{13}$	ara(2 → 1)glu	H	CHO	OH	CH_3	OH	a	Takemoto et al. (1984d)
LIV	$C_{41}H_{70}O_{13}$	ara(2 → 1)glu	H	CH_2OH	OH	OH	CH_3	a	Takemoto et al. (1984d)
LV	$C_{47}H_{80}O_{17}$	glu	H	CH_2OH	H	O-glu(6 → 1)xyl	CH_3	a	Takemoto et al. (1984c)
LVI	$C_{53}H_{90}O_{23}$	glu(2 → 1)glu	OH	CH_3	OH	O-glu(6 → 1)xyl	CH_3	a	Takemoto et al. (1986b)
LVII	$C_{47}H_{80}O_{18}$	glu	OH	CH_3	OH	O-glu(6 → 1)xyl	CH_3	a	Takemoto et al. (1986b)
LVIII	$C_{52}H_{88}O_{21}$	ara(2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)xyl	CH_3	a	Takemoto et al. (1986b)
LIX	$C_{41}H_{70}O_{14}$	H	OH	CH_3	OH	O-glu(6 → 1)xyl	CH_3	b	Takemoto et al. (1986b)
LX	$C_{41}H_{70}O_{14}$	H	OH	CH_3	OH	O-glu(6 → 1)xyl	CH_3	c	Takemoto et al. (1986b)
LXI	$C_{53}H_{90}O_{24}$	glu(2 → 1)glu	OH	CH_3	OH	O-glu(6 → 1)xyl	CH_3	b	Yoshikawa et al. (1986)
LXII	$C_{53}H_{90}O_{23}$	glu(2 → 1)glu	H	CH_2OH	OH	O-glu(6 → 1)xyl	CH_3	a	Yoshikawa et al. (1986)
LXIII	$C_{53}H_{90}O_{22}$	glu(2 → 1)glu	H	CH_2OH	H	O-glu(6 → 1)xyl	CH_3	a	Yoshikawa et al. (1986)

LXIV	$C_{47}H_{80}O_{18}$	glu	H	CH_2OH	OH	O-glu(6 → 1)xyl	CH_3	a	Yoshikawa et al. (1986)
LXV	$C_{41}H_{70}O_{13}$	H	H	CH_2OH	OH	O-glu(6 → 1)xyl	CH_3	a	Yoshikawa et al. (1987a)
LXVI	$C_{42}H_{72}O_{13}$	H	H	CH_2OH	OH	O-glu(6 → 1)rha	CH_3	a	Yoshikawa et al. (1987a)
LXVII	$C_{53}H_{90}O_{23}$	glu(2 → 1)glu	OH	CH_2OH	H	O-glu(6 → 1)xyl	CH_3	a	Yoshikawa et al. (1986)
LXVIII	$C_{53}H_{90}O_{24}$	glu(2 → 1)glu	OH	CH_3	OH	O-glu(6 → 1)xyl	CH_3	c	Yoshikawa et al. (1987b)
LXIX	$C_{53}H_{90}O_{23}$	glu(2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)xyl	CH_3	c	Yoshikawa et al. (1987b)
LXX	$C_{53}H_{90}O_{23}$	glu(2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)xyl	CH_3	b	Yoshikawa et al. (1987b)
LXXI	$C_{53}H_{90}O_{23}$	glu(2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)xyl	CH_3	d	Yoshikawa et al. (1987b)
LXXII	$C_{48}H_{82}O_{18}$	glu(6 → 1)rha	H	CH_2OH	OH	O-glu	CH_3	a	Yoshikawa et al. (1987a)
LXXIII	$C_{48}H_{82}O_{17}$	glu	OH	CH_3	H	O-glu(6 → 1)rha	CH_3	a	Yoshikawa et al. (1987a)
LXXIV	$C_{42}H_{72}O_{14}$	H	OH	CH_3	OH	O-glu(6 → 1)glu	CH_3	a	Yoshikawa et al. (1987c)
LXXV	$C_{42}H_{72}O_{13}$	H	H	CH_3	OH	O-glu(6 → 1)glu	CH_3	a	Yoshikawa et al. (1987c)
LXXVI	$C_{36}H_{62}O_9$	H	H	CH_2OH	OH	O-glu	CH_3	a	Yoshikawa et al. (1987c)
LXXVII	$C_{41}H_{70}O_{13}$	H	OH	CH_3	OH	O-glu(6 → 1)xyl	CH_3	a	Yoshikawa et al. (1987c)
LXXVIII	$C_{41}H_{70}O_{12}$	H	OH	CH_3	H	O-glu(6 → 1)xyl	CH_3	a	Yoshikawa et al. (1987c)
LXXIX	$C_{42}H_{72}O_{13}$	glu	H	CH_2OH	H	O-glu	CH_3	a	Yoshikawa et al. (1987a)
Gynos A	$C_{60}H_{102}O_{27}$	glu(6 → 1)rha (2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)glu	CH_3	a	Takemoto et al. (1982)
Gynos B	$C_{60}H_{102}O_{26}$	glu(6 → 1)rha (2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)rha	CH_3	a	Takemoto et al. (1982)
Gynos F	$C_{54}H_{92}O_{22}$	glu(6 → 1)rha (2 → 1)glu	H	CH_3	OH	O-glu	CH_3	a	Takemoto et al. (1982)
Gynos O	$C_{60}H_{102}O_{27}$	glu(6 → 1)rha (2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)rha	CH_3	b	Takemoto et al. (1982)
Gynos Q	$C_{52}H_{88}O_{21}$	glu(2 → 1)xyl	H	CH_3	OH	O-glu(6 → 1)xyl	CH_3	a	Takemoto et al. (1982)
Gynos R	$C_{53}H_{90}O_{21}$	glu(2 → 1)xyl	H	CH_3	OH	O-glu(6 → 1)rha	CH_3	a	Takemoto et al. (1982)
Gynos T	$C_{60}H_{102}O_{28}$	glu(6 → 1)rha (2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)glu	CH_3	b	Takemoto et al. (1982)
Gynos U	$C_{42}H_{72}O_{14}$	H	H	CH_3	OH	O-glu(6 → 1)glu	CH_3	b	Takemoto et al. (1982)
Gynos TN-1	$C_{36}H_{62}O_9$	H	OH	CH_3	OH	O-glu	CH_3	a	Nagai et al. (1981) and Takemoto et al. (1984e)
Gynos TN-2	$C_{42}H_{72}O_{13}$	H	OH	CH_3	OH	O-glu(6 → 1)rha	CH_3	a	Nagai et al. (1981)
Gynos TR-1	$C_{36}H_{62}O_{10}$	H	OH	CH_3	OH	O-glu	CH_3	d	Huang et al. (2005)
XXIII-Eg[b,c]	$C_{30}H_{52}O_4$	H	H	CH_2OH	H	CH_2OH	OH	a	Nippon Shoji Co., Ltd and Takemoto (1983)
XXVIII-Em[d]	$C_{35}H_{58}O_7$	ara	H	CHO	H	OH	CH_3	a	–
XXV-Em[b,c]	$C_{35}H_{58}O_8$	ara	H	CHO	H	CH_2OH	OH	a	Nippon Shoji Co., Ltd and Takemoto (1983)
XXVII-Em	$C_{36}H_{62}O_8$	glu	H	CH_2OH	H	OH	CH_3	a	Nippon Shoji Co., Ltd and Takemoto (1983)

Table 1. Continued.

Gypenoside	Formula	R1	R2	R3	R4	R5	R6	R7	References
I-AH[d]	$C_{48}H_{82}O_{17}$	glu(2 → 1)glu | (6 → 1)rha	H	CH_3	OH	OH	CH_3	a	–
I-EH (ProgynosA2)	$C_{54}H_{92}O_{22}$	glu(6 → 1)rha	H	CH_3	OH	O-glu(6 → 1)glu	CH_3	a	Takemoto and Nippon Shoji Co., Ltd (1984b)
Progynos A-AH	$C_{48}H_{82}O_{17}$	glu(6 → 1)rha(2 → 1)glu	H	CH_3	OH	OH	CH_3	a	Takemoto et al. (1982)
Progynos O1	$C_{36}H_{62}O_9$	H	H	CH_3	OH	O-glu	CH_3	b	Takemoto et al. (1982)
Gypentonoside A	$C_{54}H_{88}O_{21}$	glu(2,3,6 → 1)rha	H	CH_3	=O	OH	CH_3	f	Fang and Zeng (1996)
Gymnemaside II	$C_{48}H_{80}O_{18}$	glu(2 → 1)glu	H	CHO	H	O-glu	CH_3	a	Hu et al. (1996)
1	$C_{54}H_{92}O_{22}$	glu(2 → 1)glu	H	CH_2OH	H	O-glu(6 → 1)rha	CH_3	a	Hu et al. (1997)
2	$C_{54}H_{90}O_{22}$	glu(2 → 1)glu	H	CHO	H	O-glu(6 → 1)rha	CH_3	a	Hu et al. (1997)
3	$C_{47}H_{78}O_{17}$	ara(2 → 1)rha	H	CHO	H	O-glu	CH_3	a	Hu et al. (1997)
1	$C_{42}H_{72}O_{14}$	glu	OH	CH_3	OH	O-glu	CH_3	a	Liu et al. (2003)
1	$C_{54}H_{90}O_{23}$	glu(2 → 1)glu	OH	CH_3	=O	O-glu(6 → 1)rha	CH_3	a	Hu et al. (1996)
2	$C_{53}H_{88}O_{23}$	glu(2 → 1)glu	OH	CH_3	=O	O-glu(6 → 1)xyl	CH_3	a	Hu et al. (1996)
3	$C_{48}H_{82}O_{18}$	glu(2 → 1)glu	H	CH_2OH	H	O-glu	CH_3	a	Hu et al. (1996)
1	$C_{55}H_{92}O_{22}$	glu(2 → 1)rha |\ \ | (6 → 1)CH_3CO (3 → 1)xyl	H	CH_3	H	OH	CH_2O-glu	a	Yin et al. (2004b)
2	$C_{54}H_{92}O_{22}$	glu(2 → 1)rha | (3 → 1)glu	H	CH_3	H	OH	CH_2O-glu	a	Yin et al. (2004b)
3	$C_{53}H_{90}O_{21}$	glu(2 → 1)rha | (3 → 1)xyl	H	CH_3	H	OH	CH_2O-glu	a	Yin et al. (2004b)
4	$C_{52}H_{88}O_{21}$	ara(2 → 1)rha | (3 → 1)xyl	H	CH_2OH	H	OH	CH_2O-glu	a	Yin et al. (2004b)
5	$C_{53}H_{90}O_{22}$	glu(2 → 1)rha | (3 → 1)xyl	H	CH_2OH	H	OH	CH_2O-glu	a	Yin et al. (2004b)
6	$C_{52}H_{86}O_{23}$	ara(2 → 1)rha | (3 → 1)xyl	H	CHO	H	OH	CH_2O-glu	e	Yin et al. (2004b)

