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Review Article

Recent studies on *Tripterygium wilfordii*

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Introduction

Tripterygium wilfordii, a liana widely distributed in southern China, was a source of an insecticide in Chinese folklore due to its high toxicity. Roots of the plant were also used in traditional Chinese medicine for the treatment of various diseases including rheumatoid arthritis, nephritis, systemic lupus erythematous, *etc.* Isolation and identification of active compounds from this plant can be traced back to the 1930s, when Zhao *et al.* chemically isolated and identified tripterine (celastrol) from *T. wilfordii* (1). In 1972 (2), the activity-directed isolation of tumor inhibitors of plant origin yielded triptolide and tripdiolide with potent antileukemic properties. Since then, many bioactive compounds have been isolated and identified from the plant in China. They include triptonide, tripchlorolide, triptriolide, triptolidenol, triptophenolide methyl ether, 16-hydroxytriptolide, 12-methoxy-triptonoterpene, triptotriterpenic acid B, 1-hydroxy-2,6,8-trimethyl-9-fluorenone and salaspermic acid (3, 4). These natural products showed diverse biological properties such as antitumor, anti-HIV, antiinflammatory, immunosuppressive and antifertility activities. The extract from the roots of this plant has been introduced into clinical trials for the treatment of several types of disease and has shown good therapeutic effects without severe adverse reactions. Thus, studies of the pharmacological actions of the most interesting compounds from this plant is the focus of this review.

Source and chemistry

T. wilfordii, often called Lei-gong-teng (Thunder God vine) in China, is a woody vine-like rambling shrub native to southern China. The plant belongs to the family Celastraceae and is propagated easily from cuttings. Studies have demonstrated that the plant's main toxicity is present in the root bark and, consequently, the plant is cultivated in China as a source of an insecticide. Medical use of the herb can be traced back about 2000 years, when the plant was used for the treatment of fever, chills, edema and inflammation in traditional Chinese medicine. Western-trained physicians have also been using the plant to treat rheumatoid arthritis, nephritis and various skin disorders including psoriasis, allergic angiitis, *etc.* with some promising results. However, side effects and the quality of crude preparations used clinically cannot be easily controlled. Therefore, purification of the root extract after removal from the bark resulted in the production of a fraction known as "Lei-gong-teng duo-dai" (LGTDD) or glycosides of *T. wilfordii* (GTW). This fraction is extracted from the root xylem with water, then with chloroform and finally obtained by separation on column chromatography. The term GTW is not correct because it chemically contains no glycosides; however it will be used here to describe the hydrophilic fraction of *T. wilfordii* which has a similar solubility to glycosides.

To date, more than 60 pure components have been isolated from *T. wilfordii* and are mainly classified into alkaloids, diterpenoids and triterpenoids. Several alkaloids, including wilforine, wilfordine, wilforgine, wilfortrine and wilforzine, exhibit insecticidal activities. Their chemical structures are very similar, containing the same polyhydroxy nucleus but different esterified linkages. Since Kupchan *et al.* (2) reported the isolation and structure of two antileukemic diterpenoid triepoxides in 1972, considerable interest has been generated in finding more diterpenoids from the plant. Several triterpenoids, including celastrol, have also been isolated from the extract of the plant. These triterpenoids are mostly hydroxylated carboxylic acids, where the hydroxyl or carboxylic groups are located in the triterpene skeletons with different positions and configurations. Interestingly, few fluorenones are of natural origin. However, 1-hydroxy-2,6,8-trimethyl-9-

fluorenone possesses the same structural skeleton first discovered in *T. wilfordii*. Due to low yields during isolation, alternative sources have also been considered, including total synthesis and production by tissue culture of the plant. The chemical structures of some compounds of *T. wilfordii* are shown in Figure 1.

Pharmacological actions

Although much research is needed before the exact pharmacological properties of *T. wilfordii* are known, the plant demonstrates *in vitro* and *in vivo* activity in various experimental models.

