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EXPERIMENTAL STUDY

Uric acid lowering effect of Tibetan Medicine RuPeng15 powder in animal models of hyperuricemia

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Abstract

OBJECTIVE: To evaluate the influence of the Tibetan medicine RuPeng15 powder (RPP15) on uric acid levels, and explore its possible mechanisms of action in hyperuricemic animal models.

METHODS: Hyperuricemic mice were generated by orally administering yeast extract paste twice daily (30 g/kg) for 8 days, to mimic human hyperuricemia induced by high-protein diets. Hyperuricemic rats were generated by intraperitoneal injection of 250 mg/kg potassium oxonate to each animal 1 h before the last oral administration of test compounds, which raised the serum uric acid level by inhibiting the decomposition of uric acid. Levels of uric acid and creatinine in serum and urine were detected by the phosphotungstic acid and picric acid methods respectively, and the activity of xanthine oxidase (XOD) was assayed using a commercial test kit.

RESULTS: RPP15 (0.4, 0.8, 1.2 g/kg) significantly decreased the level of serum uric acid in healthy rats ($P < 0.05$). Furthermore, hyperuricemic rats treated with RPP15 (0.4, 0.8, 1.2 g/kg) had lower serum uric acid levels ($P < 0.05$), accompanied by lower urine uric acid ($P < 0.05$). For the hyperuricemic mice, the levels of uric acid in the serum decreased significantly ($P < 0.05$) and the activity of XOD in the liver was restored to normal levels after treatment with RPP15 ($P < 0.05$).

CONCLUSION: RPP15 (0.4, 0.8, 1.2 g/kg) demonstrated an anti-hyperuricemic effect on both healthy and hyperuricemic animals, and the mechanism is most likely associated with inhibiting the activity of XOD.

Key words: RuPeng15 powder; Hyperuricemia; Gout; Uric Acid; Xanthine Oxidase

INTRODUCTION

Hyperuricemia is characterized by abnormally high levels of uric acid in the blood. In general, the upper end of the normal range is 360 μmol/L (6 mg/dL) for women and 416 μmol/L (7.0 mg/dL) for men.[1] Hyperuricemia has also emerged as a metabolic disease which threatens human health, and is considered as an important risk factor for gout and may be associated with metabolic syndromes, stroke incidence, chronic kidney disease and cardiovascular disease.[2-4] Current anti-hyperuricemic agents in use include: xanthine oxidase

(XOD) inhibitors, which inhibit the activity of XOD, an enzyme involved in purine metabolism, of which allopurinol is the most often prescribed; uricosuric agents, which act on the proximal tubules in the kidneys to interfere with the absorption of uric acid from the urine back into the blood, and include probenecid, benzbromarone and sulfinpyrazone; and the enzyme urate oxidase, including the recombinant form rasburicase, which catalyzes the oxidation of uric acid to the more soluble allantoin which is more readily excreted via the kidneys. However, these existing anti-hyperuricemic agents possess undesirable effects. For example, allopurinol, which is the drug of choice, has side effects including gastrointestinal irritation, bone marrow suppression, hypersensitivity syndromes, hepatitis and worsening renal function, which are unable to be tolerated by approximately 5% of patients. Uricosuric agents are used in patients with allopurinol-allergic syndromes as well as in under excreters with normal renal function and no history of urolithiasis. However, uricosuric agents, such as benzbromarone, also have issues. Though benzbromarone is still marketed in several countries by other drug companies, it was withdrawn by Sanofi-Synthélabo in 2003 after reports of serious hepatotoxicity. Similarly, the uricosuric agents probenecid and sulfinpyrazone have been reported to be nephrotoxic when used to treat hyperuricemia associated with moderate chronic renal insufficiency.[5-11] Enzyme therapy using urate oxidase is only for treating severe hyperuricemia and is not widely used. Thus, anti-hyperuricemic agents have been limited in their clinical use due to their severe side effects. Therefore, it is important to search for alternative anti-hyperuricemic agents with more favorable toxicological profiles, and in particular from natural sources.

