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Original Article

Pharmacokinetics, bioavailability, tissue distribution and excretion of tangeretin in rat

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ABSTRACT

Tangeretin, 4′,5,6,7,8-pentamethoxyflavone, is one of the major polymethoxyflavones (PMFs) existing in citrus fruits, particularly in the peels of sweet oranges and mandarins. Tangeretin has been reported to possess several beneficial bioactivities including anti-inflammatory, anti-proliferative and neuroprotective effects. To achieve a thorough understanding of the biological actions of tangeretin *in vivo*, our current study is designed to investigate the pharmacokinetics, bioavailability, distribution and excretion of tangeretin in rats. After oral administration of 50 mg/kg bw tangeretin to rats, the C_{max}, T_{max} and $t_{1/2}$ were 0.87 ± 0.33 μg/mL, 340.00 ± 48.99 min and 342.43 ± 71.27 min, respectively. Based on the area under the curves (AUC) of oral and intravenous administration of tangeretin, calculated absolute oral bioavailability was 27.11%. During tissue distribution, maximum concentrations of tangeretin in the vital organs occurred at 4 or 8 h after oral administration. The highest accumulation of tangeretin was found in the kidney, lung and liver, followed by spleen and heart. In the gastrointestinal tract, maximum concentrations of tangeretin in the stomach and small intestine were found at 4 h, while in the cecum, colon and rectum, tangeretin reached the maximum concentrations at 12 h. Tangeretin excreted in the urine and feces was recovered within 48 h after oral administration, concentrations were only 0.0026% and 7.54%, respectively. These results suggest that tangeretin was mainly eliminated as metabolites. In conclusion, our study provides useful information regarding absorption, distribution, as well as excretion of tangeretin, which will provide a good base for studying the mechanism of its biological effects.

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1. Introduction

Flavonoids are ubiquitously in fruits, cereals, seeds and vegetables, as well as some beverages including wine and tea. The typical structure of flavonoids is a fifteen-carbon skeleton consisting of two phenyl rings. Many *in vitro* and *in vivo* studies have reported that flavonoids possess numerous health benefits [1–3]. Polymethoxyflavones (PMFs) are a unique group of methylated flavonoids existing exclusively in citrus fruits, particularly the peel of sweet oranges (*Citrus sinensis*) and mandarins (*Citrus reticulata*). The contents and types of PMFs vary depending on the different varieties of citrus species. In some countries, orange peel is used as traditional medicine for relieving skin inflammation and stomach upset, as well as muscle pain. Over the past few years, numerous *in vitro* and *in vivo* studies have indicated that PMFs are the major bioactive flavonoids in citrus peel, possessing several biological activities, including anti-proliferative, anti-inflammatory, anti-angiogenic and neuroprotective properties [4–7].

Tangeretin is one of the most abundant PMFs in citrus peel (Fig. 1). Concentrations vary depending on the different citrus varieties. For example, among 45 citrus fruits, the concentrations of tangeretin in the peel ranged from 0.1 to 174 mg/100 g (fresh weight), while its concentration in commercial citrus beverages was 0.08–0.60 mg/L [8,9]. Numerous studies have reported tangeretin to possess a broad spectrum of biological activities [10–16]. Among 27 citrus flavonoids, tangeretin exhibited potent anti-proliferative effects against lung and gastric carcinoma, melanoma and leukemia cell growth [14]. A recent study reported that tangeretin effectively suppressed glioblastoma cell growth in a dose- and time-dependent manner [17]. Tangeretin treatment arrested glioblastoma cells at G2/M phase by modulating phosphatase and tensin homolog and cyclin-D and ccd-2 mRNA expression. Additionally, tangeretin suppressed lipid accumulation in HepG2 cells by activating peroxisome proliferator-activated receptor and decreasing diacylglycerol acyltransferase and microsomal triglyceride transfer protein [18]. Recently a similar study revealed that supplementation of 1% PMF containing tangeretin for 8 weeks significantly reduced triacylglycerol, body weight and the relative weights of white adipose tissue pads in high cholesterol diet-fed hamsters [16]. These effects were associated with decreased fatty acid synthase, sterol regulatory element binding protein-1c and increased lipoprotein lipase. Finally, tangeretin has shown neuroprotective effects through alleviation of the inflammatory responses in lipopolysaccharide-stimulated microglial cells [15,19].

