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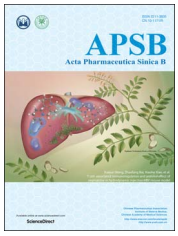

SHORT COMMUNICATION

Antihyperuricemic effect of mangiferin aglycon derivative J99745 by inhibiting xanthine oxidase activity and urate transporter 1 expression in mice

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KEY WORDS

Antihyperuricemic effect;
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Urate transporter 1

Abstract A mangiferin aglycon derivative J99745 has been identified as a potent xanthine oxidase (XOD) inhibitor by previous *in vitro* study. This study aimed to evaluate the hypouricemic effects of J99745 in experimental hyperuricemia mice, and explore the underlying mechanisms. Mice were orally administered 600 mg/kg xanthine once daily for 7 days and intraperitoneally injected 250 mg/kg oxonic acid on the 7th day to induce hyperuricemia. Meanwhile, J99745 (3, 10, and 30 mg/kg), allopurinol (20 mg/kg) or benzbromarone (20 mg/kg) were orally administered to mice for 7 days. On the 7th day, uric acid and creatinine in serum and urine, blood urea nitrogen (BUN), malondialdehyde (MDA) content and XOD activities in serum and liver were determined. Morphological changes in kidney were observed using hematoxylin and eosin (H&E) staining. Hepatic XOD, renal urate transporter 1 (URAT1), glucose transporter type 9 (GLUT9), organic anion transporter 1 (OAT1) and ATP-binding cassette transporter G2 (ABCG2) were detected by Western blot and real time polymerase chain reaction (PCR). The results showed that J99745 at doses of 10 and 30 mg/kg significantly reduced serum urate, and enhanced fractional excretion of uric acid (FEUA). H&E staining confirmed that J99745 provided greater nephroprotective effects than allopurinol and benzbromarone. Moreover, serum and hepatic XOD activities and renal URAT1 expression declined in J99745-treated hyperuricemia mice. In consistence with the ability to inhibit XOD, J99745 lowered serum MDA content in hyperuricemia mice. Our results

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suggest that J99745 exerts urate-lowering effect by inhibiting XOD activity and URAT1 expression, thus representing a promising candidate as an anti-hyperuricemia agent.

1. Introduction

Hyperuricemia characteristic with excessive uric acid in blood leads to gout, and increases the risk of cardiovascular diseases, metabolic disorder and chronic renal disease[1,2]. It is widely regarded relevant to the progress and prognosis of gout, nephrosis and cardiovascular diseases. Adequate control of hyperuricemia contributes to prevention and treatment of these diseases[3].

Uric acid is a product of the metabolic breakdown of purine nucleotides. The enzyme xanthine oxidase (XOD) catalyzes the oxidation of hypoxanthine or xanthine to uric acid. The renal excretion of uric acid is mainly dependent on the kidney urate transport system including glomerular filtration, as well as reabsorption into and secretion from proximal tubular cells. Urate transporter 1 (URAT1) located at the luminal membrane and glucose transporter type 9 (GLUT9) at the apical membranes of the renal proximal tubules constitute the main pathway of urate reabsorption in the kidney[4,5]. However, 90% of urate reabsorption is obtained through renal URAT1. Moreover, renal organic anion transporter 1 (OAT1) localized in the basolateral membrane and ATP-binding cassette transporter G2 (ABCG2) located at the apical membrane have been identified as main secretory urate transporters[6,7].

