a structural chromosomal abnormality is found. As can be seen from the karyotypes reported in Table 3 of our article;[1] the karyotypes of those with an unbalanced structural chromosomal abnormality inherited from a carrier parent with the balanced structural abnormality are designated as either "mat" or "pat".

In future studies, we hope to further analyze the genotype and phenotype correlation of specific types of chromosome abnormalities, and add more clinical evidence to the existing database to benefit the clinicians more. Some of these have already been published.[2-4]

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## Tripterygium wilfordii Hook F is efficacious in the treatment of Henoch-Schönlein purpura nephritis in children

I read with interest the recently published article by Huang et al.[1] The article is very informative and has brought an utmost important insight on chronic glomerulonephritis in children. It is an interesting issue, because glomerulonephritis such as Schonlein-Henoch nephritis (HSPN) may lead to renal failure in children and adolescents. The well-presented clinical features and histopathological changes described in the article are valuable for pediatricians in diagnosing HSPN in the high-risk population.

Huang et al[1] reported nine HSPN patients with the severest histopathological changes. They were classified as the International Study of Kidney Disease in Children (ISKDC) grade VI, and all had moderate to heavy proteinuria; all the patients in that series recovered well after treatment. Their treatment protocol is an imperative hint for managing HSPN patients. We found that 7/9 patients were given oral tripterygium glycosides; and the authors especially stressed in the methods section that tripterygium glycosides was only used in China. As they stated that tripterygium glycosides has been widely used in China as an effective immunosuppressant. It has been used for the treatment of glomerulonephritis for more than 30 years with dramatic antiproteinuric effects.[2-5] Disappointingly, they did not provide more information on tripterygium glycosides use for treatment of glomerulonephritis in the discussion section.

To our knowledge, tripterygium glycosides is the major active component of tripterygium wilfordii Hook F, which was firstly used in the nephritis treatment in 1977 by Li et al.[2] Tripterygium glycosides has been used in more than 100 000 patients in his institute.[6] It has been proven with multi-immunosuppress efficacy but with less side-effects than other immunosuppressant agents in animal and cell researches. Randomized-controlled studies have been carried out in adults. Due to the ethical issues, no clinical trials have been carried out in children; however, a nearly forty-year clinical experience in China has shown that this agent is safe, economical and efficacious for treating nephritis diseases in children. Therefore, we think that the author should introduce more information in the discussion section; the experience of treating severe HSPN patients will be helpful for pediatricians and nephrologists worldwide.

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Our retrospective study was aimed to define the clinical manifestations, pathological features and prognosis of children with grade VI HSPN, our results also showed that tripterygium glycosides (T glycosides) alone or combined with glucocorticoid had nephroprotective effects on grade VI HSPN in children.[1]

T glycosides (leigongteng multi-glycosides tablets) used in this study is the debarked root preparation of Tripterygium wilfordii Hook F (TWHF), which is known as leigongteng or thunder god vine in traditional Chinese medicine. Since the 1960s, as an