7	$C_{53}H_{90}O_{24}$	glu(2 → 1)glu ara(2 → 1)rha | (3 → 1)xyl	H	CH_3	OH	O-glu(6 → 1)xyl	CH_3	e	Yin et al. (2004b)
8	$C_{52}H_{86}O_{22}$		H	CHO	H	OH	CH_2O-glu	d	Yin et al. (2004b)
1	$C_{46}H_{76}O_{18}$	ara(2 → 1)rha | (3 → 1)xyl	H	CHO	H	OH	CH_2OH	e	Yin et al. (2004a)
3	$C_{53}H_{90}O_{21}$	glu(2 → 1)rha | (3 → 1)xyl	H	CH_3	H	OH	CH_2O-xyl	g	Yin et al. (2004a)
Gylongiposide I	$C_{46}H_{76}O_{16}$	ara(2 → 1)rha | (3 → 1)xyl	H	CHO	H	OH	CH_2OH	a	Yin et al. (2004a)
3	$C_{53}H_{90}O_{22}$	ara(2 → 1)glu	H	CH_3	H	O-rha	CH_3	h	Piacente et al. (1995)
4	$C_{53}H_{90}O_{22}$	ara(2 → 1)glu	H	CH_3	H	OH	CH_2O-glu	i	Piacente et al. (1995)
Ginsenosides									
Rb_1 (Gyp III)	$C_{54}H_{92}O_{23}$	glu(2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)glu	CH_3	a	Takemoto et al. (1983a)
$Rb_1$6″-malonyl	$C_{57}H_{94}O_{26}$	glu(2 → 1)glu(6 → 1)mal	H	CH_3	OH	O-glu(6 → 1)glu	CH_3	a	Kuwahara et al. (1989)
Rb_3 (Gyp IV)	$C_{53}H_{90}O_{22}$	glu(2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)xyl	CH_3	a	Takemoto et al. (1983a)
Rd (Gyp VIII)	$C_{48}H_{82}O_{18}$	glu(2 → 1)glu	H	CH_3	OH	O-glu	CH_3	a	Takemoto et al. (1983a)
Rd 6″-malonyl	$C_{51}H_{84}O_{21}$	glu(2 → 1)glu(6 → 1)mal	H	CH_3	OH	O-glu	CH_3	a	Kuwahara et al. (1989)
F_2	$C_{42}H_{72}O_{13}$	glu	H	CH_3	OH	O-glu	CH_3	a	Takemoto et al. (1983a)
Rg_3	$C_{42}H_{72}O_{13}$	glu(2 → 1)glu	H	CH_3	OH	OH	CH_3	a	Qin et al. (1992)
Rb_2	$C_{53}H_{90}O_{22}$	glu(2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)ara	CH_3	a	Hu et al. (1997)
Rc	$C_{53}H_{90}O_{22}$	glu(2 → 1)glu	H	CH_3	OH	O-glu(6 → 1)araF	CH_3	a	Ma et al. (1995)
Rf (proto-panaxatriol)	$C_{42}H_{72}O_{14}$note: at C-6 O-glu(2 → 1)glu	H	H	CH_3	OH	OH	CH_3	a	Ma et al. (1995)

Note: () = alternate name; Gynos = Gynosaponin; Gyp = Gypenoside; mal = -$COCH_2COOH$; ζ = either bond; F = furanose.

[a]Not in Scifinder.

[b]Gypenosides have ζ bond at C-20 in Scifinder.

[c]Currently available stereochemistry shown. Incompletely defined substance for: Gypenoside XXIII-Em (C_{36} H_{62} O_9); Gypenoside XXIV-Em (C_{36} $H_{60}O_9$).

[d]Scifinder reference only.

[e]Gypenoside A (C_{54} H_{92} O_{23}): glycosyl sequence similar to Gypenoside XLIII (Yao et al., 1994 ; Liu et al., 1997).

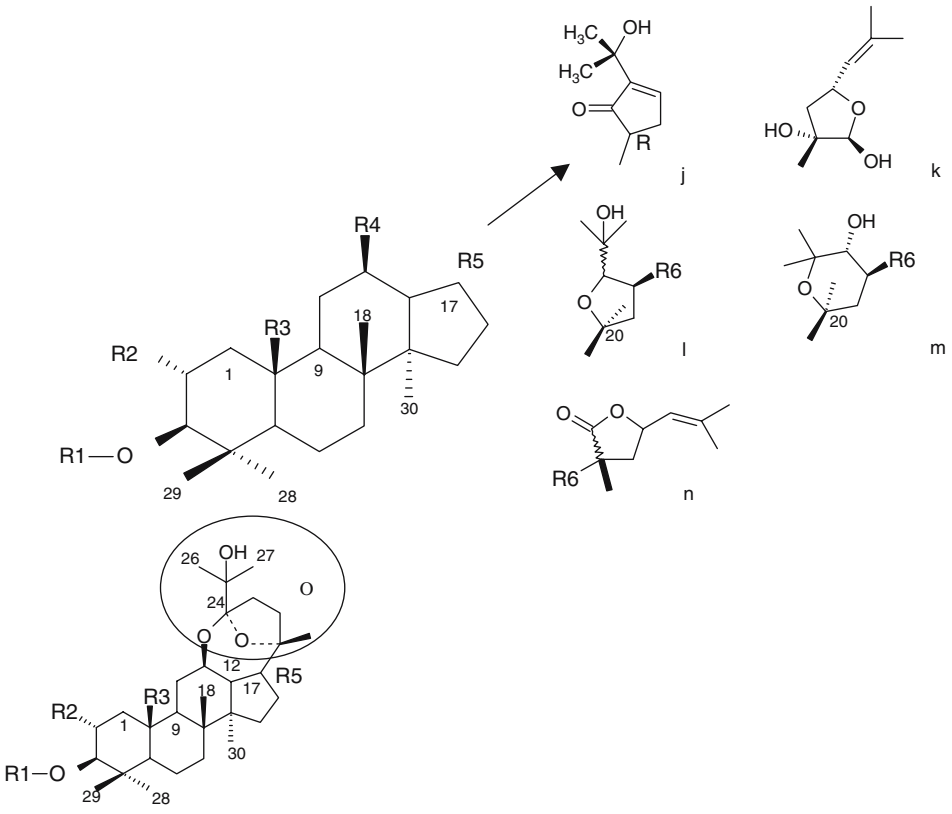

Figure 2. Cyclopentenone (j) and epoxy dammarane-type glycosides from *G. pentaphyllum.*

study, gynosaponin (200 mg kg^{-1}) reduced total cholesterol (TC), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) of mice and rats. Both high-density lipoprotein (HDL) and the ratio of HDL/LDL were raised (China Pharmaceutical University, 1996). In high-fat diet-induced obese rats treated for 4 weeks with *G. pentaphyllum* crude fraction, there was a significant decrease in TG levels and the raised TC cholesterol level was suppressed slightly (Jang et al., 2001). In another study performed in Wistar rats fed with high sugar and fat food, 7 weeks treatment with 100 mg kg^{-1} of total gynosaponin lowered TC and TG levels by 32% and 34%, respectively, whereas the group treated with 500 mg kg^{-1} of gynosaponin lowered the level of TC and TG parallel to that of normal rats. In addition to reducing blood lipid level, the lipid peroxides (LPO) of blood serum and liver also decreased significantly (Kimura et al., 1983; Guo and Wang, 1993). In hyperlipidaemic mice, gypenosides (300 mg kg^{-1}) reduced serum cholesterol and TG by 12% and 39.1%, respectively. Gypenosides (400 mg kg^{-1}) in quails reduced serum cholesterol, TAG and LDL by 33.2%, 44.2% and 48.3%, respectively. HDL was increased by 6.3%. Protection against atherosclerosis and lipoidosis in the liver of the quails was also detected (Qi et al., 1996). Gypenosides (700 mg kg^{-1}) in hyperlipidaemic mice decreased the level of serum cholesterol, TAG and β-lipoprotein by 60.7%, 41.3% and 37.8%, respectively and increased HDL by 50.6% (Xu et al., 1994).

In rat epidermis cultured in the presence of gynosaponin, fat cells were prevented from producing fatty acids and synthesising neutral fat, with release significantly decreased by 28% and 50%, respectively (Kimura et al., 1983). *G. pentaphyllum* was also examined in a poloxamer P407 induced hyperlipidaemia rat model. Both acute (4 days) and chronic (12 days) treatment with gypenoside extract (250 mg kg^{-1}) reduced TG

Table 2. Structures of the cyclopentenone and epoxy dammarane-type glycosides in *G. pentaphyllum*.

Compound	Formula	R1	R2	R3	R4	R5	R6	References
Gynogenin II	$C_{30}H_{48}O_3$	H	H	CH_3	H	j		Mackay et al. (1991)
Phanoside	$C_{47}H_{78}O_{17}$	lyx(2 → 1)rha | (3 → 1)glu	H	CH_3	H	k		Norberg et al. (2004)
Gynoside A	$C_{41}H_{70}O_{13}$	xyl(2 → 1)glu	H	CH_3	OH	l	H (24*S*)	Liu et al. (2004)
Gynoside B	$C_{42}H_{72}O_{14}$	glu(2 → 1)glu	H	CH_3	OH	l	H (24*S*)	Liu et al. (2004)
Gynoside C	$C_{41}H_{70}O_{13}$	xyl(2 → 1)glu	H	CH_3	OH	l	H (24*R*)	Liu et al. (2004)
Gynoside D	$C_{41}H_{70}O_{14}$	xyl(2 → 1)glu	H	CH_3	OH	l	OH (24*S*)	Liu et al. (2004)
Gynoside E	$C_{41}H_{70}O_{13}$	xyl(2 → 1)glu	H	CH_3		o		Liu et al. (2004)
2	$C_{41}H_{70}O_{14}$	glu(2 → 1)xyl glu(2 → 1)xyl	H	CH_3	OH	l	OH	Yin et al. (2004a)
9	$C_{46}H_{78}O_{18}$	| (6 → 1)xyl glu(2 → 1)glu	H	CH_3	OH	m	OH	Yin et al. (2004b)
10	$C_{47}H_{80}O_{19}$	| (6 → 1)xyl	H	CH_3	OH	m	OH	Yin et al. (2004b)
11	$C_{41}H_{70}O_{14}$	xyl(2 → 1)glu	H	CH_3	OH	m	OH	Yin et al. (2004b)
12	$C_{41}H_{70}O_{14}$	glu(2 → 1)xyl	H	CH_3	OH	m	OH	Yin et al. (2004b)
13	$C_{42}H_{70}O_{14}$	xyl(2 → 1)xyl	H	CH_3	OH	m	OAc	Yin et al. (2004b)
14	$C_{43}H_{72}O_{15}$	glu(2 → 1)xyl glu(2 → 1)xyl	H	CH_3	OH	m	OAc	Yin et al. (2004b)
15	$C_{48}H_{80}O_{19}$	| (6 → 1)xyl	H	CH_3	OH	m	OAc	Yin et al. (2004b)
1	$C_{47}H_{76}O_{17}$	ara(2 → 1)glu	H	CH_3	H	n (20*S*)	rha	Piacente et al. (1995)
2	$C_{47}H_{76}O_{17}$	ara(2 → 1)glu	H	CH_3	H	n (20*R*)	rha	Piacente et al. (1995)

(53% and 85%, respectively) and TC levels (10% and 44%, respectively) (Megalli et al., 2005).

The active components have been reported as gynosaponin E (Takemoto and Nippon Shoji Co., Ltd, 1984a), G, K, progypenoside A2 (Takemoto and Nippon Shoji Co., Ltd, 1984b), I, J (Takemoto and Nippon Shoji Co., Ltd, 1984c), M, N and O (Takemoto and Nippon Shoji Co., Ltd, 1984d).

