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Anti-hyperuricemic peptides derived from bonito hydrolysates based on *in vivo* hyperuricemic model and *in vitro* xanthine oxidase inhibitory activity

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ABSTRACT

Traditional drugs used to treat hyperuricemia have adverse effects. In this study, to identify safer anti-hyperuricemic bioactive peptides isolated from food-derived protein hydrolysates, a hyperuricemia rat model induced by potassium oxonate (PO) was used to evaluate the activity of bonito hydrolysates (BH), dephenolised walnut hydrolysates (DWH), and soybean hydrolysates (SH). The serum uric acid level of rats in the BH group (95.4 ± 27.4 μM, $p < 0.01$) was significantly reduced compared to that in the model group (212.00 ± 30.00 μM) to a level even lower than that in allopurinol group (114.3 ± 53.0 μM). Furthermore, BH alleviated renal impairment caused by PO *in vivo* and exhibited the greatest xanthine oxidase (XOD) inhibitory activity (65.5 ± 8.0%) *in vitro* compared to the other hydrolysates. Two peptides identified from BH bound the catalytic site of XOD, among which the hydrophobic peptide WML entered the active site of XOD more easily compared to the hydrophilic peptide PGACSN, possibly because of hydrophobic interactions. The chemically synthesized WML demonstrated high XOD inhibitory effect compared to PGACSN and a significant change in the secondary structure of XOD. Therefore, hexapeptide PGACSN and tripeptide WML are partially responsible for the anti-hyperuricemic activity of BH, and hydrophobic amino acids play important roles in the XOD inhibitory activity of peptides.

1. Introduction

Hyperuricemia is a metabolic disease resulting from overproduction of uric acid or uric acid excretion disorder in the body. Excessive uric acid in serum can cause uric acid nephrolithiasis and gout, even resulting in hyperlipidaemia, hypertension, type II diabetes, and cardiovascular diseases [1,2]. Furthermore, chronic hyperuricemia is directly linked to interstitial nephritis and progressive renal failure [3]. Serum uric acid (SUA) is derived from exogenous purine food and endogenous purine metabolism [4]. Compared to other mammals, humans are more likely to develop urate nephropathy and gout arthritis because they lack of urate oxidase, which can degrade uric acid to allantoin [5]. To prevent and treat hyperuricemia and gout, reducing the intake of high-purine foods can reduce the production of overdose uric acid. Furthermore, either inhibiting uric acid synthesis or promoting uric acid excretion is effective for controlling blood uric acid levels *in vivo*.

Xanthine oxidase (XOD), a pivotal enzyme in purine metabolism, catalyses the oxidation of xanthine or hypoxanthine to uric acid [6]. The production of uric acid in the serum was decreased by inhibiting XOD activity [7]. Previous studies demonstrated XOD is an important therapeutic target for hyperuricemia treatment [8]. Some drugs (*e.g.*, allopurinol) have been developed as XOD inhibitors which can effectively prevent the synthesis of uric acid and decrease the SUA level [9]. Uricosuric agents (*e.g.*, probenecid, benzbromarone, and lesinurad) may act on the uric acid transporter and contribute to uric acid excretion [10]. Although these drugs could alleviate pain caused by gout in the short term, they are not curative treatments. Moreover, adverse effects limit their use [11,12]. Thus, novel food-derived components are highly needed for to prevent hyperuricemia and gout.

Bonito, walnut, and soybean are important sources of animal protein and plant proteins, which have been shown to have diverse bioactivities. Protein hydrolysates from walnut and soybean were widely reported for their antioxidant efficacy [13]. Bonito is a marine migratory fish with powerful exercise capability and tight binding proteins. In recent years, researchers found that bonito hydrolysates (BH) have a high content of carnosine and anserine, which showed