**Table.** Summary of 15 trials on T glycosides administered in the treatment of HSPN in children

| Studies | No. of Pts | Age (y) | Sex m/f | Pathol grade | Intervention | | | | Adverse effects | Follow-up dur (mon) | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Experimental group | | Control group | Background therapy | | | |
| | | | | | Dosage | Dur (mon) | | | | | |
| Zhao et al[9] (2015) | 80 | 2-14 | 44/36 | Unknow | T glycosides tab 1 mg/kg/d max <60 mg/d | 3-6 | Usual care | Prednisone 1.5-2 mg/kg/d | Unknow | 15 | T glycosides combined with prednisone was superior to prednisone alone |
| Xu et al[10] (2014) | 75 | 2-16 | 45/30 | Unknow | T glycosides tab 1.5 mg/kg/d max <90 mg/d | 3 | Prednisone 1 mg/kg/d | No | Unknow | 3 | T glycosides was superior to prednisone |
| Xiang et al[11] (2014) | 42 | 4-12 | 22/20 | Unknow | T glycosides tab 1 mg/kg/d | 3 | Usual care | Prednisone 1 mg/kg/d | Digestive, 3 Hepatotoxity, 2 Leukopenia, 1 | 12 | T glycosides combined with prednisone was superior to prednisone alone |
| Wang[12] (2013) | 59 | 5-14 | 42/17 | Unknow | T glycosides tab 1 mg/kg/d max <60 mg/d | 3 | Prednisone 1-2 mg/kg/d | No | Unknow | 3 | T glycosides was superior to prednisone |
| Ding et al[13] (2012) | 172 | 2-18 | 98/74 | I-III cre ≤25% | T glycosides tab 1.5 mg/kg/d max <90 mg/d | 3 | Prednisone 1 mg/kg/d | No | Not obvious | 3 | T glycosides was superior to prednisone |
| Wang et al[14] (2012) | 104 | 3-12 | 56/48 | Unknow | T glycosides tab 1 mg/kg/d max <60 mg/d | 3-6 | Usual care | Prednisone 1.5-2 mg/kg/d | Digestive, 7 Hepatotoxity, 2 Leukopenia, 4 | 24 | T glycosides combined with prednisone was superior to prednisone alone |
| Hu et al[15] (2011) | 60 | 3.5-14.6 | 37/23 | I-III | T glycosides tab 1-1.5 mg/kg/d max <60 mg/d | 3 | Usual care | Captopril 1 mg/kg/d | Hepatotoxity, 3 Leukopenia, 2 | 3 | T glycosides was effective |
| Pang et al[16] (2011) | 64 | 3-12 | 48/16 | Unknow | T glycosides tab 1 mg/kg/d max <45 mg/d | 6-9 | Usual care | Prednisone 1.5-2 mg/kg/d | Hepatotoxity, 3 | 9 | T glycosides combined with prednisone was superior to prednisone alone |
| Zheng et al[17] (2009) | 66 | 3-18 | 34/32 | Unknow | T glycosides tab 1 mg/kg/d max <60 mg/d | 2 | Usual care | General therapy | Unknow | 2 | T glycosides can be effective for preventing HSPN |
| Liao et al[18] (2008) | 46 | 8-17 | Unknow | Unknow | T glycosides tab 1 mg/kg/d | 6 | Leflunomide 1 mg/kg/d | Prednisone 1 mg/kg/d | Unknow | 6 | T glycosides had comparable efficacy versus leflunomide |
| Zhou et al[19] (2007) | 29 | 3.5-13.5 | 16/13 | Unknow | T glycosides tab 1.5 mg/kg/d | | Usual care | Prednisone 1-2 mg/kg/d | Unknow | 12 | T glycosides was effective in HSPN with nephrotic level proteinuria |
| Ma et al[20] (2007) | 38 | 5-14 | 18/20 | Unknow | T glycosides tab 1 mg/kg/d | 6-9 | Usual care | Prednisone 1.5-2 mg/kg/ | Not obvious | 9 | T glycosides combined with prednisone was superior to prednisone alone |
| Zhang et al[21] (2006) | 53 | 2.5-13 | 29/24 | Unknow | T glycosides tab 1 mg/kg/d | 3 | Usual care | Prednisone 1.5-2 mg/kg/d in NS | Unknow | 3 | T glycosides was effective |
| Zhang et al[22] (2002) | 50 | 3-16 | 33/17 | Unknow | T glycosides tab 1-1.5 mg/kg/d | 3 | Usual care | Dexamethasone, 0.3-0.5 mg/kg/d for 5-7 d, then prednisone 1-1.5 mg/kg/d | Unknow | 12 | T glycosides combined with prednisone was superior to prednisone alone |
| Wang[23] (1994) | 43 | 3-14 | Unknow | Unknow | T glycosides tab 1.5 mg/kg/d | 3 | Prednisone 1.5 mg/kg/d | No | Unknow | 18-72 | T glycosides had comparable efficacy versus prednisone |

The study from Ding et al[13] was a randomized multi-center, and other studies were randomized single center studies. All references were written in Chinese. Pts: patients; y: year; m/f: male/female; Pathol: pathology; mon: month; dur: duration; tab: tablets; HSPN: Schonlein-Henoch nephritis; NS: nephrotic syndrome; Dur: duration.

immunosuppressive agent, TWHF preparations (T glycoside tablets, Tripterygium hypoglaucum Hutch tablets, and Tripterygium granules or extracts) were often used for the treatment of many kidney diseases,[2] rheumatoid arthritis (RA),[3,4] crohn's disease,[5] systemic lupus erythematosus,[6] and solid tumors.[7]

The efficacy and safety of TWHF preparations have not been fully identified; however, TWHF preparations have been used to treat Schonlein-Henoch nephritis (HSPN) successfully in China for many decades. A national survey[8] on status of diagnosis and treatment of childhood renal diseases in the Chinese population showed that glucocorticoid with or without T glycosides was always given to the patients with grade I and II HSPN. Furthermore, in the 669 patients with nephrotic syndrome, 139 (20.8%) were treated with glucocorticoid and T glycosides and 22 (3.3%) with T glycosides alone.[7]

We reviewed 15 trials in which T glycosides with or without glucocorticoid versus standard treatment, glucocorticoid alone, or leflunomide were assessed in therapies of HSPN (Table).[9-23] The outcomes included:

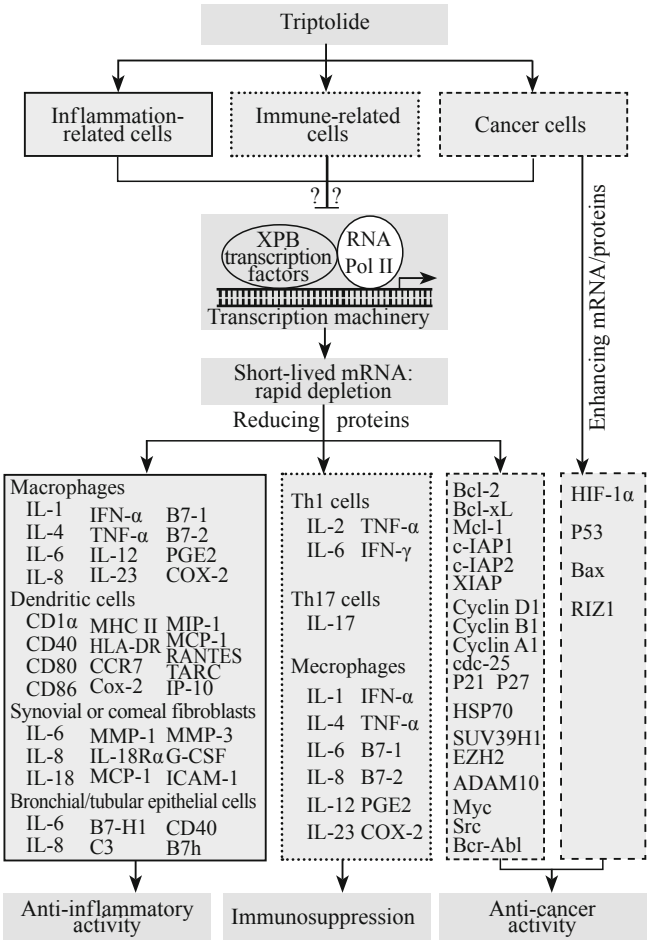


**Fig.** An overview of the mechanisms of action of triptolide.[26]

1) T glycosides was superior to prednisone; 2) T glycosides combined with prednisone was superior to prednisone alone; 3) T glycosides had comparable effect versus prednisone; 4) T glycosides was more effective in the treatment of HSPN with nephrotic level proteinuria, and 5) T glycosides had comparable effect versus leflunomide. These results suggested that T glycosides was efficacious in the treatment of HSPN and also showed nephroprotective effects. However, high-quality trials with larger sample size are needed to adequately address the effects of T glycosides and also to elucidate whether TWHF preparations is superior to other immunosuppressive agents for the treatment of HSPN.

Triptolide is well known as a principal ingredient of T glycosides, and displays potent biological activities. Initially, triptolide was shown to specifically target some transcription factors.[24,25] Recently, several triptolide-binding proteins, including xeroderma pigmentosum B (XPB), polycystin-2 (pc-2), and dCTP pyrophosphatase 1 (DCTPP1), have been identified to update the mechanisms of triptolide action.[26,27] XPB is a subunit of the general transcription factor TF II H that is essential for RNA polymerase II to recognize promoters and nucleotide excision repair in response to DNA damage. Triptolide can bind covalently to human XPB and inhibite RNA polymerase II-mediated transcription and probably interfere with repairing DNA damage. RPB1 is the largest RNA polymerase II subunit, and critical for mRNA transcription. RPB1 level can be lowered by triptolide.[28] Therefore, at present, triptolide has been identified as a global transcription inhibitor (Fig.).[26]

In our study, histopathological features of grade VI HSPN showed diffuse glomerular mesangial and endocapillary proliferation with double contour of the capillary walls and mesangial cell interposition. The therapeutic effects of T glycosides with/without glucocorticoid on children with grade VI HSPN may be related partially to the global transcription inhibition by triptolide.

In addition to its transcription inhibition function, triptolide also showed the transcription-independent actions through binding to PC-2, DCTPP1 and the other proteins,[29,30] and enhanced the mRNA or protein levels of several molecules, including p53, nerve growth factor (NGF), etc. Therefore, the action mechanism of triptolide and other components isolated from TWHF should be investigated in depth in order to provide more evidence for the future therapeutic choice.

Systemic toxicities of TWHF preparations are extensively involved in multiple tissues and organs, including the digestive tract, bone marrow, heart, urogenital system and skin.[31-33] Those toxicities are dose-dependent and could be monitored by dosage adjustments. TWHF preparations may cause ovarian

injury resulting in menstruation, which is reversible if the agent is withdrawn in time.[34] TWHF preparations have also been reported to cause reversible infertility in male patients in numerous studies. However, one animal study showed that the long-term (82 days) administration of triptolide induced deleterious effects on spermatogenesis and irreversible infertility even after cessation of the treatment.[35] Therefore, the reproductive toxicity of TWHF preparations is difficult to monitor in clinical treatment especially in children. Indeed, the potential systemic and reproductive toxicity limits the clinical application of TWHF preparations in children. We try to reduce the side effects by shortening treatment duration, closer clinical observation and laboratory examination in patients treated with HSPN in our department.

In future, continuous efforts should be made to clarify the molecular targets of TWHF components, produce new derivatives to reduce toxicity, and design high-quality trials to confirm the balance between benefits and adverse effects in children and adults.

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