LXR is a nuclear receptor involved in cholesterol homeostasis. In a study by Huang et al. (2005), a novel gynosaponin, TR1, activated the nuclear receptor LXR-α *in vitro* and showed greater selectivity for the LXR-α over the LXR-β isoform. ABCA1 and apoprotein E gene expression was also enhanced. Thus, biological activity of gypenosides would primarily be dependent on the structure of the aglycone, the type and number of sugar chains, the steric orientation of the chains (e.g. the point of attachment of the sugars to the aglycone) and the nature of other functional groups present (Hostettmann et al., 1995).

Clinical studies of *G. pentaphyllum* on lipometabolism have been undertaken in many universities, institutes and hospitals in China. A particular clinical trial included 158 hyperlipidaemic patients, with 106 patients on gypenosides drink and 52 on gypenosides tablets, both equivalent to 120 mg per day for 2 months. The blood lipid change was 85% and 69%, respectively. Another trial with gypenosides tablet (120 mg daily) involved 39 hyperlipidaemia patients. Among the 14 hypercholesterolaemic patients, the serum cholesterol level dropped by 17%. Among the 25 hypertriglyceridaemic patients, the serum TG level dropped by 35% (Zheng et al., 1998). Gypenoside tablets (120 mg per day) decreased cholesterol by 17.2% and TG by 37.8% in patients with hyperlipidaemia (Yu, 1993).

In a multicenter clinical trial of the serum lipid-lowering effects of a *Monascus purpureus* (red yeast) rice preparation, *G. pentaphyllum* was used as a positive control consisting of a group of 94 patients. After 8 weeks, *Gynostemma* significantly

reduced the level of TC (by 6.7%), TG (by 12.8%), LDL cholesterol (by 8.3%) and ratio of non-HDL/HDL cholesterol (by 10.4%) and increased the level of HDL cholesterol (by 8.4%) ($P < 0.001$) (Wang et al., 1997a). Another trial involving 300 patients from the Sino-Japan Friendship Hospital, the Third Affiliated Hospital of Beijing University of Medical Sciences and the First Hospital of Hunan University of Medical Sciences, capsules of total gynosaponin extract had a significant effect on reducing cholesterol, TG, fibrinogen and increasing the level of HDL (Guo and Wang, 1993).

Other clinical studies showed *G. pentaphyllum* is effective in the treatment of aging, deficiency, migraine, chronic bronchitis, hepatitis-B, dysrhythmia, chronic gastritis, gastric ulcer, leukopaenia and leukopaenia caused by radiotherapy (Zheng et al., 1998).

Therefore, from the above studies, gynosaponins may improve and regulate the lipid metabolic process.

Effects on cardiovascular system

G. pentaphyllum can influence cardiovascular activity (Purmova and Opeltel, 1995). In a study by Circosta et al. (2005), a protective effect against pitressin-induced coronaryspasm, arrhythmias and pressor response was achieved in guinea pigs treated with an aqueous extract of *Gynostemma* (2.5, 5 and 10 mg kg^{-1} intravenous (i.v.)). Gypenosides III and VIII had comparable protective outcomes.

Total gypenosides (100 mg kg^{-1} intraperitoneal (i.p.)) administered to rabbits reduced the area of cardiac infarct caused by ligation of coronary arteries and inhibited post-infarct elevation of free fatty acid. In rats, the same dose decreased propandial content in infarcted cardiac muscle and protected myocardial superoxide dismutase and phosphocreatine kinase activities. In cultures of neonatal rat myocardium, gypenosides (50, 100 and 200 μg ml^{-1}) displayed protective effects on myocardial cells by inhibiting damage caused by glucose and oxygen depletion and also inhibiting creatine phosphokinase and lactate dehydrogenase (LDH) release (China Pharmaceutical University, 1996). Total gypenoside (5 and 10 mg kg^{-1} i.v.) provided to anaesthetised dogs increased coronary artery flow. There was a decrease in blood pressure, heart rate, cardiac tension-time index, total peripheral and arterial resistance in cerebral and coronary arteries (China Pharmaceutical University, 1996). In toads, total gypenosides (5 mg kg^{-1} i.v.) antagonised the reduction in the T wave on the ECG after induction with pituitrin. Total gypenosides (25 mg kg^{-1} i.p.) decreased the area of cardiac infarct (ischaemic time = 24 h) in coronary-ligated rats and significantly decreased serum protein kinase (CPK) and LDH levels in ischaemic rats (ischaemic time = 6 and 10 h) (China Pharmaceutical University, 1996). Pharmaceutical granules containing *G. pentaphyllum* saponins for cardiovascular or cerebrovascular disease have been patented (Zhao et al., 1994).

Recently, it was demonstrated that gypenosides dose-dependently decreased the production of nitrite by stimulation of RAW 264.7 murine macrophages after initial stimulation with lipopolysaccharide (LPS), a surface component of Gram-negative bacteria known to initiate a number of major cellular inflammatory responses. Furthermore, gypenosides dose-dependently hampered the activity and expression of iNOS at the transcriptional level via decreasing LPS-induced NF-κB activity (Aktan et al., 2003) Similarly, a previous study showed that gypenosides elicited vasorelaxation effects through release of nitric oxide (NO) on porcine coronary rings antagonised by the NO synthase inhibitor *N*(G)-nitro-L-arginine methyl ester (Tanner et al., 1999). Thus, suppression of NO production via inhibition of iNOS expression and/or activity is an attractive therapeutic target in controlling numerous pathological processes, including inflammation and atherosclerosis (Bogdan, 2001). These results signify the importance of gypenosides in directly stimulating NO release (Tanner et al., 1999).

Effect on hyperglycaemia

Saponin fractions obtained from *G. pentaphyllum* (1 mg kg^{-1}) significantly lowered plasma glucose level in streptozotocin (STZ)-induced diabetic rats for 2 weeks (Jang et al., 2001). Recently, it was shown that phanoside (a new dammarane-type saponin) from *G. pentaphyllum* stimulated insulin-release from isolated rat pancreatic islets. When given orally to rats, phanoside (40 and 80 mg ml^{-1}) improved glucose tolerance and enhanced plasma insulin levels at hyperglycaemia

(Norberg et al., 2004). Gypenoside extract (100 and 200 mg kg^{-1} intragastric (i.g.)) administered for 2 months prevented hypoglycaemia in fasting senile rats and improved glycaemic tolerance in senile rats fed glucose (2 g kg^{-1} i.g.) (China Pharmaceutical University, 1996). Gypenosides (250 mg kg^{-1}) reduced exogenous glucose-induced hyperglycaemia in Zucker diabetic fatty rats by improving sensitivity to insulin receptors (Megalli and Roufogalis, 2005).

Effects on central nervous system

Total gypenoside (50 mg kg^{-1} i.v.) administered to rabbits had protective effects on cerebral ischaemia resulting from bi-carotid-artery ligation. After 60 min of cerebral ischaemia, the electrocerebralgram recorded significant improvement. There were also decreased activities of LDH and CPK in cerebral veins and improved morphological changes in post-ischaemic brain tissues (Wang and Qui, 1992). *Gynostemma* extract (450 mg kg^{-1}) had an inhibitory effect on the spontaneous activities of mice, while analgesic effects were observed in mice using the hot plate test (China Pharmaceutical University, 1996) *G. pentaphyllum* alleviated dysmnesia caused by anisodine (using platform-jumping test) in mice after 4–5 days treatment with ethanol extracts (3 g kg^{-1} subcutaneous (s.c.)) obtained from the plant (Chang et al., 1988). Gypenosides (200 mg kg^{-1} i.g.) have also been shown to significantly improve the injury of DNA and RNA in cerebral cortex and hippocampus in vascular dementia rat (Zhang et al., 2002). Gypenosides (40 mg kg^{-1}) demonstrated a protective effect against ischaemia reperfusion damage of hippocampal structure in rats by decreasing neuronal damage, tissue superoxide dismutase activity, ATPase activity, malondialehyde content and ultrastructure changes in the hippocampus (Wang et al., 1997c). In cerebral ischemia-reperfusion injury in rats, gypenosides (100 mg kg^{-1}) abated DNA and RNA damage (Qi et al., 2000). Gypenosides dose-dependently restrained microsomal Na+, K(+)-ATPase enzyme activity rapidly and reversibly from rat hearts and brains *in vitro*. The IC_{50} of the gypenosides for the heart and brain was 58.79 ± 8.05 and 52.07 ± 6.25 mg l^{-1}, respectively. Gypenosides were also found to be an uncompetitive inhibitor of ATP (Han et al., 1996).

Effects on immune functions

Gypenosides displays immuno-potentiating properties. Total gypenosides (400 mg kg^{-1} i.g.) administered for 5 days to mice counteracted cyclophosphamide induced-reduction in serum haemolysin antibody level. About 150 and 300 mg kg^{-1} i.g. for 15 days in rats counteracted plaque forming cells (PFC) in spleen, specific rosette forming cells (SRFC) and reduction of antibody secreted by spleenocyte (QHS) induced by cyclophosphamide. Gypenoside (400 mg kg^{-1} i.g.) administered for 12 days counteracted the reduction of PFC, SRFC and QHS in S180 sarcoma mice. Gypenoside also alleviated cyclophosphamide-induced atrophy of immune organs in mice (Zhang et al., 1990). In mice, gypenoside (200 and 400 mg kg^{-1} i.g.) administered for 10 days displayed significant antagonistic effects on cyclophosphamide-induced thymus and spleen atrophy and a decrease in serum haemolysin antibody levels and a reduction in E-rosette (Zhang et al., 1990). In normal mice, gypenoside (50 and 100 mg kg^{-1} i.g.) administered for 10 days resulted in a bi-directional regulatory effect on thymus, spleen, haemolysin and E-rosette. Gypenoside (400 mg kg^{-1} i.g.) administered for 12 days counteracted cyclophosphamide-induced reduction of NK cell activities. Gypenoside (10 and 30 mg kg^{-1} s.c.) enhanced Con-A induced splenic T-lymphocyte and LPS-induced splenic B-lymphocyte proliferation and increased splenic cell IL-2 formation (Zhang et al., 1990).

Gypenoside (300 mg kg^{-1} i.g.) administered to mice for 7 days increased phagocytic functions of celiac macrophages, increased serum complement activity and decreased haemolysin antibody level. There was an increase in serum IgG content and an extended survival time of mice with myocardial transplant (China Pharmaceutical University, 1996). Gypenoside water extract (250 and 500 mg kg^{-1}) dispensed for 6 days resisted the cyclophosphamide-induced depletion of peripheral blood leukocytes in mice.

Total gypenosides (10 and 20 mg kg^{-1} i.p.) administered for 7 days enhanced rat splenic cell proliferative response to mitogen Con-A (the effect was more prominent in the 10 mg kg^{-1} group) and also decreased the noradrenaline content in the hypothalamus and spleen. There was also a negative correlation with the proliferation of splenic

cells. Plasma cortisol level was also decreased, suggesting that gypenosides affected immune response by exerting immune-enhancing effects on the neuro-endocrinoimmunologic regulatory network (China Pharmaceutical University, 1996).

Gypenoside (10–80 mg l^{-1} *in vitro* or 100 and 200 mg kg^{-1} i.p. injection) acted synergistically with Con A to significantly increase interleukin (IL)-2 production in normal murine splenic cells. Gypenoside (10–40 mg l^{-1} *in vitro* or 50–200 mg kg^{-1} i.p.) acted synergistically with Con-A to elevate the depressed IL-2 activity level in a 'Rhubarb spleen deficiency mouse model,' gradually returning the level to near normal (China Pharmaceutical University, 1996).

