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Effect of *Aralia chinensis* on serum TNF-a, IL-4 and IL-10 level in rats with adjuvant-induced arthritis

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Abstract

Our study investigated the effect of *Aralia chinensis* on serum tumor necrosis factor-α (TNF-α), Interleukins (IL-4, IL-10) in rats with adjuvant-induced arthritis. Adjuvant-induced arthritis rats had more slowly increased body weight, dramatically increased TNF-α level but reduced IL-4, IL-10 levels compared with control group. *A. chinensis*, *Tripterygium wilfordii* and control group had significantly increased body weight, IL-4, IL-10, and markedly reduced arthritis index and TNF-α level compared with the adjuvant-induced arthritis group. *A. chinensis* and *T. wilfordii* group had significantly increased IL-4 and IL-10 levels and markedly reduced TNF-α level compared with control group. *A. chinensis* could significantly increase the IL-4 level compared with the control group and it can balance the cytokines in arthritis rats, which attributes to the improvement of adjuvant induced arthritis.

Introduction

Rheumatoid arthritis is an autoimmune disease characterized by symmetrical arthritis in multiple joints, chronic inflammation in the synovium and progressive destruction of joints. It may cause damage to multiple organs including heart, lung and kidney. Late stage may result in ankylosis, joint deformity and severe joint dysfunction, which significantly influence the health and quality of life. In the present study, the effect of *Aralia chinensis* L on the serum tumor necrosis factor-α (TNF-α), Interleukins (IL-4, IL-10) was investigated in rats with adjuvant arthritis aiming to explore the pathogenesis of rheumatoid arthritis.

Materials and Methods

Animals

Male SD rats (specific pathogen free) weighing 200 ± 20 g and aged 8-10 weeks were purchased from the Experimental Animal Center of Xi'an Jiaotong University. Animals were given *ad libitum* access to food and water.

Main reagent, drugs and instrument

A. chinensis (Shenlong Hospital of Traditional Chinese Medicine), liquid extract 1 g/mL), tripterygium wilfordii (Huangshi Feiyun Pharmaceutical Co. Ltd; Z33020422), incomplete Freund's adjuvant and detection kits for TNF-α, IL-4 and IL-10 (Sigma-ALDRICH) were used in this study. Vernier calliper (TESA, Swiss), GTZA precision balance (GTZA, Jiangsu, China), 721 grating spectrophotometer (Suzhou Qile Electronic Technology Co., Ltd), and refrigerated centrifuge (Xiangyi Centrifuge Co., Ltd) were used in the present study.

Preparation of the animal model

SD rats were allowed to accommodate to the environment for 2 weeks and then divided into 2 groups randomly. In the control group, 8 rats were

included and received no treatment. Remaining rats received subcutaneous injection of incomplete Freund's adjuvant at the right hind paw (0.1 mL). From the second day, edema of the paw was present. A second injection was done at day 8. At 14 days after first injection, adjuvant arthritis animal model was induced.

Grouping and treatment

In the control group, rats received no treatment. The remaining rats were divided randomly into 3 groups (n = 8 per group): Adjuvant arthritis group, *T. wilfordii* group and *A. chinensis* extract group. In the *T. wilfordii* group, rats were intragastrically treated with *T. wilfordii* at 6.0 mg/kg (3 mL) once daily; in the *A. chinensis* extract group, rats were intragastrically treated with *A. chinensis* extract at 1 g/mL (3 mL) once daily. Treatment was done at 15 days after first injection of incomplete Freund's adjuvant and continued for 28 days. In the control and adjuvant arthritis groups, rats received intragastrically treatment with normal saline of equal volume once daily for 28 days.

Observations and detection

a) Observation of general condition: Before and after preparation of animal model and treatment, the spirit, hair, appetite and activity of these animals were observed, and the body weight, thickness of voix pedis and arthritis index were detected; b) Detection of biochemical parameters: At 28 days after treatment, blood was collected from the femoral artery and placed in a dry tube followed by centrifugation at 3,000 rpm for 8 min. The supernatant was obtained. The serum levels of TNF-α, IL-4 and IL-10 were detected according to the manufacturer's instructions.