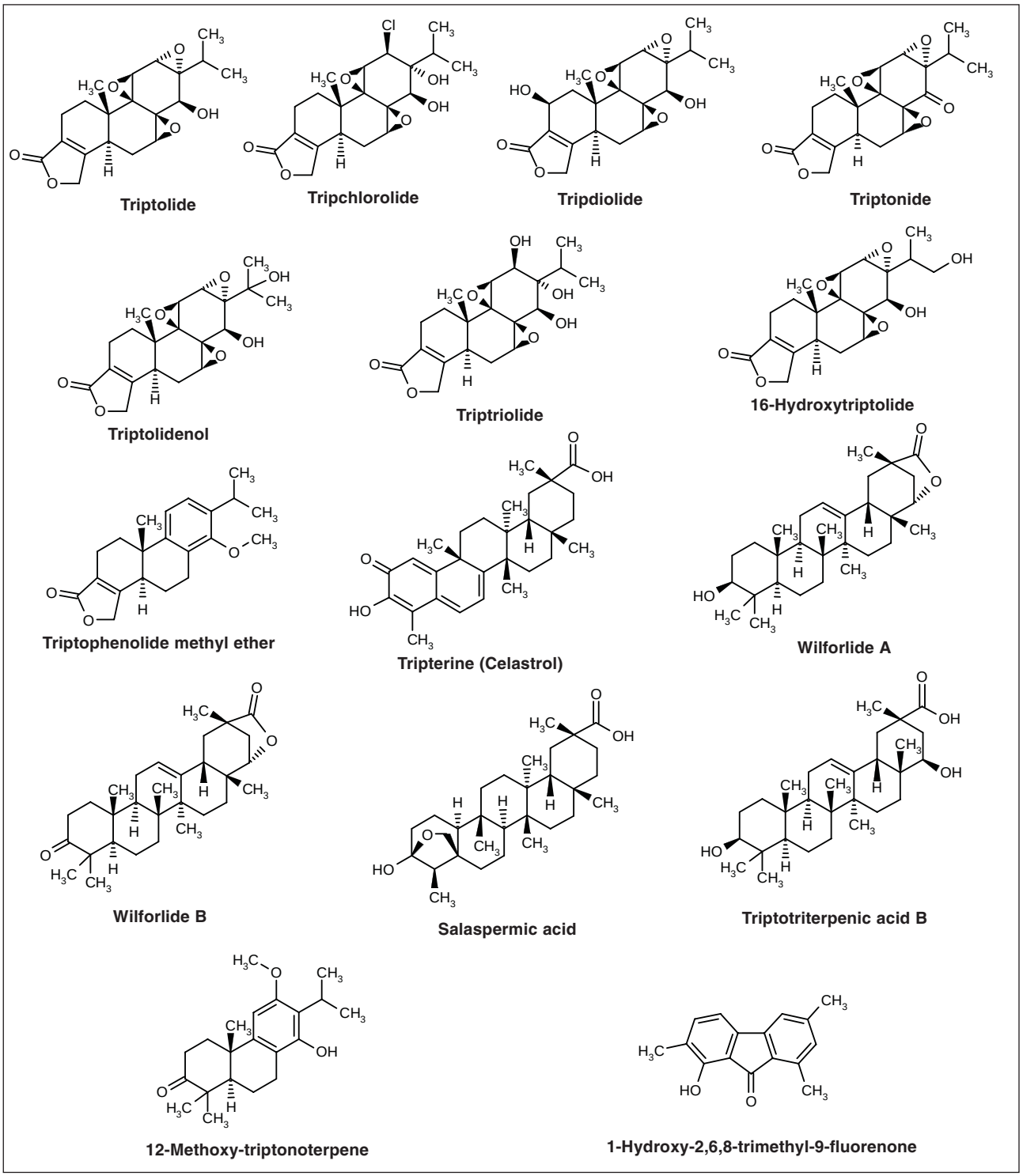

Fig. 1. Chemical structures of some compounds isolated from *T. wilfordii*.

Table I: IC_{50} and IC_{70} values of human cancer cell lines after continuous exposure to triptolide.

Cell line	IC_{50} (μg/l)	IC_{70} (μg/l)
Breast cancer		
MCF-7	0.50	1.19
BT-20	0.77	1.55
Stomach cancer		
MKN-45	1.22	1.96
MKN-7	0.90	1.76
KATO-III	9.54	17.30
Leukemia		
HL-60	0.90	2.09

Table II: Inhibition of HIV-1 reverse transcriptase by salaspermic acid.

Template-primer	EC_{50} (μg/ml)
Poly(rA)-oligo(dT)	16
Poly(rC)-oligo(dG)	15
Poly(rU)-oligo(dA)	>100[a]
Poly(rG)-oligo(dC)	>100[b]

[a]63% of control at 100 μg/ml; [b]96% of control at 100 μg/ml.