In a study by Liu et al. (1994), Gynosaponin P from *Gynostemma pentaphyllum* increased the surface fluidity of lymphocytes in the elderly. The mechanisms involved changes in membrane fluidity, surface antigens, receptor structures and protein synthesis.

Effects on cancer

Some of the saponins of *Gynostemma* were effective in the treatment of tumours (Wang, 1988; Zhou, 1988). The effects of gypenosides on the inhibition of *N*-acetyltransferase (NAT) activity, AF-DNA adduct formation and NAT gene expressions in a human cervix cancer cell line (Ca Ski) were examined (Chiu et al., 2003). It was found that the NAT activity and NAT mRNA expression in the human cervix intact cancer cells and cytosols were suppressed by gypenosides in a dose-dependent manner. The apparent values of K_m and V_{max} of NAT of human cervix cancer cells were also decreased by gypenosides in cytosols. It is speculated that gypenosides may act as non-competitive inhibitors. *G. pentaphyllum* reversed epithelial dysplasia in carcinogenesis of golden hamster cheek pouches after 3 weeks of exposure to dimethylbenzanthracene (Zhou et al., 1996a). Similarly, *G. pentaphyllum* opposed the carcinomatous conversions of leukoplasia of golden hamster cheek pouches (Zhou et al., 1998). In a study by Wang et al. (1995), *G. pentaphyllum* (2% in boiled water) displayed preventative and blocking effect on oesophageal cancer in rats. *G. pentaphyllum* prevented the free C_{20}-OH, which causes mutation of Ha-ras oncogene influencing canceration of leukoplakia in hamsters (Zhou et al., 2000). *G. pentaphyllum* blocked the development of oral mucosal premalignancy in golden hamster cheek pouch (Zhou et al., 1996b). *G. pentaphyllum* included in a conventional tonic mixture strengthened body resistance and inhibited tumour cells in human lung (Han et al., 1995). Gypenoside inhibited the proliferation viability of human hepatoma cell lines (Hep3B and HA22T) in a dose-dependent manner by apoptosis (Chen et al., 1999). Similarly, gypenoside-induced apoptosis was also observed in human hepatoma Huh-7 cell lines, where there was an up-regulation of Bax, Bak and Bcl-X(L), down-regulation of Bcl-2 and release of mitochondrial cytochrome *c* and activation of caspase cascade (Wang et al., 2002). Total gypenoside (50 mg kg^{-1} i.g. for 7 days) had inhibitory effects on mice sarcoma (S180) (Arichi et al., 1985a). Total gypenoside (30 and 300 mg kg^{-1} i.g. or 120 mg kg^{-1} i.p.) administered for 10 days hampered mice sarcoma (S180). Gypenoside (0.38–0.75% *in vitro*) had direct cytotoxic effects on S180 cells (China Pharmaceutical University, 1996). Gypenosides may also protect DNA via competing with mutagens for binding sites and also inhibit related metabolic enzymes. For example, gypenosides (0.33 mg ml^{-1}) inhibited 70% of EROD activities of microsomal protein cytochrome P_{448} *in vitro* (Mo et al., 1997). Gypenosides have also prevented cyclophosphamide-induced mutagenesis in mice and promoted DNA recovery (Wang and Bai, 1994; Qian, 2001). Gypenoside XXVII (20–40 mg kg^{-1} i.p. every other day) prolonged the survival of mice with ascites tumour (Takemoto and Odashima, 1983).

Effects on platelet aggregation and arachidonic acid metabolism

Total gypenosides (50 mg kg^{-1} s.c.) administered to rats inhibited the formation of platelet and venous thrombi. At 0.25, 0.5 and 1.0 mg ml^{-1}, gypenoside inhibited rabbit platelet TXA_2 formation. Gypenoside (1 mg ml^{-1}) inhibited 6-keto-PGF1 formation of rabbit aorta annulus. IC_{50} for TXB_2 and 6-ketoPGF_1 formation were 1.07 and 1.15 mg ml^{-1}, respectively (China Pharmaceutical University, 1996).

The hot water extracts of *G. pentaphyllum* at 1/100 and 1/200 concentrations had an aggregatory effect on bovine platelet preparations *in vitro*. This effect was inhibited by PGI_2 but not by aspirin

and could be abolished by β-glycosidase but not with protease. This suggested that the substance was a glycoside or polysaccharide (Takagi et al., 1985). *Gynostemma* as an anti-thrombotic agent was also studied by Tan et al. (1993), where *G. pentaphyllum* decreased the activity of multiple coagulation factors and accelerated the erythrocyte electrophoresis rate in human blood samples. Another study showed that *G. pentaphyllum* (40 mg kg^{-1}) hampered platelet aggregation in rabbit plasma by increasing the platelet cAMP level and reducing the releasing reaction of the platelet (Wu et al., 1990).

Other protective effects

G. pentaphyllum displays protective effects against toxicity. During radio- and chemo-therapy, *G. pentaphyllum* tablets taken at 180–240 mg per day protected patients' cellular immunity (Qian et al., 1995). Similarly, *G. pentaphyllum* taken at the beginning of chemotherapy prevented immunosuppression in patients by enhancing lymphocyte transformation (Hou et al., 1991). In γ-irradiated mice, *G. pentaphyllum* (32 mg kg^{-1}) improved decreased leukocyte counts, glutamic oxalacetic transaminase (GOT), GPT and IgG in serum and inhibited the proliferation of splenocytes stimulated by PHA, LPS and Con A (Chen et al., 1996). *G. pentaphyllum* (125 μg ml^{-1}) decreased the ultraviolet induction of bacteriophage lambda in lysogenic cells by 70% due to its scavenger effect for free radical (Zhu et al., 2001).

Gypenoside (10 mg kg^{-1} i.p.) administered for 10 days counteracted dexamethasone-induced atrophy of adrenal gland and thymus and decreased plasma cortisol in rats (Arichi et al., 1985b; China Pharmaceutical University, 1996). Tablets have been developed with *G. pentaphyllum* saponins and prednisone (Xu et al., 1994a) and dexamethasone (Xu et al., 1994b).

Gypenoside (20 and 40 mg kg^{-1} i.p.) reduced the toxicity of lidocaine and also decreased the mortality rate of the mice (China Pharmaceutical University, 1996). Gypenoside (20 and 40 mg kg^{-1} i.p.) facilitated growth of neonatal mice. There was a significant increase in body weight of the gypenoside group when compared to the control group.

Gypenosides also show hepatoprotective activity. Gypenoside (50 mg kg^{-1} s.c.) administered for 6 days hindered CCl_4-induced elevation in serum γ-glutamine transaminase in rats. There were also stimulatory effects on hepatic regeneration of rats after partial hepatic excision. *Gynostemma* water extract (100, 300 and 500 mg kg^{-1}) dose-dependently enhanced the recovery of liver injury via decreased necrosis of the centribular area, sinusoidal congestion, infiltration of the lymphocytes and Kupffer cells around the hepatic central vein. The loss of cell boundaries and ballooning degeneration was also decreased (Lin et al., 2000). Similarly, in rats with CCl_4 liver injury, the increase of SGOT, SGPT activities were significantly reduced by treatment with gypenoside (Chen et al., 2000). Total gypenosides (100 and 500 mg kg^{-1} mixed with food) reduced serum levels of β-glutamine transaminase, as well as hepatic lipid peroxides in rats with liver damage as a result of hyperlipidaemia caused by high fat and sugar diet (Kimura et al., 1983).

Anti-senescent and anti-oxidant activities are also observed with administration of *G. pentaphyllum*. Water extracts of gypenoside (0.5 and 1%) mixed in culture medium and fed to fruit flies extended the average life span of the flies and facilitated the growth and development of fruit fly larvae. In a D-galactose-induced subacute model of senescence in mice, gypenoside (15 mg per individual) administered for 40 days antagonised the decreased ability in learning active escape response, increased cerebral lipofuscin and also counteracted the abnormal increase in cerebral MAO-B activities. Gypenoside extract (0.5–1% aqueous solution) fed to houseflies lengthened their life span, increased cerebral superoxide dismutase activity and decreased the content of malondialdehyde (MDA). Gypenosides (50 mg l^{-1}) reversed changes in refractory periods, excitability and autonomicity in *in vitro* cardiac papillary muscles of guinea pigs. Free radical injury caused by xanthine – xanthine oxidase and MDA content in the myocardium were reduced. This suggests that gypenoside has a protective effect on free radical injuries of guinea pig myocardium. Gypenosides (25–100 μg ml^{-1}) dose-dependently protected rabbit thoracic aorta from electrolytic-free radical injury. At a concentration of 100 μg ml^{-1}, gypenosides counteracted electrolytic free radical-induced contraction of basilar arteries in rabbits. Gypenoside (15.6–500 mg l^{-1}) had inhibitory effects on MDA formation in rat hepatic microsomes (including spontaneous,

Fe^{2+}-cysteine, vitamin C–NADPH and CCl_4-induced peroxidation of hepatic microsomal lipid in rats). Gypenoside (2.5–160 mg l^{-1}) had protective effects on damaged hepatic microsome and mitochondria membrane fluidity. A gypenoside mixture (0.1 g per 2.5 g feed) fed to 5-month-old mice for 4 months significantly increased spontaneous activities and stamina in swimming. The gypenoside group also had a higher survival rate than the control group (China Pharmaceutical University, 1996). In an *in vitro* study conducted by Li and Lau (1993), gypenosides (20–160 μg ml^{-1}) were effective in lowering the O_2 and H_2O_2 content in activated human and murine phagocytes. Gypenosides also reversed the decreased membrane fluidity of liver microsomes and mitochondria, enhanced mitochondrial enzyme activity and decreased intracellular LDH in vascular endothelial cells. This result was also confirmed in a study by Li et al. (1993). The inhibition of lipid peroxidation in liver microsomes and vascular endothelial cells suggest that gypenosides may help in preventing and treating atherosclerosis, liver disease, other cardiovascular disease and inflammation. *G. pentaphyllum* also showed scavenging effects where it decreased O^{2-} and OH radicals (Ma and Yang, 1999).

Other medicinal effects

G. pentaphyllum exhibits anti-fatigue, anoxia tolerance and anti-hyperthermia effects. Total gypenoside administered orally at 200 mg kg^{-1} increased the swimming vitality of mice (Arichi et al., 1985c). Gypenoside at 200 mg kg^{-1} i.g. was given for 14 days to rats which swam for 1–2 h per day. This maintained a higher glycaemic level and decreased the depletion of muscle glycogen. Using the swimming test, gypenoside extract (450 mg kg^{-1} i.g.) increased the anoxia tolerance, anti-fatigue and anti-hyperthermia ability of the mice (42 ± 0.5 °C). Gypenoside (50 mg kg^{-1} i.g. for 3 days) extended the continuous swimming times in mice. Gypenoside (50 and 400 mg kg^{-1} i.g.) increased the anti-anoxia ability of mice. Gypenoside (75 and 100 mg kg^{-1} i.g.) extended the swimming and rod-climbing time of mice. At 100 and 200 mg kg^{-1} i.p., gypenoside increased the anti-anoxia ability of mice (China Pharmaceutical University, 1996).

G. pentaphyllum also showed prominent anti-inflammatory activity against carrageenan-induced paw oedema in rats (Lin et al. 1993). *G. pentaphyllum* could also be useful as a sedative and analgesic (Oshio et al., 1987).