Statistical analysis

Quantitative data were expressed as mean ± SD and statistical analysis was done with SPSS version 15.0. One-way analysis of variance was employed for comparisons among groups and 't'-test was used for comparisons between two groups.

Results

At 4 days after first injection, rats developed lassitude, less activities, loss of appetite and lameness, and significant edema was found in the right hind paw. At 9 days after first injection, the hair lost luster, inflammatory nodules were present sequentially at the tail, and congestion of nasal mucosa, mental fatigue, loss of appetite and edema of left hind paw were also observed. At 12 days after treatment, the mental status and appetite in the control group, *A. chinensis* extract group and *T. wilfordii* group were improved gradually, but remained unchanged in the adjuvant arthritis group. None died during the experiment.

Table I

Body weight of rats in different groups before and after treatment

Group	n	Before (g)	After (g)
Control	8	255.5 ± 10.5	298.6 ± 9.3^{c}
Adjuvant arthritis	8	255.5 ± 11.4	264.0 ± 11.3^{a}
T. wilfordii	8	250.1 ± 11.1	277.1 ± 13.1^{ab}
A. chinensis	8	252.8 ± 3.6	279.0 ± 9.7^{ab}

^{a}p<0.01 vs control group; ^{b}p<0.05; ^{c}p<0.0 vs AA group

Table II

Arthritis index in different groups before and after treatment

Group	n	Before	After
Adjuvant arthritis	8	7.9 ± 0.8	10.0 ± 1.5
T. wilfordii	8	8.6 ± 1.3	8.3 ± 1.6^{a}
A. chinensis	8	7.8 ± 1.4	7.5 ± 0.8^{a}

Data are mean ± SD; ^{a}p<0.05 vs AA group

After introduction of adjuvant arthritis, the body weight gain was slower than that in the control group. After treatment with *A. chinensis* extract or *T. wilfordii*, the body weight gain was significantly higher than that in the adjuvant arthritis group (p<0.05). There was no marked difference in the body weight gain among *A. chinensis* extract group, *T. wilfordii* group and control group (p>0.05; Table I).

There was no significant difference in the arthritis index among groups before treatment (p>0.05). After

Table III

Changes in serum levels of TNF-α, IL-4 and IL-10 after treatment

Group	n	TNF-α (pg/mL)	IL-4 (pg/mL)	IL-10 (pg/mL)
Control	8	83.1 ± 11.5^{d}	54.4 ± 4.5^{c}	25.1 ± 1.7^{d}
Adjuvant arthritis	8	268.8 ± 22.9^{b}	49.3 ± 0.7^{a}	15.8 ± 1.9^{b}
T. wilfordii	8	159.5 ± 12.0^{bd}	65.1 ± 2.1^{bd}	31.1 ± 1.5^{bd}
A. chinensis	8	178.5 ± 11.2^{bd}	76.1 ± 2.8^{bde}	29.2 ± 1.7^{bd}

Data are mean ± SD; Note: ^{a}p<0.05, ^{b}p<0.01 vs control group; ^{c}p<0.05, ^{d}p<0.0 vs Adjuvant arthritis group; ^{e}p<0.01 vs *T. wilfordii* group

treatment, the arthritis index in the *A. chinensis* extract group and *T. wilfordii* group was markedly reduced ($p<0.05$). No significant difference was observed between *T. wilfordii* group and *A. chinensis* extract group ($p>0.05$; Table II).

When compared with control group, the TNF-α level increased significantly but the IL-4 and IL-10 reduced markedly ($p<0.05$ or <0.01). In the *T. wilfordii* group and *A. chinensis* extract group, the TNF-α level reduced and the IL-4 and IL-10 increased ($p<0.01$). Moreover, the increased in IL-4 in the AT group was higher than that in the *T. wilfordii* group ($p<0.01$; Table III).