Antitumor

An alcohol extract of *T. wilfordii* was found to have significant effects against leukemia in mice. Systematic fractionation led to the isolation of triptolide and tripdiolide as the active antileukemic principle in 1972 (2, 5). Treatment with the compounds (0.1 mg/kg) significantly prolonged the life span in mice with L1210 lymphoid leukemia (≥ 230 days). Triptolide was also found to inhibit the growth of several other leukemia cell lines such as P388, L615 and HL-60 (6). In addition, triptolide had suppressive effects on the growth of several human solid tumors (7). As shown in Table I, triptolide inhibited colony formation of MCF-7 and BT-20 breast cancer and MKN-45 and MKN-7 stomach cancer cell lines at 10 nM with a magnitude similar to the effects observed on the HL-60 leukemia cell line when cells were continuously exposed to the agent. With the exception of the KATO-III stomach cancer cell line, the IC_{70} value was around 100 nM. Triptolide also inhibited the growth of KB nasopharyngeal, Lewis lung and HeLa carcinomas, as well as S37 sarcoma. These results suggest that triptolide may have potential therapeutic effects on some types of solid tumors.

Anti-HIV

GTW was found to have significant anti-HIV activity. Bioassay-directed fractionation of GTW led to the isolation and characterization of salaspermic acid as the active anti-HIV principle (8). Salaspermic acid inhibited HIV replication in H9 lymphocyte cells with an EC_{50} value of 5 mcg/ml (10 μM) and suppressed uninfected H9 cell growth with an IC_{50} value of 25 μg/ml (53 μM). Salaspermic acid also inhibited HIV-1 recombinant reverse transcriptase activity. Interestingly, this effect appeared to be template-primer dependent, so that different EC_{50} values could be estimated using the different template-primers. As shown in Table II, the enzyme was more sensitive when the agent contained poly(rC)-oligo(dG) or poly(rA)-oligo(dT) as the template-primer and was less sensitive with poly(rU)-oligo(dA) and almost insensitive at 100 μg/ml using poly(rG)-oligo(dC). This particular activity could be due to changes in the conformation of the binding position for the inhibitor as the result of interaction between reverse transcriptase and templates. The activity of salaspermic acid was also tested against HIV-2 recombinant reverse transcriptase activity, but the degree of inhibition appeared to be lower.

Antiinflammatory

Various formulations of *T. wilfordii* (*e.g.*, tablet, extract, microcapsule, PAP patcher and GTW) have demonstrated inhibitory effects in various experimental models of inflammation such as acetic acid-induced vascular permeability in mice, carrageenan-induced paw edema in rats and cotton pellet granulomatosis in rats (9-12). GTW administered intragastrically (i.g.) significantly inhibited joint swelling in rats with adjuvant-induced arthritis. The products of lipid peroxidation play an important role in inflammatory injuries and a good correlation was found between lipid peroxidation and the degree of edema. GTW inhibited lipid peroxidation and increased the levels of the free radical scavengers superoxide dismutase and glutathione peroxidase, indicating that the antiinflammatory action of GTW may be associated with inhibition of lipid peroxidation and free radical formation (Table III).

Other studies indicated that triptolide inhibited the increased vascular permeability induced by acetic acid in mice, carrageenan- and formaldehyde-induced hind paw edema in rats as well as granuloma proliferation induced by cotton pellets in rats. However, the compound had no effect on carrageenan-induced edema in adrenalectomized rats, indicating that it is able to stimulate the

Table III: Effect of GTW on experimental adjuvant arthritis and free radicals in rats.

	Joint circumference (mm)	LPO	SOD	GSH-Px	GSH-Px/LPO
Before treatment	67.0	7.47	1096	15.7	2.09
After treatment	13.2	2.26	1464	24.6	10.87

LPO: lipid peroxidation; SOD: superoxide dismutase; GSH-Px: glutathione peroxidase.

Table IV: Comparison of antiinflammatory, immunosuppressive and antifertility activities of 7 diterpene lactone epoxide compounds and total glycosides from T. wilfordii.

