REVIEW

The Active Constituents of Tripterygium wilfordii and Their Pharmacological Actions and Clinical Application

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Tripterygium wilfordii Hook. f. (TW), a liana of Tripterygium wilfordii genus of winged euonymus family, is widely used for the treatment of diseases of various systems caused by dysimmunity with good therapeutic effects. The present paper is a review on the screening and identification of its chemical constituents and active components, their pharmacological mechanism and clinical application, as well as toxic and side-effects.

The Screening of Its Chemical Constituents and Active Components

Since Zhao Chenggu reported for the first time in 1936 that triperine, a terpenoid pigment was extracted from the root of TW, nearly 70 constituents have been isolated from plants of Tripterygium wilfordii genus by Chinese and foreign scholars, chiefly alkaloids, diterpenes, triterpenes, sesquiterpenoids and saccharides. There are five principal alkaloids: wilforgine, wilfordine, wilforine, wilfortrine, and wilforzine. Among the eleven kinds of diterpenes obtained from ethanol extracts from the skin of the root of TW, IV-XI are all new chemical compounds, which may be the active components for leukemia. There are five principal alkaloids: wilforgine, wilfordine, wilforine, wilfortrine, and wilforzine. Among the eleven kinds of diterpenes obtained from ethanol extracts from the skin of the root of TW, IV-XI are all new chemical compounds, which may be the active components for leukemia. Among the seven kinds of triterpenes extracted from the skinned root of TW (T1~T7), T7 has obvious inhibitory action on lymphocytosis induced by Concanavalin A (Con A). Three sesquiterpenoid alkaloid compounds are extracted from the stem and leaves of TW, namely wilforgine (I), wilfortrine (II), and wilforine (III). I and II have inhibitory action on humoral immu-

nity and II is an active component for the treatment of rheumatoid arthritis. Glucosides of TW are an active mixture for various kinds of skin diseases and rheumatoid arthritis isolated by the Institute of Dermatology of Chinese Academy of Medical Sciences for the first time in the 1970s. Since it contains several glucosides, it is called glucosides of Tripterygium Wilfordii (GTW), comprising trace diterpenes, small quantity of alkaloids, and some pentacyclic triterpenes. It is generally held that the chief toxic substances of TW are diterpenoids and then alkaloids, while GTW is the least toxic. From the total glucosides of TW (T1) are derived eight components T1~T8 and from the eight components were further derived five monomers: T2, T3, T4, T6, and T8, all of which have definite anti-inflammatory action. and T4 has both inhibitory action on the formation of antibody and antifertility action. and its titer is 100~200 times higher than that of component T1. So it can serve as the quality index of T1. The immunodepressant and antifertility effect of T4 monomer cannot be separated from each other, which restricts the practical value of TW as an antifertility drug, and brings on side-effects that cannot be neglected when TW is used as an anti-inflammatory and immunodepressant drug.

In a word, TW possesses multiple pharmacological activities and complex components. Isolation of the active monomers of TW and elucidation of their structure will undoubtedly promote pharmacological and clinical studies in the interest of exploitation of this drug.

Pharmacological Studies of TW
Immunoregulatory Action

1. Regulation of cellular immunity
TW can significantly inhibit proliferation of T cells induced by Con A but has no inhibitory effect on the proliferation of B cells induced by lipopolysaccharide. It can also remarkably reduce the level of interleukin 2 (IL-2) produced by splenocytes in mice, which indirectly indicates the function of T helper lymphocytes (TH) is affected. Mitogen can stimulate lymphocytes to synthesize and secrete IL-2. The cell membrane expresses IL-2 receptors and synthesis of DNA. These three exhibit that the T cells are activated. TW has rather strong inhibitory action on the synthesis of DNA induced by Con A, on the production of IL-2 and expression of IL-2 receptors on the cell surface, but it cannot inhibit IL-2 production completely, which suggests that the chief action of TW is to inhibit the activation of the spleen cells, instead of inhibiting directly DNA synthesis and cytotoxicity. *Tripterygium wilfordii* produced in north-east China can suppress the reaction of mononuclear to the anti-Type I collagen specific proliferation and retarded Type of hypersensitivity on arthritic model rats. Observation was made on the changes of subgroups of T lymphocytes of peripheral blood of 33 children with bronchial asthma before and after taking GTW with monoclonal antibody (OKT series). The result showed that after taking the drug, the OKT4+ cells decreased and the OKT8+ cells increased obviously, and the ratio of T4/T8 dropped significantly (*P*<0.05). Studying the function of TW with half heart graft of the mouse showed TW can significantly activate the inhibitory cells in vivo and in vitro experiments and thus prolong the survival of the graft. *Tripterygium wilfordii* Hook. f. produced in Guangxi province does have significant dose-dependent inhibitory action on such cellular immuno-response as phagocytosis, lymphocyte transformation, and biphasic mixed lymphocyte culture.

2. Influence on humoral immunity
Extract from TW can inhibit in various degrees the formation of serolysin in mice and suppress significantly thymus-dependent antigen-induced antibody response, but cannot inhibit nonthymus-dependent antigen-induced antibody response, which indicates that the suppression expressed by humoral immune response might be brought about indirectly through inhibiting the function of helper T cells, not through direct action on the B cells. As for anti-Type I collagen specific humoral immunity in arthritic model animals, it can inhibit the formation of antibody induced by anti-Type I collagen either in arthritic model animals or in rats which have been induced but have not become disease.

3. Influence on non-specific immunity
Ethyl acetate extract of TW has inhibitory action on the thymus. Small dose of T4 can increase the toxicity of natural killer cells and increase the lyso units of spleen cells and raise the relative cytotoxicity, while larger dose has inhibitory effect. The larger the dose, the greater is the inhibitory effect. Wilfortrine and euonine can markedly lower the speed of carbon granular clearance in mice, which indicates that they have inhibitory action on phagocytosis of the reticuloendothelial system, suggesting they have effect on nonspecific immunity, too.

Anti-inflammatory Action
Three hundred µg/kg of lactone of TW (TW3A) has inhibitory action on the swelling of mouse ear induced by croton oil and on the rise of capillary permeability in the abdominal cavity of the mouse induced by acetic acid, which suggests that this drug has obvious inhibitory action on the rise of vascular permeability, exudation and edema appearing at the early stage of inflammation. It has been proved by in vitro test on stability of red cell membrane of rat that TW3A can markedly inhibit the rupture of red cell membrane an action similar to that of hydrocortisone, which might be one of the anti-inflammatory mechanisms of this drug.