Gypenosides also display anti-ulcer effects (Zhou, 1988; Nippon Shoji Co, 1985). Recently, a butanol fraction from *G. pentaphyllum* displayed anti-gastric ulcer properties. Pretreatment with the butanol fraction markedly preserved gastric wall mucus and hexosamine content in ethanol-induced ulcerated rats (Rujjanawate et al., 2004). In rats, gypenosides have been beneficial in reversing gastric ulcer induced by *Helicobacter pylori* (Zhang et al., 1999). Gypenosides XXX–XLI display anti-pectic ulcer activity (Nippon Shoji Co, 1983).

Toxicology and stability

Information provided by Ankang Pharmaceutical Institute of the Beijing Medical University indicates total gypenoside extracts are safe, without side effect and without toxicity. The Dictionary of Chinese Medicine describes *Gynostemma* as having 'no toxicity'. In a clinical trial using powder of *G. pentaphyllum* (2.5–3 g), prepared as tablets or capsules, administered 3 times a day for 10 days, 537 patients were treated for bronchitis: 4.7% were cured, 24.8% achieved significant effects, 49.5% achieved some effect and 21% had no effect. Adverse effects affecting a small number of patients included vomiting, abdomen tension, diarrhoea (or constipation), dizziness, blurred vision and tinnitus. These symptoms were mild and did not stop the patients from taking the medicine (Jian Su New Medical College, 1986). In the Practical Chinese Herbal Preparations Handbook, it was stated that gypenoside extract tablets and capsules have no contraindications. If patients felt any discomfort after taking a large dosage, the medicine should be stopped. Patients could continue to take the medicine as soon as any side effects were relieved (Song, 1996).

Mean lethal dosage (LD_{50}) in rat is 1.85 g kg^{-1} by the total gynosaponin injected into the abdominal cavity. Rats given 8 g kg^{-1} orally for one month showed no toxicity, adverse or side-effects. LD_{50} in mice is 755–838 mg kg^{-1} by total gynosaponin injected into the abdominal cavity and no toxicity with oral use (Guo and Wang, 1993). LD_{50} of gypenoside i.p. on mice was 402 ± 18.2 mg kg^{-1}.

LD_{50} of *Gynostemma* water extract i.g. on mice was 4.5 g kg^{-1}. LD_{50} of *Gynostemma* water extract i.p. on mice was 2.86 ± 0.3 g kg^{-1} (China Pharmaceutical University, 1996).

In subacute and subchronic toxicity tests, rats fed with gypenosides at levels of 1/5, 1/10, 1/20 of LD_{50} for 4 weeks, or at levels of 1/10, 1/20 of LD_{50} for 90 days did not show observable histopathological changes in the heart, liver, kidney, testes, ovaries, red and white blood cells, haemoglobin or changes in liver and kidney function (Ankang Pharmaceutical Institution of Beijing Medical University, promotional material, 1999). Recent studies on rats showed that the water extract of *G. pentaphyllum* had no chronic toxicity after 6 month of treatment (6, 30, 150 and 750 mg kg^{-1} orally) daily for 24 weeks (Attawish et al., 2004).

In accumulative toxicity experiments, gypenosides at levels of 1/5 its LD_{50} was fed to mice for 30 days. The accumulative toxicity index measured the accumulated toxicity. No deaths were observed (1/5 $LD_{50} \times 30 = 6$ LD_{50}, showing an accumulative index larger than 6). Thus, there was no accumulative toxicity for gypenosides. In teratogenicity tests, there were no observable effects on mice embryos when the parent mice were fed with gypenosides at levels of 1/5 and $\frac{1}{2}$ of LD_{50}. The neonatal mice born showed normal development and reproductive ability. No carcinogenicity or mutagenicity was observed after various experiments (Ankang Pharmaceutical Institution of Beijing Medical University, promotional material, 1999).

It is expected that the stability of total gypenosides will be established as for ginsenosides and ginsenoside-containing preparations from *P. ginseng*. In a study on the dissolution and stability of capsules, it was shown that hydroxy propyl methyl cellulose-coated micropills of total glycosides of *G. pentaphyllum* were stable at 40 °C and 75% relative humidity for 3 months (Liu et al., 1996). Testing of the stability of gypenoside extract capsules was carried out at the Ankang Pharmaceutical Institution of Beijing Medical University. Three batches of sample were stored at room temperature and examined every 6 months over a period of 36 months and compared with those of initial testing. The results showed that there were no significant changes in the colour of granules, TLC pattern, examination and content ($P < 0.05$ mean of three determinations) (Xu and Wang, 1999).

Pharmacokinetics and metabolism

The hydrolysis of gypenosides in the gastrointestinal tract will most likely emulate ginsenosides. In the rat large intestine, the breakdown products of Rb_1 included gypenoside XVII, ginsenoside Rd and F_2. Though both 20(*S*)-protopanaxadiol saponins, the decomposition modes of Rb_1 and Rb_2 in the rat large intestine could be dependent on the hydrolysis rate in the terminal sugar moiety at the C-20 hydroxyl group (Karikura et al., 1991). Gypenoside (300 mg kg^{-1} intramuscular (i.m.) in rat) in a blood assay sampled at 0.25, 0.5, 1.0, 0.5, 2.0, 3.0, 4.0, 6.0, 10.0 and 24 h had non-linear, two-compartment model pharmacokinetic characteristics. The main pharmacokinetic parameters were: $T_{1/2}$ ka = 0.289 h (half-life for max. rate of absorption), $T_{1/2}$ ke = 16.44 h (half-life for max. rate of excretion), $T_p = 1.878$ h (time for peak concentration), $C_{max} = 163.598\ \mu g\ ml^{-1}$ (peak concentration), AUC = 0.4170 ± 0.4 mg l h^{-1} (area under the curve).

In rats after gypenoside administration (300 mg kg^{-1} i.m.), the distribution of gypenosides (1 h post-administration) was mainly in the adrenal gland, brain, heart, liver, spleen, lung. In rabbits, the blood concentration of gypenoside (300 mg kg^{-1} i.m.) showed a double-peak phenomenon (1.8, 6.0 h). The second peak in the blood concentration was lost after bile drainage ($T_p = 1.112$ h). Bile excretion was the main excretion pathway of gypenosides from the body. Gypenosides excreted in bile for 24 h accounted for 2.03% of total drug administered. Gypenosides excreted in bile for the first 6 h accounted for 74.32% of the total gypenosides excreted in bile in the 24 h period. Further studies on dogs (300 mg kg^{-1} i.m.) using cross bile perfusion experiments showed that the double-peak phenomenon observed in the blood concentration was mainly due to hepato-enteric shunting (China Pharmaceutical University, 1996).

Potential therapeutic value

The more recent clinical application for *Gynostemma* is for the treatment of hyperlipidaemia (China Pharmaceutical University, 1996). *Gynostemma* tablets, composed mainly of gypenosides were approved by the Chinese government

in 1987 for lowering blood lipid (Guo and Wang, 1993). An 'elixir to life', its adaptogenic properties may be beneficial to overall health, strengthening the immune system, improving mind and digestive function, increasing stamina and preventing the signs of aging. By adjusting sugar levels and blood fat, healthy metabolic function can be achieved. *Gynostemma* may become an alternative supplement for sport athletes in an attempt to increase performance.

The herb can be prepared as a crude drug in tablet, capsule or oral fluid form. The most popular form is a tea bag containing the raw herb (Juchi, 1986). It can be made into a sports health beverage and can be added to mineral water, cola, wine, beer, biscuits and noodles (Osaka Yakuhin Kenkyusho, 1985a, b; Gao and Yu 1993). Other products include face wash, vanishing cream, freckle cream, soap, shampoo, bath liquid, hair oil, toothpaste and powder for body odour (Takemoto et al., 1986a; Guo and Wang, 1993).

Conclusion

There is significant interest in *G. pentaphyllum* as a mainstream herbal medicine, with the chemistry, biology and toxicology continually updated in the literature. In particular, the saponin content of the plant has become the centre of extensive investigation which includes a variety of biological activities congruent to the very popular expensive herbal medicine, *P. ginseng*. Both contain dammarane-type gylcosides, some of which are common to both plant species. Many chromatographic and spectroscopic techniques are available to isolate and identify gypenosides, respectively. However, the absolute stereochemistry of gypenosides is difficult to ascertain due to the difficulty of obtaining crystals of the compounds. Thus, further development of more specific methods for gypenoside analysis is required.

The major interest of *G. pentaphyllum* originated from its lipid lowering effects observed in animal models and human studies. Further research has revealed the herb's diverse pharmacological actions on the cardiovascular and immune systems. In many of these biological studies, however, gypenoside extracts were utilised. Thus, to fully comprehend the mechanism of action of *G. pentaphyllum*, individual gypenosides will need to be isolated and examined at the molecular level. The aglycone and sugar sequence of the gypenosides could determine activation or antagonism of particular nuclear receptors affecting the homeostasis of the biological function. Furthermore, the combination of the pharmacological effects plus its safety profile will provide potential clinical applications for hyperlipidaemia, cancer management, diabetes and other chronic conditions.

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References

Akihisa T, Shimizu N, Tamura T & Matsumoto T (1986) Structures of three new 24,24-dimethyl-Δ^7-sterols from *Gynostemma pentaphyllum*. Lipids 21(8): 515–517.

Akihisa T, Tamura T & Matsumoto T (1987) 14α-Methyl−5α-ergosta-9(11),24(28)-dien−3β-ol, a sterol from *Gynostemma pentaphyllum*. Phytochemistry 26(8): 2412–2413.

Akihisa T, Mihara H, Fujikawa T, Tamura T & Matsumoto T (1988) 24,24-Dimethyl-5-α-cholestan-3-β-ol, a sterol from *Gynostemma pentaphyllum*. Phytochemistry 27(9): 2931–2933.

Akihisa T, Kanari M, Tamura T & Matsumoto T (1989a) 24(*R*)- and 24(*S*)-14-α-methyl-5α-ergost-9(11)-en-3-β-ols from *Gynostemma pentaphyllum*. Phytochemistry 28(4): 1271–1273.

Akihisa T, Tamura T, Matsumoto T, Kokke WCMC & Yokota T (1989b) Isolation of acetylenic sterols from a higher plant. Further evidence that marine sterols are not unique. J. Organic Chem. 54(3): 606–610.

Akihisa T, Kokke WCMC, Yokota T, Tamura T & Matsumoto T (1990) 4-α,14-α-dimethyl-5-α-ergosta-7,9(11), 24(28)-trien-3-β-ol from *Phaseolus vulgaris* and *Gynostemma pentaphyllum*. Phytochemistry 29(5): 1647–1651.

Aktan F, Henness S, Roufogalis BD & Ammit AJ (2003) Gypenosides derived from *Gynostemma pentaphyllum* suppress NO synthesis in murine macrophages by inhibiting iNOS enzymatic activity and attenuating NF-κB-mediated iNOS protein expression. Nitric Oxide 8: 235–242.

Ankang Pharmaceutical Institution of Beijing Medical University, promotional material, 1999.

Arbain D, Cannon JR, Afriastini Kartawinata K, Djamal R, Bustari A, Dharma A, Rosmawaty Rivai H, Zaherman Basir D, Sjafar M, Sjaiful Nawfa R & Kosela S (1989) Survey of some West Sumatran plants for alkaloids. Econ. Bot. 43(1): 73–78.

Arichi S, Takemoto T & Uchida Y (1985a) Saponins of *Gynostemma pentaphyllum* as neoplasm inhibitors, Patent-Japan Kokai Tokkyo Koho-60 105, 627.