Code	LD_{50} (mg/kg i.g.)	ED_{50} (mg/kg i.p.) AIA	ISA	TI (i.p.) AIA	ISA	CSF (i.p.) AIA	ISA	LESD in AFA (mg/kg x 33 d)	Dose ratio (i.g.) AIA/AFA	ISA/AFA
1	>500 (i.p.)	26.70	-	>19.0	-	>19.0	-	-	-	-
2	0.94	0.05	0.06	17.0	13.7	4.3	3.5	0.024	5.4	6.7
3	3.26	0.30	0.09	9.6	30.7	1.4	7.1	0.054	27.6	5.3
4	0.80	0.09	0.08	7.3	8.8	1.4	2.5	0.020	19.5	10.5
5	5.68	0.87	0.68	5.9	7.5	1.7	2.5	0.142	16.3	11.5
6	1.65	0.15	0.08	9.0	16.7	1.7	5.1	0.026	20.4	6.5
7	0.92	0.12	0.05	6.6	15.8	1.3	3.6	0.027	20.0	6.3
8	156.3	15.70	7.90	8.5	16.8	1.4	4.7	7.800	9.9	2.7

1: triptriolide; 2: triptolide; 3: triptolidenol; 4: tripdiolide; 5: triptonide; 6: tripchlorolide; 7: 16-hydroxytriptolide; 8: total glycosides. AIA: anti-inflammatory action (croton oil-induced ear swelling in mice); ISA: immunosuppressive action (hemolysin antibody formation in mice); AFA: antifertility action; TI: therapeutic index; CSF: certain safety factor; LESD: lowest effective single dose (i.g.) in AFA LD_{50} = 1/40 for 2,4,5,7; 1/60 for 3,6; 1/20 for 8.

pituitary-adrenal axis (13). Celastrol was also found to reduce joint swelling in rats with experimental adjuvant-induced arthritis, which may also be correlated with the inhibition of lipid peroxidation and free radical formation (4).

The ED_{50}, therapeutic index (TI) and certain safety factor (CSF) of 7 diterpene lactone epoxide compounds with antiinflammatory action were evaluated using croton oil-induced ear edema in mice (14). The results indicated that all 7 compounds exhibited antiinflammatory activity, with the TI being in the following order: triptriolide, triptolide, triptolidenol, tripchlorolide, tripdiolide, 16-hydroxytriptolide and triptonide. The CSF for all compounds was greater than 1 (Table IV).

Immunosuppressive

T. wilfordii was shown to inhibit splenocyte proliferation induced by Con A, PHA and LPS, delayed-type hypersensitivity induced by dinitrofluorobenzene or collagen and hemolysin responses induced by sheep red blood cells (SRBC) in mice. The release of interleukin-1 (IL-1) from peritoneal macrophages in normal rats and rats with adjuvant arthritis was also suppressed by the plant (4, 11). The plant enhanced serum complement levels in patients with systemic lupus erythematosus (15). It also inhibited Th cell activity and, as a result, IL-2 production of splenocytes; Ts cell activity was also stimulated by the plant. A bidirectional effect of the plant on macrophages was observed with phagocytosis of macrophages increased at low doses and suppressed at high doses. Furthermore, GTW was found to inhibit delayed-type hypersensitivity, mixed lymphocyte reaction and cytotoxic T cells activity in mice. GTW also inhibited mitogen-induced T- and B-cell proliferation, antibody formation challenged with SRBC and allogeneic bone marrow transplantation rejection (4, 16). In addition, GTW increased serum complement level and decreased IL-2 activity of lymphocytes (4, 16). In rats with adjuvant arthritis, GTW treatment decreased Con A-induced splenocyte proliferation, peritoneal macrophage production of IL-6 and IL-8 and tumor necrosis factor (TNF), splenic lymphocyte production of IL-6 and -8, serum IL-1 and IL-6 levels and IL-1, IL-6, IL-8 and TNF content in joint fluids (10). Thus, GTW had therapeutic effects on rat adjuvant arthritis via its immunosuppressant action. GTW treatment also resulted in suppression of autoimmunity induced by *Campylobacter jejuni* infection (17) and decreased Th cell counts while increasing Ts cell counts, resulting in a decreased Th/Ts ratio in children suffering from asthma (18).

Celastrol was shown to be a potent immunosuppressant. It inhibited the proliferation of splenic cells induced by mitogens including PHA, Con A, LPS and PWM in mice. Intraperitoneal injection of celastrol reduced antibody formation as measured by spleen plaque forming cell counts and serum hemolysin analysis in mice challenged with SRBC. The agent increased serum complement C3 levels and decreased circulating immune complex content. In mice, LPS-induced IL-1 and Con A-induced IL-2 production were decreased in peritoneal macrophages and splenic lymphocytes, respectively. Delayed-type hypersensitivity and macrophage function were also inhibited by celastrol treatment (4) and prostaglandin E_2 release from rabbit knee joint synovial cells was reduced (19).