Currently, there are a few urate-lowering drugs in clinical use while most of them have severe side effects or are insensitive to kidney function impairment[8,9]. XOD inhibitors and uricosuric drugs are two major therapies to reduce blood urate levels. Allopurinol and febuxostat are two major XOD inhibitors used

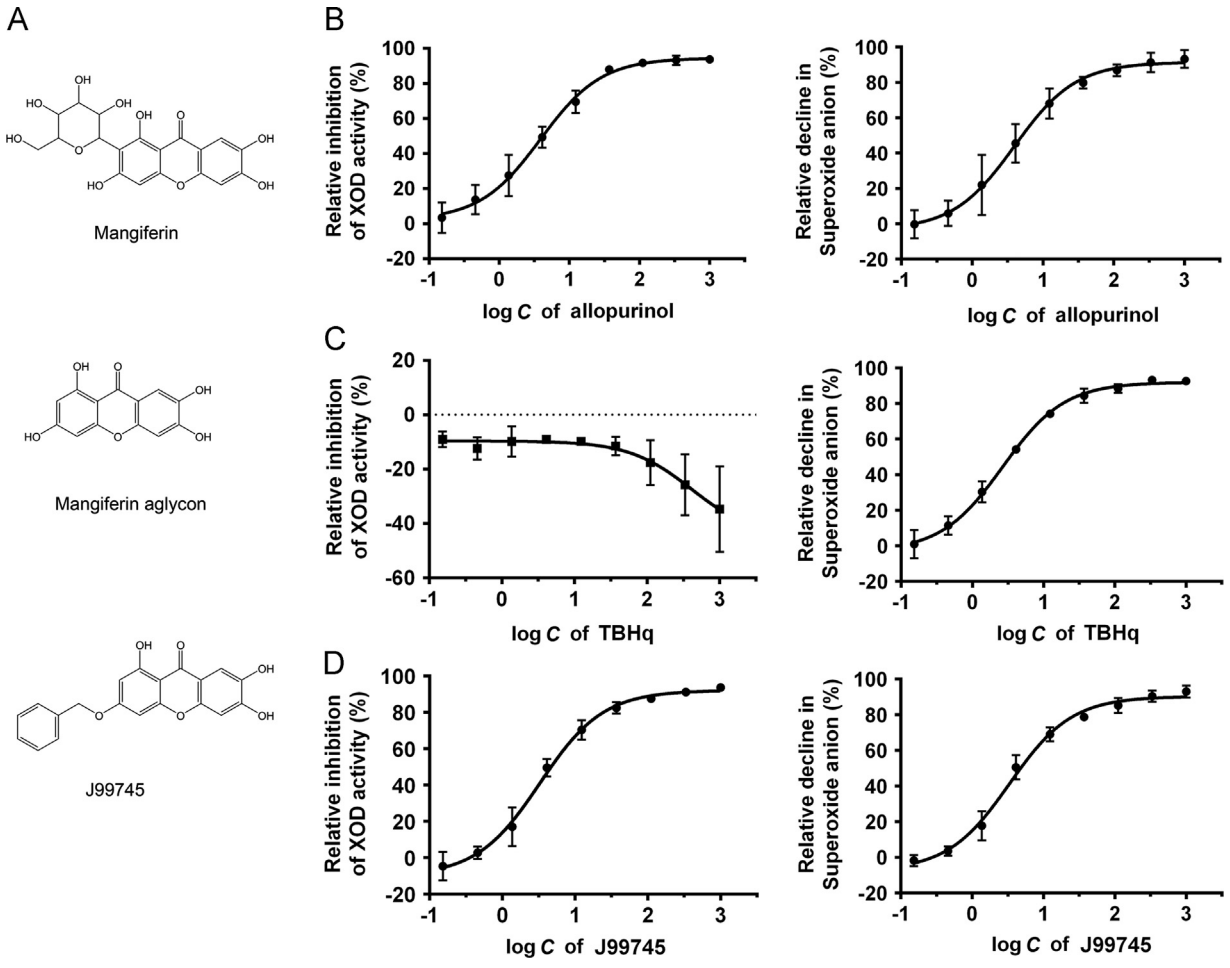

Figure 1 Chemical structure of J99745 (A) and its effect–concentration curve on XOD activity and superoxide anion scavenging *in vitro* (D). The effect–concentration curves of allopurinol (B) and TBHq (C) are also showed. Data are mean ± SD ($n = 3$). XOD, xanthine oxidase; TBHq, tert-butylhydroquinone.

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