Arichi S, Takemoto T & Uchida Y (1985b) Prevention of glucocorticoid side effects by saponins of *Gynostemma pentaphyllum*, Patent-Japan Kokai Tokkyo Koho-60 105, 625.

Arichi S, Takemoto T & Uchida Y (1985c) Saponins of *Gynostemma pentaphyllum* as tonics, Patent-Japan Kokai Tokkyo Koho-60 105, 626.

Attawish A, Chivapat S, Phadungpat S, Bansiddhi J, Techadamrongsin Y, Mitrijit O, Chaorai B & Chavalittumrong P (2004) Chronic toxicity of *Gynostemma pentaphyllum*. Fitoterapia 75: 539–551.

Blumert M & Liu JL (1999) Jiaogulan China's "Immortality" Herb. Torchlight Publishing Inc., Badger, USA.

Bogdan C (2001) Nitric oxide and the immune response Nat. Immunol. 2(10): 907–916.

Chang S, Kuang P, Zhang JT, Chen YY & Ru CM (1988) Memory facilitation induced by *Gynostemma pentaphyllum* and gypenoside ll (Ginsenoside Rb_1) in mice. Acta Chin. Pharmacol. 4(6): 358–361.

Chang CK, Chang KS, Lin YC, Liu SY & Chen CY (2005) Hairy root cultures of *Gynostemma pentaphyllum* (Thunb.) Makino: a promising approach for the production of gypenosides as an alternative of Ginseng saponins. Biotechnol. Lett. 27(16): 1165–1169.

Chen JC, Chung JG & Chen LD (1999) Gypenoside induces apoptosis in human Hep3B and HA22T tumour cells. Cytobios 100: 37–48.

Chen JC, Tsai CC, Chen LD, Chen HH & Wang WC (2000) Therapeutic effect of gypenoside on chronic liver injury and fibrosis induced by CCl4 in rats. Am. J. Chin. Med. 28(2): 175–185.

Chen WC, Hau DM, Chen KT, Wang MI & Lin IH (1996) Protective effects of *Gynostemma pentaphyllum* in gamma-irradiated mice. Am. J. Chin. Med. 24(1): 83–92.

Cheng JG, (1990) Investigation of the plant Jiaogulan and its analogous herb. Wulianmei. Zhong Cao Yao 21(9): 424.

China Pharmaceutical University (1996) In: Yan Y-Q (ed.) Encyclopedia of Chinese Herbs Vol. 2, 1st ed. (pp. 1878–1882). China Medicine, Science and Technology Publisher, China.

Chiu TH, Chen JC & Chung JG (2003) *N*-acetyltransferase is involved in gypenosides-induced *N*-acetylation of 2-aminofluorene and DNA adduct formation in human cervix epidermoid carcinoma cells (Ca Ski). In Vivo 17(3): 281–288.

Circosta C, De Pasquale R & Occhiuto F (2005) Cardiovascular effects of the aqueous extract of *Gynostemma pentaphyllum* Makino. Phytomedicine 12: 638–643.

Cui JF, Eneroth P, Bruhn JG, Arihara S & Yoshikawa K (1998) Alkaline cleavage of gypenosides and characterization of dammarane-type aglycones by gas chromatography–mass spectrometry. Phytochem. Anal. 9(3): 128–133.

Cui JF, Eneroth P & Bruhn JG (1999) *Gynostemma pentaphyllum*: identification of major sapogenins and differentiation from Panax species. Eur. J. Pharmaceut. Sci. 8: 187–191.

Deng S, Li X, Chen B, Deng F & Zhou X (1994) Analysis of amino acids, vitamins, and chemical elements in *Gynostemma pentaphyllum* (Thunb) Makino. Hunan Yike Daxue Xuebao (Bulletin of Hunan Medical University) 19(6): 487–490.

Ding S & Zhu Z (1992) Resources of genus Gynostemma and determination of their total saponins contents. Zhongcaoyao 23(12): 627–629.

Fang ZP & Zeng XY (1989) Isolation and identification of flavonoids and organic acid from *Gynostemma pentaphyllum* Makino. Zhongguo Zhongyao Zazhi 14(11): 676–678.

Fang ZP & Zeng XY (1996) Structure of Gypentonoside A from *Gynostemma pentaphyllum* Makino. Acta Pharmaceut. Sin. 31: 680–683.

Gao Y & Yu B (1993) Wuxi Inst. Light Ind., Wuxi Inst. Ind., Wuxi, Peop. Rep. China. Preparation of *Gynostemma pentaphyllum* wine. Wuxi Qinggongye Xueyuan Xuebao 12(3): 183–186.

Guo S, Wang Q, Wang G & Ma Y (1987) Advances in the researchs on fiveleaf gynostemma (*Gynostemma pentaphyllum*). Zhongcaoyao 18(7): 325–328.

Guo WY & Wang WX (1993) Cultivation and utilisation of *Gynostemma pentaphyllum*. Publishing House of Electronics, Science and Technology University, pp. 1–261.

Hostettmann K & Marston A (1995) Chemistry and Pharmacology of Natural Products: Saponins. Cambridge University Press, New York.

Han MQ, Liu JX & Gao H (1995) Effects of 24 Chinese medicinal herbs on nucleic acid, protein and cell cycle of human lung adenocarcinoma cell. Zhongguo Zhong Xi Yi Jie He Za Zhi 15(3): 147–149.

Han X, Wei H, Wang Y & Luo C (1996) Inhibitory effects of gypenoside on rat heart and brain $Na+$, $K+$(-)ATPase activity. Zhongguo Zhong Yao Za Zhi 21: 299.

Hou J, Liu S, Ma Z, Lang X, Wang J, Wang J & Liang Z (1991) Effects of *Gynostemma pentaphyllum* on the immunological function of cancer patients. J. Traditional Chin. Med. 11(1): 47–52.

Hu LH, Chen ZL & Xie YY (1996) New triterpenoid saponins from *Gynostemma pentaphyllum*. J. Nat. Prod. 59(12): 1143–1145.

Hu LH, Chen ZL & Xie YY (1997) Dammarane-type glycosides from *Gynostemma pentaphyllum*. Phytochemistry 44(4): 667–670.

Huang C, Wu Z, Yao Y & Xu X (2004) Photosynthetic characteristics of *Gynostemma pentaphyllum* under shade. Ying Yong Sheng Tai Xue Bao 15: 2099–2103.

Huang TH-W, Razmovski-Naumovski V, Salam NK, Duke RK, Tran VH, Duke CC & Roufogalis BD (2005) A novel LXR-α activator identified from the natural product *Gynostemma pentaphyllum*. Biochem. Pharmacol. 70(9): 1298–1308 (DOI:10.1016).

Jang YJ, Kim JK, Lee MS, Ham IH, Whang WK, Kim KH & Kim HJ (2001) Hypoglycemic and hypolipidemic effects of crude saponin fractions from *Panax ginseng* and *Gynostemma pentaphyllum*. Yakhak Hoechi 45(5): 545–556.

Jian Su New Medical College (1986) The Dictionary of Chinese Medicine (Zhong Yao Da Ci Dian). Shanghai Science and Technology Press, Shanghai, China.

Jork H, Funk W, Fischer W & Wimmer H (1990) Thin-Layer Chromatography. Reagent and Detection Methods. Volume 1a. Physical and Chemical Detection Methods: Fundamentals, Reagents I. (pp. 412). VCH Verlagsgesellschaft mbH, Weinheim, Germany.

Juchi S (1986) Preparation of a tea-like beverage containing *Gynostemma pentaphyllum* saponins. Osaka Yakuhin Kenkyusho K. K. Patent-Japan Kokai Tokkyo Koho-61 104, 772.

Karikura M, Miyase T, Tanizawa H, Taniyama T & Takino Y (1991) Studies on absorption, distribution, excretion and metabolism of ginseng saponins. VII. Comparison of the decomposition modes of ginsenoside-Rb1 and -Rb2 in the