Triptolide was found to exhibit suppressive effects on some types of cellular and humoral immunity. *In vitro*, it inhibited mouse lymphocyte proliferation induced by Con A and LPS, suppressed the one-way mixed lymphocyte reaction and induced Ts cells. In mice *in vivo*, special antibody production, delayed-type hypersensitivity reaction induced by dinitrofluorobenzene and IL-2 activity of spleen cells were inhibited. The Th/Ts ratio of mouse thymus cells was reduced and the serum total complement level was enhanced in rats. Triptolide reduced the expression of IL-3, IL-5 and GM-CSF mRNA in airway tissue from asthmatic guinea pigs, and had a marked suppressive effect on enhanced delayed-type hypersensitivity reaction induced by cyclophosphamide in mice (6, 9, 20, 21). Mouse graft *versus* host reaction was also suppressed by triptolide in the skin allograft test (22).

Triptonide inhibited the proliferation of mouse splenocytes induced by Con A and LPS and the one-way mixed lymphocyte reaction *in vitro*. Suppressive effects on clearance of charcoal particles, serum anti-SRBC antibody (hemolysin) formation and delayed-type hypersensitivity reaction were also observed in mice. Triptonide induced increases in Ts cells and reduced the Th/Ts ratio. However, the agent exhibited no obvious effect on spleen cell IL-2 activity and graft *versus* host reaction in mice (23).

Tripchlorolide reduced the production of immunoglobulins by peripheral blood mononuclear cells of healthy subjects and patients with rheumatoid arthritis. The content of immunoglobulins in single synovial cells of patients with rheumatoid arthritis was also decreased by tripchlorolide (24).

A comparison of the diterpene lactone epoxide compounds in the mouse hemolysin antibody formation model indicated that 6 compounds exhibited immunosuppressive activity (14). The TI of the immunosuppressive activity of these compounds was in the following order of potency: triptolidenol, tripchlorolide, 16-hydroxytriptolide, triptolide, tripdiolide and triptonide. The certain safety factor (CSF) parameters of the immunosuppressive action of the 6 active compounds were all higher than 1 (Table IV).

Antifertility

Some compounds of *T. wilfordii* have exhibited reversible antifertility effects. Tripchlorolide reduced the motility and density of the epididymal spermatozoa of rats after oral administration. In another study tripchlorolide was shown to inhibit calcium influx of human ejaculated sperm, suggesting a possible mechanism by which the agent inhibits sperm motility. However, tripchlorolide had no significant effect on calcium-dependent contractions of rat aorta and vas deferens, indicating that it acts selectively on epididymides (25).

In triptolidenol-treated male rats, only mild testicular changes were observed, although there was severe epididymal damage. Spermatozoa showed various structural abnormalities including cracked midpieces and decapitation of sperm heads. The antispermatozal potency of triptolidenol was 100 times stronger than that of GTW (26).

When the male antifertility activity of the diterpene lactone epoxide compounds was further compared in mice, results showed that the lowest effective single doses of triptonide, tripdiolide, triptolide and 16-hydroxytriptolide were below 1/40 of the LD_{50}, while those of tripchlorolide and triptolidenol were below 1/60 of the LD_{50}; triptriolide had no antifertility effects (Table IV) (27).

Pharmacokinetics

Preliminary pharmacokinetic studies of some of the *T. wilfordii* compounds have been performed in rats and mice. Following single oral administration of triptolide in rats and mice, rapid absorption from the gastrointestinal tract was observed. Peak blood levels were reached at 1.04 and 0.69 h in rats and mice, respectively. The blood concentration-time curve fit a two-compartment open model. Distribution of the drug was high in the liver, moderate in the spleen, lungs and intestine and low in the heart and brain after i.v. and oral administration. The drug was excreted in urine and feces mainly in the unchanged form. About 7% of the administered dose was detected in bile after 24 h, demonstrating hepatointestinal circulation. The plasma protein binding rate of triptolide was about 65% (28).

Concentration-time curves after administration of triptonide (0.7, 1.4 and 2.8 mg/kg i.v.) were also fitted to a two-compartment open model with $t_{1/2\alpha}$ and $t_{1/2\beta}$ values of 0.167-0.195 and 4.95-6.49 h, respectively. The AUC was dose-linear. Mean residence time of the three doses was 3.26-5.14 h by noncompartmental analyses. Systemic clearance was independent of dose and a wide tissue distribution was observed in rats. High levels of the drug were detected in lung and liver, moderate levels in heart, kidney, spleen and muscle, and low levels in testis, intestine and brain. Results of urinary and biliary excretion indicated that only a small amount of unchanged drug was excreted. The plasma protein binding rate of triptonide was about 75% (29).