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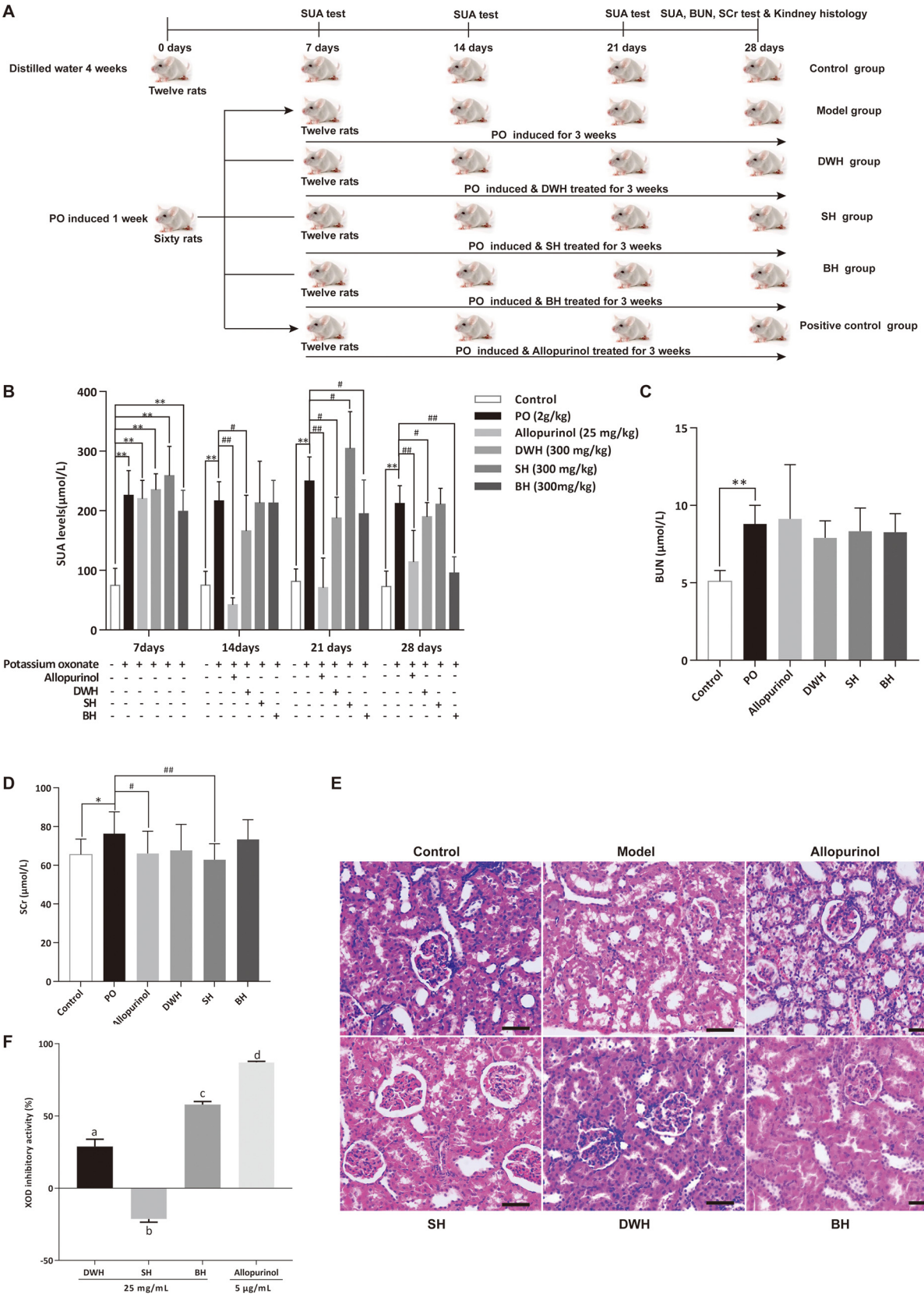

Fig. 1. Anti-hyperuricemic activity and XOD inhibitory activity of food protein hydrolysates and histopathological observation. (A) Flow chart of animal experiments *in vivo* **(B)** The SUA level of rats on the 7th,14th, 21st, and 28th days. The concentration of BUN **(C)** and SCr **(D)** of rats monitored on the 28th day. Data were presented as the means ± SD (n = 12). Significant difference was shown at $^{*}p < 0.05$ (compared to the control); $^{\#\#}p < 0.01$, $^{\#}p < 0.05$(compared with PO group). **(E)** Histopathological examination of renal tissue of rats (haematoxylin & eosin, scale bars 50 μm). **(F)** The XOD inhibitory effects of SH, DWH, and BH. Data are presented as the means ± SD (n = 3). Data marked with different letters (a, b, c, and d) indicate significant differences ($p < 0.01$). PO, potassium oxonate; SUA, serum uric acid; SCr, serum creatinine; BUN, blood urea nitrogen; XOD, xanthine oxidase; DWH, dephenolised walnut hydrolysates; SH, soybean hydrolysates; BH, bonito hydrolysates.