Research Article

Pharmacokinetics and Biodistribution of Zinc-Enriched Yeast in Rats

Shuangqing Zhang, Yan Zhang, Ning Peng, Haibo Zhang, Juan Yao, Zhihong Li, and Liegang Liu

1 Division of Nutrition and Health, Angel Yeast Co. Ltd., 168 Chengdong Avenue, Yichang 443003, China
2 Department of Nutrition and Food Hygiene, Hubei Key Laboratory of Food Nutrition and Safety, State Key Laboratory of Environment Health (Incubation), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Correspondence should be addressed to Liegang Liu; lgliu@mails.tjmu.edu.cn

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Zinc-enriched yeast (ZnY) and zinc sulfate (ZnSO₄) are considered zinc (Zn) supplements currently available. The purpose of the investigation was to compare and evaluate pharmacokinetics and biodistribution of ZnY and ZnSO₄ in rats. ZnY or ZnSO₄ were orally administered to rats at a single dose of 4 mg Zn/kg and Zn levels in plasma and various tissues were determined using inductively coupled plasma-optical emission spectrometry. Maximum plasma concentration values were 3.87 and 2.81 µg/mL for ZnY and ZnSO₄, respectively. Both ZnY and ZnSO₄ were slowly eliminated with a half-life of over 7 h and bone had the highest Zn level in all tissues. Compared to ZnSO₄, the relative bioavailability of ZnY was 138.4%, indicating that ZnY had a significantly higher bioavailability than ZnSO₄.

1. Introduction

Essential trace elements are very important for the proper functioning of living organisms, such as growth and maintenance, neuromodulation, and regulation of cellular function, and thus their deficiency is associated with an enormous health risk that can ultimately lead to death [1]. Zinc (Zn) is an essential trace element for plants, microorganisms, animals, and humans and plays numerous central roles in structure and function of proteins, metabolism of RNA and DNA, signal transduction, gene expression, and regulation of apoptosis [2]. Zn deficiency affects nearly two billion people in the developing countries and is associated with many diseases, including depressed growth, diarrhea, impotence and delayed sexual maturation, alopecia, eye and skin lesions, impaired appetite, altered cognition, impaired host defense properties, defects in carbohydrate utilization, and reproductive teratogenesis [3, 4]. Zn deficiency is usually caused by insufficient dietary intake but can be associated with many diseases, such as malabsorption, acrodermatitis enteropathica, chronic liver disease, chronic renal disease, sickle cell disease, diabetes, malignancy, and other chronic illnesses [4]. Zn supplements help prevent disease and reduce mortality, especially among children with low birth weight or stunted growth. Zn supplements include Zn chloride and Zn sulfate (ZnSO₄) as inorganic salts for parenteral administration, Zn gluconate, Zn gluconate/glycine, Zn acetate, and Zn propionate as salts of organic acids for oral usage, and Zn-enriched yeast (ZnY) or Zn-enriched grains as biologically organic forms for oral intake [5].

ZnY, a biological source of Zn with rich proteins, peptides, and amino acids, is naturally integrated by the growing yeast into its own structure to improve the bioavailability of Zn and reduce the side effects of Zn. ZnY is used as the raw material of foods, functional foods, and medicines, such as dairy products, biscuits, beverages, and flour. So far, only
two studies of ZnY reported that ZnY was more bioavailable than Zn gluconate in rat liver and human [6, 7]. The purpose of the present investigation was to compare and evaluate pharmacokinetics and biodistribution of ZnY and ZnSO₄ in rats.

2. Materials and Methods

2.1. Materials. ZnY was provided by Angel Yeast Co. Ltd. (Yichang, Hubei, China). ZnSO₄ was obtained from Sigma Aldrich (St. Louis, MO, USA). Nitric acid and perchloric acid were the guaranteed reagents. All other reagents were of analytical grade and obtained through commercial sources.

2.2. Pharmacokinetics and Biodistribution. All procedures involving animals were approved by our Institutional Animal Care and Use Committee. Adult Sprague-Dawley rats, weighing 250 ± 11 g, were obtained from Jackson Laboratory (Bar Harbor, ME, USA) and housed in standard cages and allowed free movement and access to food and water during the whole experiment. The rats were randomly assigned into two groups and orally given either ZnY or ZnSO₄ at a single dose of 4 mg Zn/kg. At designated time-points, blood was collected in a heparin-coated tube and plasma was separated by centrifugation at 5,000 g for 10 min. Supernatant was then transferred to a clean tube and immediately stored at −80°C until analysis. Immediately after the last time-point blood collection, rats were sacrificed using carbon dioxide asphyxiation and tissues (liver, heart, pancreas, spleen, kidney, and bone) were immediately excised. All tissue samples washed with tridistilled water were frozen at −80°C until analysis.