Toxicity

Acute lethal doses (LD_{50}) of some *T. wilfordii* compounds and GTW are shown in Table IV (14, 27). Microcapsules of the plant were orally administrated to rats and dogs for 90 consecutive days with no obvious toxicity observed at 5 mg/kg in rats and dogs. The drug had some toxic effects at 10 mg/kg in dogs and 15 mg/kg in rats, but animals recovered after withdrawal of the drug. At high doses in rats (35 mg/kg) and dogs (15 mg/kg), the drug increased blood urea nitrogen and sugar concentrations and increased the activity of plasma alkaline phosphatase, respectively. Plasma total protein and albumin concentrations in dogs were decreased. Histological examination showed obvious toxicity in the heart, liver, kidney and other organs of both rats and dogs although animals recovered after drug withdrawal, indicating that toxicity was reversible (30). Triptolide at doses of 40 and 80 μg/kg i.v. for 7 consecutive days was also found to have reversible toxic effects on the heart, bone marrow and gastrointestinal tract in dogs (28).

Formation of hemolysin antibodies was not inhibited by triptolide, tripchlorolide, triptonide, tripdiolide, triptolidenol and 16-hydroxytriptolide after administration of the total doses resulting in antifertility effects. The lowest doses of these compounds which had antifertility activity were 5-28 times lower than those for antiinflammatory activity and 5-12 times lower than those for immunosuppressive activity (27).

The results of genotoxicity studies indicated that triptolide was mutagenic, with 14-21% chromosome

aberration and 8-18% micronuclei formation observed in bone marrow cells of mice (14). Orally administered triptonide, tripchlorolide and triptolidenol, however, had no significant effects on chromosome aberration and micronuclei formation of spermatogenic cells of male rats as compared with those of control animals, indicating no genotoxicity (26, 31, 32).

In the treatment of rheumatoid arthritis and dermatological diseases, the main side effects of GTW at doses of 60-90 mg/kg were gastrointestinal, including nausea, vomiting, anorexia, epigastric burning, xerostomia, diarrhea and constipation. In most patients, discontinuation of medication was not necessary. Some patients experienced leukopenia and thrombocytopenia, although cell counts rapidly recovered to normal after drug withdrawal. Other infrequent side effects included menstrual disturbances, oligospermia and azoospermia; the number and motility of sperm were restored to normal 2 months after discontinuation of medication (4).

Clinical studies

In a placebo-controlled, double-blind clinical study, GTW was shown to have significant effects on rheumatoid arthritis. The antiinflammatory efficacy was almost equal to that of corticosteroids and superior to that of the currently available nonsteroidal antiinflammatory drugs. The recommended dose of GTW was 30-60 mg/kg for adults weighing 60 kg. The drug was very effective in acute and active rheumatoid arthritis. Pain, edema and joint morning stiffness were markedly improved after 3-5 days of treatment and fever disappeared within 3-10 days. In patients on corticosteroid therapy, the doses of GTW could be reduced or even eliminated. With continued medication, patients were able to maintain a normal lifestyle and return to work. Laboratory examinations showed that serum IgG, IgM, IgA, gamma-globulin, blood viscosity, ESR and C-response protein returned to normal. Rheumatoid factor was negative, and the overall efficacy rate in 1032 patients with rheumatoid arthritis was about 93% (Table V) (4).

GTW has been evaluated in other clinical studies for various indications. GTW (30-60 mg/kg) was used in the treatment of systemic lupus erythematosus and was effective in 88% of 103 patients (4). The drug was also effective in the treatment of idiopathic and lupus nephritis, although no effects was observed in hypertensive nephritis (33). In patients with Behcet's disease, 29 of 34 patients responded well within 1 week. The success rate with erythema multiforme was 96%. When large doses were used to treat 148 psoriasis patients, cutaneous lesions regressed completely in 83 patients within 1 month. Good therapeutic results were obtained in 11 patients with pemphigus who were refractory to hormonal therapy (4). Moreover, triptolide was effective in the treatment of various types of acute leukemia with a response rate of 53.3% (18/45 complete remissions and 6/45 partial remissions) (28). Clinical investigations of *Tripterygium* preparations as a male contraceptive are now in progress.

