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QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP STUDY ON HEPATIC METABOLISM OF METHOXYFLAVONES USING QUANTUM CHEMICAL GEOMETRY OPTIMIZATION

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Introduction: Methoxyflavones were reported to be chemopreventive agents against cancer, cardiovascular, and other diseases. On the other hand, there is limited data on the quantitative structure-activity relationship (QSAR) regarding pharmacokinetics and metabolism. Therefore, the present study focused on QSAR of the metabolic rate of methoxyflavones. Methods: Fifteen kinds of methoxyflavones including kaempferide, sinensetin, tangeretin, and tectochrysin were the objects of this study. The geometric, electronic, and physicochemical features of the methoxyflavones including HOMO energies, LUMO energies, logP values, and Mulliken charges on atoms were sought by quantum mechanical methods. That is, the minimal energy conformation of each methoxyflavone was searched using Merck Molecular Force Field (MMFq), and then geometry optimization was performed by the density-functional-theory (DFT) calculation (B3LYP/6-31G** basis set). Additionally, single point energy was refined by the DFT calculation (B3LYP/6-311+G**). Dragon descriptors were added. The relation between intrinsic clearances with human liver microsomes and the descriptors was investigated using statistical techniques including multi-regression analysis and partial least squares (PLS) analysis. Results and Discussion: Some multiple regression equations including Mulliken charge at position-5 carbon atom as a descriptor were acquired ($r^2 = 0.936$, $q^2 = 0.898$, $s = 0.104$, $F = 53.8$, in the best equation with three descriptors). Furthermore, the PLS regression equation was acquired with seven descriptors such as Mulliken charge values (position-5, 2' and 6') and Dragon descriptors ($r^2 = 0.973$). These parameters were important structural characters to define the intrinsic clearances of methoxyflavones and maybe related to affinities and oxidative reactions of flavones with P450.

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ALTERED EXPRESSION OF CYP ENZYMES IN TSOD MICE; A MODEL OF TYPE 2 DIABETES AND OBESITY

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Obesity and diabetes are known to cause changes in the expression levels of cytochrome P450 (CYP) enzymes. This applies also to the animal models of obesity/diabetes, resulting in different pharmacokinetics depending on the model. In the present study, the hepatic expression levels of major CYP isozymes in TSOD mice, a model of type 2 diabetes and obesity, have been compared with those in TSNO mice (control) in order to characterize their pharmacokinetic properties.

Development of diabetes and obesity in TSOD mice at 7 months were confirmed by measuring their body weight, adipose tissue weight and plasma biochemical parameters such as glucose, insulin, triglyceride etc. The hepatic mRNA levels of most of the major CYP isozymes were found to be lower in TSOD mice than in TSNO mice by real-time RT-PCR analyses. Western blot analyses indicated that the protein levels of Cyp1a, Cyp2e and Cyp4a were significantly lower in TSOD mice, while those of Cyp2c and Cyp3a were significantly higher in TSOD mice compared with TSNO mice.

In conclusion, TSOD mice showed unique expression of hepatic CYP enzymes, possibly inducing differences in pharmacokinetics compared with normal mice. Such differences should be taken into consideration when using animal models in drug development.