digestive tract of rats. Chem. Pharmaceut. Bull. (Tokyo) 39(9): 2357–2361.
Kimura Y, Okuda H, Arichi S & Takemoto T (1983) Effects of crude saponins of *Gynostemma pentaphyllum* on lipid metabolism. Shoyakugaku Zasshi 37: 272–275.
Kuwahara M, Kawanishi F, Komiya T & Oshio H (1989) Dammarane saponins of *Gynostemma pentaphyllum* Makino and isolation of malonylginsenosides-Rb1, -Rd, and malonylgypenoside V. Chem. Pharmaceut. Bull. 37(1): 135–139.
La Cour B, Molgaard P & Yi Z (1995) Traditional Chinese medicine in treatment of hyperlipidaemia. J. Ethnopharmacol. 46(2): 125–129.
Lee FC (1992) Facts about Ginseng, the elixir of life. Hollym Corporation, Seoul, Korea 69–75.
Li SZ (1985) Ben Chao Gangu Mu (Compendium of Materia Medica) vol. 2 (pp. 1326). People's Health Publisher, Beijing, China 1326.
Li L & Lau B (1993) Protection of vascular endothelial cells from hydrogen peroxide-induced oxidant injury by gypenosides, saponins of *Gynostemma pentaphyllum*. Phytother. Res. 7(4): 299–304.
Li L, Jiao LP & Lau BHS (1993) Protective effects of gypenosides against oxidative stress in phagocytes, vascular endothelial cells and liver microsomes. Cancer Biother. 8(3): 263–272.
Liang SX & Sun HW (2002) Determination of six nutritional elements in Chinese herbal medicines by graphite furnace atomic absorption spectrometry. Guang Pu Xue Yu Guang Pu Fen Xi 22(5): 847–849.
Lin CC, Huang PC & Lin JM (2000) Antioxidant and hepatoprotective effects of *Anoectochilus formosanus* and *Gynostemma pentaphyllum*. Am. J. Chin. Med. 28(1): 87–96.
Lin JM, Lin CC, Chiu HF, Yang JJ & Lee SG (1993) Evaluation of the anti-inflammatory and liver-protective effects of *Anoectochilus formosanus*, *Ganoderma lucidum* and *Gynostemma pentaphyllum* in rats. Am. J. Chin. Med. 21(1): 59–69.
Liu JD, Wang S, Lau HT, Yang LP & Nang GZ (1994) Effects of saponins from Chinese medicinal herbs on immune functions of lymphocytes in the elderly. Chin. J. Pharmacol. (Zhongguo Yaoxue Zazhi) 29(12): 717–721.
Liu X, Ye WC, Hsaio HWW, Che CT & Zhao SX (2003) Studies on chemical constituents of *Gynostemma pentaphyllum*. Zhongguo Yaoke Daxue Xuebao 34: 21–24.
Liu X, Ye W, Mo Z, Yu B, Zhao S, Wu H, Che C, Jiang R, Mak TCW & Hsaio WLW (2004) Five new ocotillone-type saponins from *Gynostemma pentaphyllum*. J. Nat. Prod. 67: 1147–1151.
Liu YP, Gao LL, Fan ZM & Guan ZW (1996) Studies on dissolution and stability of micropills of total glycosides of *Gynostemma pentaphylla*. Chin. J. Pharmaceut. Zhonogguo Yiyao Gongye Zazhi 27(8): 349–352.
Liu G, Guo D, Zhong R, Yao Z, Wen H, He W & Hu W (1997) Determination on the glycosyl sequence of gypenoside A by TLC-FABMS. Zhong Yao Cai 20(8): 398–400.
Ma YC, Zhu J, Benkrima L, Luo M, Sun LH, Sain S, Kont K & Plaut-Carcasson YJ (1995) A comparative evaluation of ginsenosides in commercial ginseng products and tissue culture samples using HPLC. J. Herbs, Spices, Med. Plants 3(4): 41–50.
Ma Z & Yang Z (1999) Scavenging effects of *Astragalus* and *Gynostemma pentaphyllum* with its product on O^{2-} and OH. Zhong Yao Cai 22(6): 303–306.
Mackay M, Wei JX & Chen YG (1991) Structure of a new dammarane-type triterpene from *Gynostemma pentaphyllum* (Thurb.) Makino. Acta Crystallogr. Sec. C: Crystal Struct. Commun. C47: 790–793.
Marino A, Elbert GM & Cataldo A (1989) Sterols from *Gynostemma pentaphyllum*. Bolletino della Societa Italiana di Biologia Sperimentale 65(4): 317–319.
Megalli S & Roufogalis BD (2005) Cholesterol lowering for healthy hearts: a herbal approach. Aust. J. Pharm. 86: 326–330.
Megalli S, Aktan F, Davies NM & Roufogalis BD (2005) Phytopreventative anti-hyperlipidemic effects of *Gynostemma pentaphyllum* in rats. J. Pharm. Pharmaceut. Sci. 8(3): 507–515.
Mo YY, Luo SQ, Dong JP & Yang Y (1997) The new progress of the anti-cancer function researches of *Gynostemma pentaphyllum*. Northwestern J. Pharmacol. (Xi Bei Yao Xue Za Zhi) 12(4): 177–178.
Nagai M, Izawa K, Nagumo S, Sakurai N & Inoue T (1981) Two glycosides of a novel dammarane alcohol from *Gynostemma pentaphyllum*. Chem. Pharmaceut. Bull. 29: 779–783.
Nippon Shoji Co., Ltd. (1983) Gypenosides. Jpn. Kokai Tokkyo Koho, JKXXAF JP 58208300 A2 19831203 Showa. JP 82-91793 19820528. CAN 14: 206696 AN 1984: 206696, Japan.
Nippon Shoji Co., Ltd. (1985) Gypenosides. Patent-Japan Kokai Tokkyo Koho-58, 208, 34: 10 pp. Chemical Abstract 14: 206696y.
Nippon Shoji Co., Ltd and Takemoto T (1983) Saponins from *Gynostemma pentaphyllum* Jpn. Kokai Tokkyo Koho, JKXXAF JP 58057398 A2 19830405 Showa. CAN 99:76853 AN 1983: 476853.
Norberg A, Hoa NK, Liepinsh E, Van Phan D, Thuan ND, Jornvall H, Sillard R & Ostenson CG (2004) A novel insulin-releasing substance, phanoside, from the plant *Gynostemma pentaphyllum*. J. Biol. Chem. 279(40): 41361–41367.
Osaka Yakuhin Kenkyusho KK (1985a) Saponins from *Gynostemma pentaphyllum* as health food supplements. Patent-Japan Kokai Tokkyo Koho-60 43, 358.
Osaka Yakuhin Kenkyusho KK (1985b) Rice vinegar containing saponins as health food supplement. Patent-Japan Kokai Tokkyo Koho-60 37, 960.
Oshio H, Kuwahara M & Komiya T (1987) Ginsenoside – Rd. Takeda Chemical Industries Ltd. Patent-Brit UK Pat-2, 179, 042.
Piacente S, Pizza C, De Tommasi N & De Simone F (1995) New dammarane-type glycosides from *Gynostemma pentaphyllum*. J. Nat. Prod. 58(4): 512–519.
Purmova J & Opletal L (1995) Phytotherapeutic aspects of diseases of the cardiovascular system. 5. Saponins and possibilities of their use in prevention and therapy. Ceska Slov Farm. 44(5): 246–251.
Qian XW (2001) Repairing function of *Gynostemma pentaphyllum* on damaged DNA induced by potassium aluminium sulfate or cyclophosphamide. Zhongguo Gonggong Weisheng 17(11): 1009–1010.
Qin Z, Zhao L, Bi S & You L (1992) Saponin constituents and resource of *Gynostemma pentaphyllum*. Tianran Chanwu Yanjiu Yu Kaifa 4(1): 83–98.
Qi G, Zhang L & Li C (1996) Influence of gypenoside on serum lipoprotein and atherosclerosis in hyperlipidemia animals. Zhongguo Zhongyao Zazhi 21: 562–564.
Qi G, Zhang L, Xie WL, Chen XY & Li JS (2000) Protective effect of gypenosides on DNA and RNA of rat neurons in cerebral ischemia-reperfusion injury. Acta Pharmacol. Sin. 21(12): 1193–1196.

Qian H, Fu S, Jiang G, Wang L, Fu X, Ye M & Zhao S (1995) Protective effect of Jiaogulan on cellular immunity of the patients with primary lung cancer treated by radiotherapy plus chemotherapy. Acta Acad. Med. Shanghai 22(5): 363–366.

Razmovski-Naumovski V, Li GQ & Duke CC (2005a) *Gynostemma pentaphyllum* and its cultivation in Sydney, Australia. J. Appl. Hort. (in press).

Razmovski-Naumovski V, Duke RK, Turner P & Duke CC (2005b) (20*S*), 2α, 3β, 12β- Trihydroxydammar-24-ene 20-*O*-β-D-glucopyranoside (Gynosaponin TN1) as the 2,5-methanol solvate. Acta Crystallogr. Sec. E 61(5): o1239–o1241.

Rujjanawate C, Kanjanapothi D & Amornlerdpison D (2004) The anti-gastric ulcer effect of *Gynostemma pentaphyllum* Makino. Phytomedicine 11(5): 431–435.

Scifinder Scholar, Version 2004 copyright© 2003 American Chemical Society.

Song CZ (1996) Practical Chinese Herbal Preparations Handbook People's Army Medical Press, Beijing, China.

Takagi J, Imada T, Kikuchi T, Saito Y & Inada Y (1985) A new platelet aggregation factor from *Gynostemma pentaphyllum* Makino. Chem. Pharmaceut. Bull. 33(12): 5568–5571.

Takemoto T & Nippon Shoji Co., Ltd (1984a) Gynosaponin E extraction from *Gynostemma pentaphyllum*. Jpn. Kokai Tokkyo Koho, JKXXAF JP 59080698 A2 19840510 Showa. JP 83–170424 19830914, CAN 101: 235568, AN 1984: 635568.

Takemoto T & Nippon Shoji Co., Ltd (1984b) Gynosaponins G, K, and progynosaponin A2 extraction from *Gynostemma pentaphyllum*. Japan Kokai Tokkyo Koho, JKXXAF JP 59080697 A2 19840510 Showa. JP 83-170423 19830914, CAN 101: 216398, AN 1984: 616398.

Takemoto T & Nippon Shoji Co., Ltd (1984c) Gynosaponins extraction from *Gynostemma pentaphyllum*. Japan Kokai Tokkyo Koho, JKXXAF JP 59080696 A2 19840510 Showa. JP 83-170422 19830914, CAN 101: 216399, AN 1984: 616399.

Takemoto T & Nippon Shoji Co., Ltd (1984d) Gynosaponins M, N, and O extraction from *Gynostemma pentaphyllum*. Japan Kokai Tokkyo Koho JKXXAF JP 59080699 A2 19840510 Showa. JP 83-170425 19830914, CAN 101: 235567, AN 1984: 635567.

Takemoto T, Arichi S, Arihara S, Nakajima T, Okuhira M & Uchida Y (1981) Gynosaponins and drug preparations containing these compounds. Ger. Offen. DE 80-3042117 19801107. CAN 96: 24789. AN 1982: 24789.

Takemoto T, Arichi S, Arihara S, Nakajima T, Okuhira M & Yoshihiro U (1982) Gynosaponins, their use and a process for preparing the same. Patent 4339422, SN: 205377, INTL: A01N 031/00, US: 424/182.

Takemoto T, Arihara S, Nakajima T & Okuhira M (1983a) Studies on the constituents of *Gynostemma pentaphyllum* MAKINO. I. Structures of Gypenoside I-XIV. Yakugaku Zasshi 103(2): 173–185.

Takemoto T, Arihara S, Nakajima T & Okuhira M (1983b) Studies on the constituents of *Gynostemma pentaphyllum* MAKINO. II. Structures of Gypenoside XV–XXI. Yakugaku Zasshi 103(10): 1015–1023.

Takemoto T & Odashima T (1983) Antitumor saponins from *Gynostemma pentaphyllum*. Rhoto Pharmaceuticals Ltd. Japan Kokai Tokkyo Koho, JKXXAF JP 58059921 A2 19830409 Showa. JP 81-157925 19811002. CAN 99: 47915 AN 1983: 447915.

Takemoto T, Arihara S, Yoshikawa K, Nakajima T & Okuhira M (1984a) Studies on the constituents of Cucurbitaceae Plants. VIII. On the saponin constituents of *Gynostemma pentaphyllum* MAKINO.(4). Yakugaku Zasshi 104(4): 332–339.

Takemoto T, Arihara S, Yoshikawa K, Nakajima T & Okuhira M (1984b) Studies on the constituents of Cucurbitaceae plants. IX. On the saponin constituents of *Gynostemma pentaphyllum* MAKINO.(5). Yakugaku Zasshi 104: 724–730.

Takemoto T, Arihara S, Yoshikawa K, Nakajima T & Okuhira M (1984c) Studies on the constituents of Cucurbitaceae plants. VII. On the saponin constituents of *Gynostemma pentaphyllum* MAKINO. (3). Yakugaku Zasshi 104(4): 325–331.

Takemoto T, Arihara S, Yoshikawa K, Nakajima T & Okuhira M (1984d) Studies on the constituents of Cucurbitaceae plants. X. On the saponin constituents of *Gynostemma pentaphyllum* MAKINO. (6). Yakugaku Zasshi 104(9): 939–945.

Takemoto T, Arihara S, Yoshikawa K, Kawasaki J, Nakajima T & Okuhira M (1984e) Studies on the constituents of Cucurbitaceae plants. XI. On the saponin constituents of *Gynostemma pentaphyllum* MAKINO. (7). Yakugaku Zasshi 104(10): 1043–1049.

Takemoto T, Arihara S, Yoshikawa K, Hino K, Nakajima T & Okuhira M (1984f) Studies on the constituents of Cucurbitaceae plants. XII. On the saponin constituents of *Gynostemma pentaphyllum* MAKINO. (8). Yakugaku Zasshi 104: 1115–1162.

Takemoto T, Arihara S & Yoshikawa K (1986b) Studies on the constituents of Cucurbitaceae plants. XIV. On the saponin constituents of *Gynostemma pentaphyllum* Makino. Yakugaku Zasshi 106(8): 664–670.

Takemoto T, Hayashi S & Nishimoto K (1986a) Gypenoside-containing extracts of *Gynostemma pentaphyllum* for the control of underarm odour. Patent-Japan Kokai Tokkyo Koho-61 76, 412: 10 pp. Chemical Abstract 105: 30100m (Rohto Pharmaceutical Co., Ltd.).

Tan H, Liu ZL & Liu MJ (1993) Antithrombotic effect of *Gynostemma pentaphyllum*. Chung-Kuo Chung His i Chieh Ho Tsa Chih (Chin. J. Integr. Traditional Western Med.) 13(5): 278–280.

Tanner MA, Bu X, Steimle JA & Myers PR (1999) The direct release of nitric oxide by gypenosides derived from the herb *Gynostemma pentaphyllum*. Nitric Oxide 3(5): 359–365.