2.3. Zn Determination. Zn levels in plasma, liver, heart, pancreas, spleen, kidney, and bone were determined using inductively coupled plasma-optical emission spectrometry (Model 720, Agilent Inc., CA, USA). Samples were prepared as follows: 100 μL of plasma or weight tissue specimen was pretreated with the mixture of nitric acid and perchloric acid (20:1, v/v) overnight and heated at the temperature of 180–200°C until samples were completely digested, that is, until the solutions were colorless and clear. The remaining acid solution was cooled and diluted with tridistilled water to an appropriate concentration for the assay. Quality control samples were employed for the validation of analytical method and the analytical error was less than 11%.

2.4. Data Analysis. Pharmacokinetic parameters of ZnY and ZnSO₄ were calculated using noncompartmental analysis of WinNonlin software (Version 5.2.1, Pharsight Corp., Mountain View, CA, USA). Results are presented as mean ± standard deviation (SD). The comparison for difference between parameters or between groups was analyzed using one-way analysis of variance (ANOVA). Differences were considered statistically significant at P < 0.05.

3. Results and Discussion

Although food is the major source of Zn, low Zn content in diet and many adverse nutritional factors are barriers to prevention and treatment of Zn deficiency [8, 9]. Zn chloride, ZnSO₄, and Zn oxide are often employed for food fortification; however there are serious shortcomings for those compounds. Zn chloride causes some adverse effects, ZnSO₄ renders unpalatable flavor, and water-insoluble Zn oxide precipitates in liquid foods; therefore, those compounds are used only in low quantities and in solid foods. ZnY has high solubility and a soft taste, and it does not modify the sensorial characteristics of food.

The concentration-time profile of ZnY and ZnSO₄ in plasma is shown in Figure 1 and their pharmacokinetic parameters are listed in Table 1. Peak plasma concentration (Cₘₐₓ) and the time to reach Cₘₐₓ (Tₘₐₓ) were 3.87 μg/mL and 2 h for ZnY and 2.81 μg/mL and 4 h for ZnSO₄, respectively. Cₘₐₓ, AUC₀−₂₄h, and AUC₀−∞ ratio values of ZnY to ZnSO₄ were 137.7%, 138.4%, and 139.2%, respectively, indicating that ZnY had a significantly higher bioavailability than ZnSO₄. Both ZnY and ZnSO₄ were slowly eliminated in vivo with respective t₁/₂ values of 7.68 and 7.93 h. During ZnY fermentation in the presence of Zn chloride or ZnSO₄, a specific strain of yeast produced specific zinc compounds conjugated with proteins, peptides, and amino acids, which helped improve bioavailability of ZnY compared to inorganic Zn via enhanced intestinal absorption. Our findings with ZnY are consistent with previous studies in which animal proteins could improve Zn absorption [6, 10], which could physiologically illustrate protein as the major dietary source of Zn.

Zn levels in liver, heart, pancreas, spleen, kidney, and bone are presented in Figure 2. The biodistribution results demonstrated that Zn was widely distributed in various rat
Table 1: The pharmacokinetic parameters of ZnY and ZnSO4 after a single oral administration of Zn compounds at a dose level of 4 mg Zn/kg. Values are presented as mean ± SD (n = 3).

| Parameter             | Unit   | ZnY       | ZnSO4      |
|-----------------------|--------|-----------|------------|
| t_{1/2,\infty}        | h      | 7.68 ± 1.82 | 7.93 ± 0.87 |
| AUC_{0-24h}           | h·µg/mL| 40.49 ± 5.48 | 29.26 ± 3.01 |
| AUC_{n-∞}             | h·µg/mL| 46.24 ± 8.97 | 33.22 ± 4.43 |
| V                     | mL/kg  | 954 ± 77   | 1381 ± 50  |
| Cls                   | mL/h/kg| 88.8 ± 17.7 | 121.9 ± 17.0 |
| MRT_{0-24h}           | h      | 7.94 ± 0.56 | 7.84 ± 0.36 |
| MRT_{n-∞}             | h      | 11.20 ± 2.31 | 11.09 ± 1.25 |

\( t_{1/2,\infty} \): terminal half-life; \( AUC_{0-24h} \): area under curve from 0 to 24 h; \( AUC_{n-∞} \): area under curve from 0 to infinite time; Cls: systemic clearance; \( V \): volume of distribution; MRT_{0-24h}: mean residence time from 0 to 24 h; MRT_{n-∞}: mean residence time from 0 to infinite time.

In conclusion, Zn from ZnY was more bioavailable than zinc from inorganic zinc salts ZnSO4; disposition and biodistribution of Zn in ZnY were similar to those of other sources of Zn.

Conflicts of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors’ Contribution

Shuangqing Zhang and Yan Zhang contributed equally to this work.

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