Table V: A 12-week, double-blind, placebo-controlled clinical trial of oral GTW in rheumatoid arthritis (4).

	Effective ratio (%)	
	GTW	Placebo
Patient's evaluation	88.8	23.5
Doctor's evaluation	85.2	23.5
Clinical expression	81.5	22.5
Laboratory findings	85.2	12.9

Conclusions

During the past decades, extensive research has been carried out on the four main components isolated from *T. wilfordii*, including diterpenoids, triterpenoids, alkaloids and a refined fraction, GTW. There are now over 6 pharmaceutical factories in China manufacturing GTW which has been clinically used to treat rheumatoid arthritis, chronic nephritis and various skin disorders. Since GTW contains only very small amounts of diterpenes and alkaloids, the main toxic components in the plant, it has a very low side effect profile. Some of the compounds, such as tripchlorolide, have shown potential as male contraceptives, which at antifertility doses do not cause significant immunosuppression or genotoxicity. The composition of the *T. wilfordii* plant is very complicated. Continued investigations of the chemical constituents, biological activities and clinical efficacy of *T. wilfordii* will hopefully result in more effective compounds with less toxicity and more selective activity.

Experimental research has demonstrated that many active components isolated from *T. wilfordii* possess similar biological activities and have combination antifertility/immunosuppressive effects. Moreover, their therapeutic doses are close to the toxic doses. Therefore, dosing should be controlled and the drugs should be administered in combination with other drugs. Other routes of administration (*i.e.,* PAP patcher) should also be considered to reduce the systemic toxicity of these compounds.

References

1. Zhao, C.P. et al. CA 1937, 31: 1161.

2. Kupchan, S.M., Court, W.A., Dailey, R.G. et al. *Triptolide and tripdiolide, novel antileukemic diterpenoid triepoxides from Tripterygium wilfordii.* J Am Chem Soc 1972, 94: 7194-5.

3. Zhang, C.P., Zhang, Y.G., Lu, X.Y. *A pentacyclic triperpene acid from Tripterygium wilfordii.* Acta Acad Med Sin 1986, 8: 204-6.

4. Li, X.Y. *Antiinflammatory and immunosuppressive components of Tripterygium wilfordii Hook.f.* Int J Immunother 1993, 9: 181-7.

5. Kupchan, S.M. *Novel plant-derived tumor inhibitors and their mechanisms of action.* Cancer Treat Rep 1976, 60: 1115-26.

6. Ji, R.Y. *Triptolide.* Drugs Fut 1985, 10: 575-7.

7. Wei, Y.S., Adachi, I. *Inhibitory effect of triptolide on colony formation of breast and stomach cancer cell lines.* Acta Pharmacol Bull 1991, 12: 406-10.

8. Chen, K., Shi, Q., Kashiwada, Y. et al. *Anti-AIDS agents, 6. Salaspermic acid, an anti-HIV principle from Tripterygium wilfordii, and the structure-activity correlation with its related compounds.* J Nat Prod 1992, 55: 340-6.

9. Li, L.Z., Cheng, S.F., Wang, F.J. *Effects of triptolide on inflammatory and immune function.* Chin Pharmacol Bull 1986, 2: 25-8.

10. Fan, Z.S., Cao, R.H., Zhang, Q.Y. et al. *The therapeutic action of glycosides of Tripterygium wilfordii on rat adjuvant arthritis and immunoregulatory mechanisms.* Chin Pharmacol Bull 1996, 12: 527-9.

11. Li, J., Liang, J.S., Zhou, A.W. et al. *Studies on pharmacodynamics of Tripterygium wilfordii Hook microcapsule.* Chin Pharmacol Bull 1994, 10: 345-8.

12. Ji, H., Sun, B., Li, N.S., Xie, Q.K. *Effect of Tripterygium wilfordii PAP patcher on adjuvant arthritis in rats.* J China Pharmaceut Univ 1995, 26: 223-5.

13. Zheng, Y.L., Lin, J.F., Lin, C.C., Xu, Y. *Antiinflammatory effect of triptolide.* Acta Pharmacol Sin 1994, 15: 540-3.

14. Zheng, J.R., Guo, K.X., Xu, L.F. et al. *A comparison of the antiinflammatory and immunosuppressive activities of 7 diterpene lactone epoxide compounds from Tripterygium wilfordii Hook.f. in vivo.* Acta Acad Med Sin 1991, 13: 391-7.