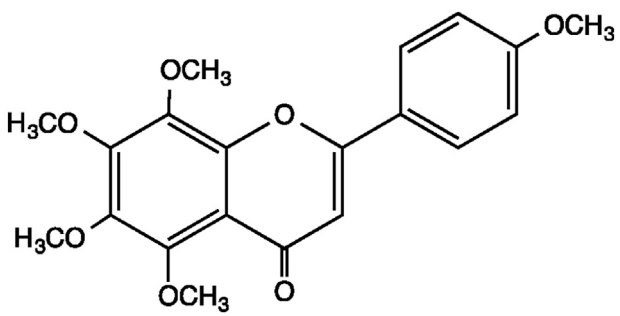

Fig. 1 – Chemical structure of tangeretin.

PMFs have attracted much attention due to their high oral bioavailabilities when compared to hydroxyflavones. The high oral bioavailability of PMFs is due to the lipophilic nature of structure's multiple methoxy groups. An early investigation revealed that PMFs, including tangeretin and nobiletin, exhibited higher anti-proliferative effects against squamous cell growth in both a dose- and time-dependent manner as compared to quercetin and taxifolin [20]. These higher activities found in PMFs resulted from the methoxy groups, leading to a decrease of hydrophilicity, followed by enhanced cellular uptake.

Many *in vitro* studies indicated flavonoids possess different bioactivities; however, poor bioavailability may make them largely ineffective *in vivo* [21,22]. Since numerous *in vitro* studies report tangeretin exhibits a broad spectrum of biological activities, absorption levels are of special interest. Previous studies on pharmacokinetics and excretion of tangeretin have been conducted [23,24]. However, a comprehensive study regarding the pharmacokinetics, tissue distribution, plus excretion of tangeretin has not been fully investigated. In current study, we first used SD rats as an animal model to determine the oral bioavailability of tangeretin, and then evaluated tangeretin distribution in the tissues, as well as tangeretin excretion in urine and feces.

2. Meterials and methods

2.1. Materials and chemicals

Tangeretin was isolated from citrus peel extract and purified using column chromatography. The purity of tangeretin was determined above 95% by HPLC using an absorbance wavelength of 270 nm. Hesperetin was purchased from Sigma Chemical Co. (St. Louis, MO, USA) and the purity was above 98%. Methanol and sodium chloride were sourced from Mallinckrodt Baker (Center Valley, PA, USA). Ethyl acetate, ethanol, formic acid, dimethyl sulfoxide and Tween 80 were purchased from Sigma Chemical Co. (St. Louis, MO, USA).

2.2. Animals and diets

Healthy, 6-week-old, male SD rats purchased from BioLASCO (Nangang, Taipei, Taiwan) were used to investigate the pharmacokinetics, distribution and excretion of tangeretin. All animals were housed in a controlled environment (22 ± 3 °C, 40–60% relative humidity, 12-h light-dark cycle, 0700-1900) and fed with a commercial diet (LabDiet, 5001, Purina, St. Louis, MO, USA) with distilled water *ad libitum* throughout the experiment. The experimental protocol was approved by the National Laboratory Animal Center (Nangang, Taipei, Taiwan). Care of the animals was in compliance with the Taiwan Government's Guide for the Care and Use of Laboratory Animals. The experimental protocol was approved by Institutional Animal Care and Use committee, National Taiwan University.

2.3. Pharmacokinetics experiment

Before initiation of the pharmacokinetics study, the animals were divided into two groups, each group containing six rats.

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