Discussion

The etiology and pathogenesis of rheumatoid arthritis is still poorly understood and has been found to be related to multiple factors. Some studies support that rheumatoid arthritis is an inflammatory disease due to the regulatory dysfunction of immune system. The inflammatory response in rheumatoid arthritis is very complex and has involvement of multiple genes (Springer, 1994; Murdoch and Finn, 2000), and a lot of cytokines have been found to participate in the regulation of complicated immune network. Among numerous cytokines in rheumatoid arthritis, TNF-α and IL are found to play important roles in the pathology of rheumatoid arthritis (Yu, 2007). TNF-α has potent biological activity. Studies have confirmed that TNF-α can induce the inflammatory response and mediate the killing of targeted cells (virus infected cells) and cancer cells, may cause fever, metabolic disorder and dyscrasia and has found to be related to the damage to articular cartilage in rheumatoid arthritis. IL-4 and IL-10 are two anti-inflammatory factors. IL-4 can promote the migration of macrophages into the inflammatory sites; IL-4 can inhibit the secretion and activities of TNF-a, IL-1 and IL-6 to antagonize the effect of IL-1; IL-4 may promote the proliferation of Th2 cells to suppress the Th1 mediated immune response (Wang and Chen, 1994). IL-10 can down-regulate Th1 mediated immune response and increase the IL-10/TNF-β producing regulatory T lymphocytes, which may inhibit the inflammation and the damage to the bone and cartilage and reduce the production of TNF-α and IL-1 (Gonzalez-Rey et al., 2007). There is evidence showing that IL-4 and IL-10 can synergistically inhibit the secretion of proteases that can degrade the cartilages, and reverse the function of decomposition factors, both of which may inhibit the damage to cartilages (Palmer et al., 2002). In healthy subjects, there is a balance between anti-inflammatory cytokines and pro-inflammatory cytokines. The disruption of this balance may induce the occurrence of rheumatoid arthritis.

T. wilfordii is a common drug used in the clinical treatment of rheumatoid arthritis having favorable efficacy. However, *T. wilfordii* may cause reduction of white blood cells and platelets and influence the reproductive system leading to menstrual disorder, compromised sperm activity and reduction of sperms. Thus, in the present study, *A. chinensis* extract with relatively less side effects was used to treat rheumatoid arthritis and the therapeutic efficacy was evaluated and compared with that of *T. wilfordii*.

Rheumatoid arthritis is one of arthralgias in Traditional Chinese Medicine. The Inner Canon of Huangdi proposed that the combination of wind-cold-damp results in arthralgias. Thus, to dispel wind, disperse cold and eliminate damp have been used in the treatment of arthralgias. *A. chinensis* is a plant of araliaceae belonging to aralia genus. *A. chinensis* is mainly distributed in the mountain area of central and west China. The type specimen is mainly obtained from Taibai in Shaanxi Province. Non-governmentally, *A. chinensis* is also known as one of seven Taibaishan herbs in Qinling of Shaanxi. It is rich in China and the skin of root and stem, the stem, the leaf and fruit of *A. chinesis* can be used as drugs (Wang et al., 1998). AT has the characteristics of dispelling wind and eliminating damp, attenuating heat and relieving pain, activating blood circulation and dissipating blood stasis, inducing diuresis and reducing edema, invigorating qi for tranquilization and liver-preservation (Wang et al., 1997). Its bioeffects are consistent with the principles of treatment based on syndrome differentiation in Traditional Chinese Medicine. Our results demonstrated that *A. chinensis* could recover the energy, increase the body weight and attenuate the inflammatory response in rats with rheumatoid arthritis, exerting therapeutic effect on rheumatoid arthritis. This effect on rheumatoid arthritis may be related to the down-regulation of TNF-α and up-regulation of IL-4 and IL-10 as well as the recovery of balance between anti-inflammatory cytokines and pro-inflammatory cytokines.

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