15. Wu, J.H., Zhu, L.F., Qin, W.Z. *Effect of Tripterygium wilfordii Hook.f. on the level of serum complements of patients with systemic lupus erythematous.* Acta Acad Med Shanghai 1996, 23: 472-3.

16. Qin, F.H., Xie, S.S., Long, Z.Z. *The effect of total glycosides of Tripterygium wilfordii Hook.f. on cellular immune responses and anti-transplantation rejection.* Chin Pharmacol Bull 1994, 10: 123-5.

17. Sun, B., Ma, B.L., Xie, Y.L. *Suppression of polyglycosides of Tripterygium wilfordii Hook.f. on autoimmunity induced by Campylobacter jejuni.* Chin J Pharmacol Toxicol 1993, 7: 190-2.

18. Zhang, X.Q., Zhang, Z.H. *Effect of polyglycosides of Tripterygium wilfordii Hook.f. on T lymphocyte subsets and lymphocyte proliferation of children with asthma.* Chin J Microbiol Immunol 1991, 11: 117-9.

19. Xu, W.M., Zhang, L.X., Cheng, Z.H. et al. *Suppressive effect of tripterine on activities of IL-1, IL-2 and release of PGE_2.* Acta Pharmaceut Sin 1991, 26: 641-5.

20. Wang, C.Z., Wang, C.X., Jin, Y.L. et al. *Effect of triptolide on expression of IL-5, IL-3, GM-CSF mRNA in airway tissue from asthma guinea pig models.* Chin J Microbiol Immunol 1998, 18: 145-8.

21. Pei, R.J., Qi, L.H., Liu, X.J. *Mechanisms of immunosuppressive effects of triptolide.* Chin Pharmacol Bull 1993, 9: 68-72.

22. Yang, J.W., Cheng, C.H., Liu, Z.H., Li, R.S. *Suppression of skin allograft rejection by triptolide.* Chin Pharmacol Bull 1997, 13: 73-6.

23. Pei, R.J., Qi, L.H., Liu, X.J. *Effects of triptonide on mouse immune functions.* Acta Pharmacol Sin 1993, 14: 238-42.

24. Zeng, X.J., Zhang, N.Z. *Effects of tripchlorolide on the production of immunoglobulins in peripheral blood mononuclear cells and synovial cells in normal persons and rheumatoid arthritis.* Acta Pharmaceut Sin 1997, 32: 171-3.

25. Wu, T., Sha, Y.S. *Tripchlorolide inhibition of Ca^{2+} influx in human ejaculated sperm, but not affecting contraction reaction of aorta and vas deferens in rats.* Chin Pharmacol Bull 1996, 12: 441-4.

26. Ye, W.S., Lu, X.Y., Fan, Y.Y. et al. *Antispermatogenic effect of triptolidenol.* Chin Pharmacol Bull 1992, 8: 115-8.

27. Zheng, J.R., Gu, K.X., Gao, J.W. et al. *A comparison of the male antifertility activity of 7 diterpene lactone epoxide compounds.* Acta Acad Med Sin 1991, 13: 398-403.

28. Xia, Z.L., Zheng, Y.L. *The pharmacological and clinical studies of triptolide.* Chin Pharmacol Bull 1992, 8: 427-31.

29. Gang, Y.Y., Zhang, Z.X., Zhang, S.Q. et al. *Pharmacokinetics and disposition of triptonide in rats.* Acta Pharmaceut Sin 1996, 31: 901-5.

30. Song, B.W., Zhao, W.Z., Chen, Z.W. et al. *Studies on the long-term toxicities of Tripterygium wilfordii Hook.f. microcapsules.* Chin Pharmacol Bull 1996, 12: 246-8.

31. Liu, D.Y., Jia, M.C. *Effect of tripchlorolide on micronucleus induction in rat spermatogenic cells.* Chin J Pharmacol Toxicol 1993, 7: 294-6.

32. Liu, Q.L., Xu, Y., Qian, S.Z. *Effect of tripchlorolide and triptonide on the rates of chromosome aberration and micronuclei formation in spermatogenic cells of male rats.* Chin J Androl 1997, 11: 89-91.

33. Li, L.S., Zhang, X., Cheng, H.P. et al. *Clinical and experimental studies on the treatment of nephritis by total glycosides of Tripterygium wilfordii Hook.f.* Chin J Med 1982, 62: 581-5.