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Pharmacokinetic profiles of trifolirhizin, (-)-maackiain, (-)-sophoranone, and 2-(2,4-dihydroxyphenyl)-5,6-methylenedioxybenzofuran after oral administration of *Sophora tonkinensis* extract in rats

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The dried roots and rhizomes of Sophora tonkinensis are traditionally used herbal medicines in Korea and China, under the named Shan-dou-gen, for the treatment of acute pharyngolaryngeal infections and sore throat. SKI3301 (SK Chemicals, Republic Korea) is a quantified extract obtained from dried 50% ethanolic extracts of Sophora tonkinensis that contains the four marker compounds, three flavonoids (trifolirhizin; TF, (-)-maackiain; Maack, and (-)-sophoranone; SPN) and one 2-arylbenzofuran derivative (2-(2,4-dihydroxyphenyl)-5,6-methylenedioxybenzofuran; ABF). After oral administration of SKI3301 at a dose of 200 mg/kg twice a day, it showed an anti-allergic property on mast cell-mediated allergic response in ovalbumin-induced asthma mouse model. These four components (TF, Maack, SPN, and ABF) probably account for the spectrum of medicinal properties of SKI3301 extract. SKI3301 is being developed as an herbal medicine for the treatment of asthma in Republic of Korea. For the preclinical evaluation of SKI3301 extract, the pharmacokinetic studies were conducted following intravenous and oral administration in male rats as single or multiple doses. In addition, pharmacokinetic properties of TF, Maack, SPN, and ABF as a pure compound were performed after oral administration TF, Maack, SPN, and ABF, respectively, at a dose of equivalent to 400 mg/kg of SKI3301 to compare their pharmacokinetics after administered as SKI3301 extract. After intravenous administration of SKI3301 at doses of 5, 10, and 20 mg/kg to rats, all pharmacokinetic markers of SKI3301, TF, Maack, SPN, and ABF, exhibited rapid elimination with half-lives of 3.26-33.7 min from plasma. At 5 mg/kg of SKI3301, data were not meaningful because plasma levels of TF, Maack, SPN, and ABF were either below their lower limit of quantifications or they were not high enough for accurate pharmacokinetic analysis. The dose-normalized AUCt values and CL values of TF, Maack, SPN, and ABF after intravenous doses were not significantly different, suggesting linear and dose-independent pharmacokinetics of TF, Maack, SPN, and ABF. After oral administration of SKI3301 at doses of 200, 400, and 1000 mg/kg, exhibited rapid absorption from gastrointestinal tract. At 1000 mg/kg of SKI3301, the values dose-normalized AUCt and dose-normalized Cmax of TF and Maack were significantly smaller than those at 200 and 400 mg/kg, suggesting non-linear pharmacokinetics. Nonlinearity in oral pharmacokinetics of TF in SKI3301 might be a result of saturation of absorption in gastrointestinal tract. After oral administration of SKI3301, the metabolic conversion rates of TF into Maack, expressed as AUCt, Maack / AUCt, TF, were approximately 37.9%, 33.1% and 34.0% at doses of 200 mg/kg, 400 mg/kg, and 1000 mg/kg, respectively. These were not changed compared when TF as a pure compound was orally administered. However, the pharmacokinetics of SPN and ABF, although variable, appear to be linear from oral doses of 200 mg/kg to 1000 mg/kg of SKI3301. Oral bioavailabilities (F) of TF, SPN, and ABF, based on oral dose of 400 mg/kg and intravenous dose 10 m/kg, were relatively low (19.3%, 0.540%, and 6.82%, respectively), which might be partly because of poor absorption and extensive first-pass metabolism in liver. When TF, Maack, SPN, and ABF as a pure compound at a dose of equivalent to 400 mg/kg of SKI3301 were orally administered respectively, only TF and SPN were detected in plasma whilst significantly lower levels than those of TF and SPN in SKI3301. It has been shown that herb extract, SKI3301, increased the bioavailability of TF or SPN in rat comparing with respective pure compounds. It may explain that the solubility or dissolution of TF, Maack, SPN and ABF could be increased and in turn to improve absorption due to synergistic effect of different components in SKI3301 extracts. After oral administration of TF, Maack (aglycone of TF) were detected in plasma. This suggested that TF (maackiain-3-O-glucoside) is hydrolyzed by β-glucosidase into Maack after absorption and Maack itself was not absorbed in the gastrointestinal tract. The metabolic conversion rate of TF into Maack was approximately 44% after oral administration of TF. There are no significant differences in the pharmacokinetic parameters of TF, Maack, SPN, and ABF between single and multiple oral administration groups. This suggested that no time-dependent auto-induction or auto-inhibition would be occurred after multiple dosing of SKI3301.

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