Wang BQ (1994) Research on the Quality of Chinese Preparative Medicines and Reference Substances China Medical and Phamaceutical Science and Technology Press, Beijing, China.

Wang C, Wang X, Li Y, Deng S, Jiang Y & Yue L (1995) A preliminary observation of the preventative and blocking effect of *Gynostemma pentaphyllum* (Thunb) Makino on esophageal cancer in rats. Hua-Hsi i Ko Ta Hsueh Hsueh Pao (J. West China Univ. Med. Sci.) 26(4): 430–432.

Wang J & Li X (1997) Leaves and stems of *Panax quinquefolium* L. (I) Isolation and identification of eleven triterpenoid saponins. Zhongguo Yaowu Huaxue Zazhi 7(2): 130–132.

Wang J, Lu Z, Chi J, Wang W, Su M, Kou W, Yu P, Yu J, Chen L, Zhu JS & Chang J (1997b) Multicenter clinical trial of the serum lipid-lowering effects of a *Monascus purpureus* (red yeast) rice preparation from traditional Chinese medicine. Curr. Ther. Res. 58(12): 964–978.

Wang M, Wu Y & Chen T (1997a) Extract of gynosaponin by column chromatography. Guizhou Gongye Daxue Xuebao 26(3): 60–63.

Wang QG, Hu SL, He LY, Jiang CE, Lei YN & Lin YS (1997c) Inhibitory effect of *Gynostemma pentaphyllum* against ische-

mia reperfusion damage of hippocampal structure in rat. Zhongguo Bingli Shengli Zazhi 13(5): 513–516.
Wang YQ (1988) Antitumor effect of gypenoside Zhong Xi Yi Jie He Za Zhi 8: 286–262.
Wang QF, Chen JC, Hsieh SJ, Cheng CC & Hsu SL (2002) Regulation of Bcl-2 family molecules and activation of caspase cascade involved in gypenosides-induced apoptosis in human hepatoma cells. Cancer Lett. 183(2): 169–178.
Wang WX, Yang Y, Deng M, Ke W, Ding MQ & Dai WP (1996) Effect of ecological factor on the total gynosaponin content of *Gynostemma pentaphyllum* (Thunb.) Makino. J. Chin. Traditional Herbal Drugs 27(9): 559–561.
Wang YG & Bai RR (1994) Effects of gypenosides (GP) on mutagenesis induced by cyclophosphamide (CP) in mice. Zhongguo Yaolixue Tongbao 10(6): 457–459.
Wang ZY & Qui P (1992) Protective effect of gypenosides on acute incomplete cerebral ischemia in rabbits. Zhongguo Yaolixue Yu Dulixue Zazhi 6(3): 204–206.
Wang QY, Guo QS, Sun JY, Zhang SD & Li YH (2004) Studies on sex identification and variation of endogenous hormones in female and male plants of *Gynostemma pentaphyllum*. Zhongguo Zhong Yao Za Zhi 29(9): 837–840.
Wei J, Chen Y & Cao S (1992) Saponins in the fruit pedicels of *Panax notoginseng* (Burk.). Zhongguo Zhongyao Zazhi 17(10): 611–613.
Wu J, Qui P, Liu J, Mu Q & Xin D (1990) Effects of gypenosides on platelet aggregation release and cAMP level in rabbits. Zhongguo Yaolixue Yu Dulixue Zazhi 4(1): 54–57.
Wu QJ (1957) Zi Wu Ming Shi Tu Kau (Textual Investigation of Herbal Plants) 2Shang Wu Publishing House, China 559.
Wu YG (ed.) (1998) Dictionary of Chinese Materia Medica, Vol. 2, 1st ed. Shanghai Science and Technological Publishing House, Shanghai, China, 1088 pp.
Xie PS & Yan YZ (1987) HPTLC fingerprint identification of commercial ginseng drugs-reinvestigation of HPTLC of ginsenosides. J. High Resolu. Chromatogr. Chromatogr. Commun. 10(11): 607–613.
Xu S, Xiang H & Zhou J (1994) Pharmacological effect of gypenosides. J. Sun Yatsen Univ. 6(Suppl.): 64–68.
Xu S, Yao L & Wang Y (1994a) Prepararation of Gulanpenisong capsules and tablets containing *Gynostemma pentaphyllum* saponin and prednisone. Ankang Medicinal Plant Development Institute. Patent-Faming Zhuanli Shenqing Gongkai Shuomingshu-1,088,783.
Xu S, Yao L & Wang Y (1994b) Pharmaceutical tablets containing dexamethasone and *Gynostemma pentaphyllum* saponins. Patent-Faming Zhuanli Shenqing Gongkai Shuomingshu-1,089,139.
Xu SM & Wang YQ (1999) Testing of the stability of Gynostemma gypenosides extract capsules. Ankang Pharmaceutical Institution of Beijing Medical University (2 page report).
Yao YP, Liu GQ, Wen HH, He WD, Zhao SK & Hu WM (1994) Determination of the glycosyl sequence of glycosides by enzymic hydrolysis followed by TLC-FABMS. J. Chromatogr. – Modern TLC 7(5): 410–412.
Yin F, Hu L & Pan R (2004a) Novel dammarane-type glycosides from *Gynostemma pentaphyllum*. Chem. Pharmaceut. Bull. 52(12): 1440–1444.
Yin F, Hu L, Lou F & Pan R (2004b) Dammarane-type glycosides from *Gynostemma pentaphyllum*. J. Nat. Prod. 67(6): 942–952.
Yoshikawa K, Takemoto T & Arihara S (1986) Studies on the constituents of Cucurbitaceae Plants. XV. On the saponin constituents of *Gynostemma pentaphyllum* MAKINO. (10). Yakugaku Zasshi 106(9): 758–763.
Yoshikawa K, Mitake M, Takemoto T & Arihara S (1987a) Studies on the constituents of Cucurbitaceae Plants. XVII. On the saponin constituents of *Gynostemma pentaphyllum* MAKINO. (12). Yakugaku Zasshi 107: 355–360.
Yoshikawa K, Takemoto T & Arihara S (1987b) Studies on the constituents of Cucurbitaceae plants. XVI. On the saponin constituents of *Gynostemma pentaphyllum* Makino. (II). Yakugaku Zasshi 107(4): 262–267.
Yoshikawa K, Arimitsu M, Kuki K, Takemoto T & Arihara S (1987c) Studies on the constituents of Cucurbitaceae plants. XVIII. On the saponin constituents of *Gynostemma pentaphyllum* MAKINO. (13). Yakugaku Zasshi 107(5): 361–366.
Yoshikawa K, Arihara S, Matsuura K & Miyase T (1991) Dammarane saponins from *Gymnema sylvestre*. Phytochemistry 31(1): 237–241.
Yoshikawa M, Murakami T, Ueno T, Yashiro K, Hirokawa N, Murakami N, Yamahara J, Matsuda H, Saijoh R & Tanaka O (1997) Bioactive saponins and glycosides. VIII. Notoginseng (1): New dammarane-type triterpene oligoglycosides, notoginsenosides-A, -B, -C, and -D, from the dried root of *Panax notoginseng* (Burk.) F. H. Chen. Chem. Pharmaceut. Bull. 45(6): 1039–1045.
Yu C (1993) Therapeutic effect of tablet gypenosides on 32 patients with hyperlipaemia. Hu Dei Zhong Yi Za Zhi 15(3): 21.
Zhang C, Yang X & Xu L (1990) Immunomodulatory action of the total saponin of *Gynostemma pentaphylla*. Zhong Xi Yi Jie He Za Zhi 10(2): 69–70, 96–98.
Zhang ZH, Liu H, Zhao LH & Han XZ (1989) Clonal propagation of *Gynostemma pentaphyllum* (Thumb.) Makino in test tubes. Zhongguo Zhong Yao Za Zhi 14: 335–336.
Zhang H, Wu Q & Liu D (1995) Protoplast culture and plant regeneration from the suspension cells of *Gynostemma pentaphyllum* (Thumb) Mak. Chin. J. Biotechnol. 11: 207–211.
Zhang L, Wu GL, Chen XY & Qi G (2002) Protective effect of gypenosides on cerebral cortex and hippocampus in vascular dementia rat. Zhongcaoyao 33(4): 330–331.
Zhang QB, Ma JJ, Chao ZX & Lin ZB (1999) Therapeutic role and its mechanism of gypenosides on delayed healing of experimental gastric ulcer induced by NCTC11637 strain HP in rats. Chin. Pharmacol. Bull. 15(3): 225–228.
Zhang Z, Xie SJ, Huang SP & Zhang Q (1993) Analysis of medicinal and nutritional components in *Gynostemma pentaphyllum*. Shanxi Daxue Xuebao Ziran Kexueban 16(3): 307–310.
Zhao C, Chen H & Zou S (1994) Pharmaceutical granules containing *Gynostemma pentaphyllum* saponins for cardiovascular or cerebrovascular disease, Patent-Faming Zhuanli Shenqing Gongkai Shuomingshu 1, 089, 140.
Zhao Z, Xing L, Ma Z & Ren HI (1995) Modified method for the extraction of total saponins from *Gynostemma pentaphyllum*. Zhongcaoyao 26(11): 580–581.
Zheng J & He W (2000) Separation and identification of2α, 3β, 12β,20(*S*)- tetrahydroxydammar-24-ene-3-*O*-β-sophoroside-20-*O*-β-rutinoside from saponins of *Gynostemma pentaphyllum* (Thumb.) Marko. Guangdong Yaoxueyuan Xuebao 16(3): 203–204.
Zheng Z, Dong ZH & She J (1998) Modern Study of Traditional Chinese Medicine. 4Xue Yuan Press, Beijing, China 3519.

Zhou B & Cheng X (1996) Assay of ginsenosides and elements in *Gynostemma pentaphylla* Mak. Guangdong Weiliang Yuansu Kexue 3(3): 58–59 .

Zhou H (1988) The saponin constituents and pharmacology of *Gynostemma pentaphyllum* Mak Yaoxue Tongbao 23(12): 720–724.

Zhou Z, Wang Y & Zhou Y (1996a) The effect of *Gynostemma pentaphyllum* mak (GP) on carcinogenesis of the golden hamster cheek pouch induced by DMBA. Zhonghua Kou Qiang Yi Xue Za Zhi 31(5): 267–270.

Zhou ZT, Zhang SL, Li WG & Jin ZG (1996b) Observation of the effectiveness of compound *Gynostemma pentaphyllum* Mak in golden hamster cheek pouch's premalignancy. Shanghai Kou Qiang Yi Xue 5(2): 74–76.

Zhou Z, Wang Y, Zhou Y & Zhang S (1998) Effect of *Gynostemma pentaphyllum* Mak on carcinomatous conversions of golden hamster cheek pouches induced by dimethylbenzanthracene: a histological study. Chin. Med. J. 111(9): 847–850.

Zhou Z, Tang G & Zhong W (2000) Experimental study on the influence of *Gynostemma pentaphyllam* Mak upon point mutation of Ha-ras oncogene in blocking leukoplakia from canceration. Zhonghua Kou Qiang Yi Xue Za Zhi 35(2): 91–94.

Zhu S, Fang C, Zhu S, Peng F, Zhang L & Fan C (2001) Inhibitory effects of *Gynostemma pentaphyllum* on the UV induction of bacteriophage lambda in lysogenic *Escherichia coli*. Curr. Microbiol. 43(4): 299–301.