# Study on the bioavailability of prenylated isoflavones, glyceollins, in rats

張, 曄

Name : Zhang Ye

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(ラットにおけるプレニル化イソフラボンであるグリセオリン類の生体利用性に関する研究）

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## Thesis Summary


Glyceollins (prenylated 6a-hydroxy-pterocarpans) are also called as phytoalexin, since they are produced in soybeans from isoflavones by environmental (*e.g.,* infection, wounding, freezing, ultraviolet light) or microbial stresses. Clinical evidence has revealed that glyceollins have diverse *in vivo* physiological functions, such as antioxidation, anti-diabetes, anti-inflammation, and antagonistic effect against estrogen receptor (ER). Irrespective to obtain insights of physiological roles of glyceollins, it is crucial to understand their absorption, distribution, metabolism, and excretion (ADME) in the body system. Due to a variety of prenyl moiety in glyceollins, the ADME behavior must be greatly different among them. Therefore, not only the analysis of intestinal absorption and metabolism, but also the analysis of accumulation in the organs, of importance for deeper understanding of bioactive glyceollins. Thus, the present study aimed to get insights of bioavailability of prenylated isoflavones, glyceollins, in terms of their intestinal absorption and tissue accumulation in animal experiments using Sprague-Dawley (SD) rats.

Firstly, prenylated isoflavones, glyceollins (glyceollin III and I) and daidzein, the mother isoflavones as control, were investigated to clarify the intestinal absorption and metabolism in SD rats. As a result of LC-TOF/MS analysis of plasma samples taken at time points up to 8 h, no peaks corresponding to glyceollin I and III as well as daidzein were detected in their intact form. In contrast, deconjugation treatment of plasma by sulfatase/β-glucuronidase enzymes revealed that absorption amounts of conjugated forms of glyceollin I was much > 8-times higher than that of daidzein ($AUC_{0\text{-}8\ h}$: glyceollin I, 8.5 ± 0.7 nmol·h/mL; glyceollin III, 1.0 ± 0.2 nmol·h/mL; daidzein, 0.6 ± 0.1 nmol·h/mL), according to the magnitude of their log *P* value or hydrophobicity. MALDI-MS and LC-TOF/MS analyses revealed that the major conjugated forms of both glyceollins were methylation, sulfation, and glucronidation, while daidzein was mainly metabolized to form hydroxylated equol during intestinal absorption process, which demonstrated that prenylated isoflavones (glyceollins) might be absorbed as conjugated forms, but not intact forms. It was demonstrated for the first time that the prenylation of isoflavones may promote intestinal absorption into rat bloodstream compared to their mother isoflavones, according to increasing hydrophobicity.

Secondly, the *in vivo* health benefits of prenylated isoflavones, glyceollins, in organs strongly

suggest that they may play a physiological role through their local accumulation. The accumulation of oral administered glyceollins into typical circulatory organs (the liver, the kidneys, the heart, the lungs, the soleus muscles, and the abdominal aorta) of SD rats were investigated. As a result of LC-TOF/MS analysis of organ accumulations, glyceollin I or III (daidzein as comparative compound) was accumulated as intact and conjugated forms (up to 6 h) in circulatory organs with $T_{max}$ of 0.5 h, in the order of the liver > the kidneys > the heart > the lungs > the soleus muscles, the abdominal aorta in single orally administered SD rats. Hydrophobic glyceollin I accumulation in organs was > 1.5-times higher than that of glyceollin III. In contrast, daidzein and equol-OH were detected only in the liver and the kidney at > 1/100-times lower amounts than those of glyceollins. Consequently, it is demonstrated firstly that prenylated isoflavones, glyceollins, were rapidly and preferably accumulated in circulatory organs.

In conclusion, the present study demonstrated firstly the conjugated absorption of prenylated isoflavones, glyceollins, to rat circulating bloodstream. Absorbed glyceollins were received metabolic degradation including methylation, sulfation, and glucuronidation during intestinal absorption process. In addition, the accumulation of oral administered glyceollins into typical circulatory organs (the liver, the kidneys, the heart, the lungs, the soleus muscles, and the abdominal aorta) of SD rats were investigated. The prenylated isoflavones, glyceollins, were preferentially distributed in the circulatory organs as intact, sulfated or glucuronidated forms up to 6 h after the intake. The present study will be essential to better assess the health-benefits of prenlated isoflavones, glyceollins.