Tibetan medicine, which has historic connections to Traditional Chinese Medicine, is an integral part of Tibetan culture and has been developed over many centuries. It is beneficial for chronic diseases such as digestive problems, arthritis, gout, asthma, and problems related to the liver, kidneys and heart.[12] RuPeng15 powder (RPP15) is a herbal multi-compound remedy comprised of 15 specific herbs that originate from traditional Tibetan medicine. It is produced by combining the Ten Tastes Frankincense powder with the Five Musks pill as detailed in the classical recipe recorded in "The Four Medical Tantras," compiled by Yuthok Yönten Gönpo in the ninth century. Both recipes have been continually improved by Tibetan doctors over the centuries. In 1813, according to Tibetan Notes, the two recipes were combined together to comprise what is now called RPP15. RPP15 has been described to have anti-gout, anti-inflammatory and anti-hyperuricemic effects.[13-15] Although RPP15 has been seen to be an effective and safe prescription in the treatment of hyperuricemia and gout for centuries, Tibetan populations have used it primarily based on classical records and clinical experience.[16,17] Its functional roles in the treatment of hyperuricemia and gout have not been completely elucidated. Thus, the aim of the present study is to evaluate the anti-hyperuricemic effect of this compound and identify the possible underlying mechanisms in animal models of hyperuricemia.

MATERIALS AND METHODS

Reagents

Potassium oxonate (PO) was purchased from Adamas Reagent Co., Ltd. (Shanghai, China). Yeast was obtained from Oxoid (Basingstoke, Hampshire, England), and allopurinol tablets from the Haizhen pharmaceutical company (Zhejiang, China). Benzbromarone capsules were from the Huashen pharmaceutical company (Chengdu, China). Uric acid test kits (phosphotungstic acid method), creatinine assay kits (picric acid method) and XOD test kits (colorimetric) were purchased from Jiancheng Biotech (Nanjing, China). All assays were carried out according to the manufacturer's instructions. The total protein assay kit (BCA) was from Pierce (Rockford, IL, USA).

Plant material and preparation

The RPP15, a herbal mixture comprised of 15 ingredients: Ruxiang (*Olibanum*), Kuanjinteng (*Caulis Tinosporae Sinesis*), Juemingzi (*Semen Cassiae Obtusifoliae*), Zhaxungao (*Brag zhun*), Huangkuizi (*Semen Abelmoschi*), Tibetan Changpu (*Bhizoma Acori Calami*), Baxiaga (*Adhatoda vasica Nees*), Ercha (*Catechu*), Hezi (*Fructus Chebulae*), Anxixiang (*Benzoinum*), Maohezi (*Fructus Terminaliae Billericae*), Tiebangchui (*Radix Aconiti Penduli*), Muxiang (*Radix Aucklandiae*), Shexiang (*Moschus*), Yuganzi (*Fructus Phyllanthi Emblicae*) was procured from the Qinghai Provincial Tibetan Medical Hospital, the authority in the area on Tibetan medicine. According to Tibetan doctors, the recommended dosage of RPP15 for adults is 2.4 g (total raw materials/day). In rats and mice, equivalent doses are approximately 7 and 10 times the human dose, respectively.[18] Based on clinical observations of the safety of the drug, we chose 10, 20 and 30 times the human dose as lower, middle and high dosage, respectively. Three doses of RPP15 were used at 0.4, 0.8 and 1.2 g/kg suspended in distilled water and administered by oral gavage for 6-10 days in the study. Allopurinol and benzbromarone were used as positive controls and similarly prepared in distilled water.

Animals

Fifty six male Sprague-Dawley rats (8-10 weeks of age, weighing 180-200 g) and 72 male Kun-Ming strain mice (24-27 g) were obtained from The Medical College Experimental Animal Center of Lanzhou University, China (Certificate of Quality: SCXK-2009-0004). Both rats and mice were fed a commercial laboratory diet (Beijing Keao Xieli Feed Co., Ltd., China) and al-