Pharmacokinetics and Tissue Distribution of ¥â-sitosterols, Campesterols, and Stigmasterols after Oral Administration of Titrated Extracts of the Unsaponifiable Fraction of Zea Mays L in Rats

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Purpose
Phytosterols are known to have a wide range of biological activities, such as the ability to lower serum cholesterol levels in humans and to give beneficial effects against colon cancer, and they are also believed to have anti-inflammatory, anti-bacterial and anti-ulcerative properties. They have applications in medicine, cosmetics and as food additives. The unsaponifiable fraction is obtained from the corn oil of Zea mays L. which is rich in phytosterols such as isomeric sitosterols, tocopherols, and waxy substances such as myricyl and ceryl alcohols. Zea mays is commonly used to reduce tooth mobility, mitigate gum swelling and promote alveolar bone repair by stimulating osteocytes. The several clinical trials have demonstrated that the titrated extract of the unsaponifiable fraction of Zea mays L. provides the major building material for growth, repair and maintenance of healthy oral cavity and a non-antibiotic medical therapy for periodontopathies such as gingivitis, periodontosis, pyorrhea alveolaris. In Korea, the titrated extract of the unsaponifiable fraction of Zea mays L. is marketed as oral tablets under the trade name Insadol (Dongguk Pharmaceuticals, Seoul, Republic of Korea) with a recommended dosage of 70 mg (two tablets) three times per day. This herbal medicine, which contains the three marker phytosterols, ¥â-sitosterol, campesterol, and stigmasterol, is widely prescribed for the prevention and/or treatment of periodontopathy, gingivitis, and periodontosis. Paradoxically, although the titrated extract of the unsaponifiable fraction of Zea mays L. is widely used, there is still limited information available concerning the pharmacokinetic properties of its marker phytosterols, ¥â-sitosterol, campesterol, and stigmasterol, in animals and humans. Based on its clinical potential, it is important to understand its pharmacokinetic characteristics and tissue distribution.

Methods
Thus, this study was mainly focused on: (1) developing an liquid chromatography-tandem mass spectrometry (LC-APCI-MS/MS) method for the simultaneous determination of three phytosterols after administration of the titrated extract of the unsaponifiable fraction of Zea mays L. (Insadol extract) in rats plasma and tissue; (2) elucidating the pharmacokinetic profiles and tissue distribution of ¥â-sitosterol, campesterol, and stigmasterol after single oral administration of Insadol extract at various doses in rats; (3) comparing the pharmacokinetic properties following administration of equivalent doses of individual pure compounds, ¥â-sitosterol, campesterol, and stigmasterol, and those following administration of Insadol extract in rats.

Results
After oral administration of Insadol extract, three marker phytosterols, ¥â-sitosterol, campesterol, and stigmasterol, could be determined in rat plasma. The AUC and Cmax values of three marker phytosterols after Insadol extract oral administration were proportional to the administered Insadol extract doses ranged from 200 mg/kg to 1000 mg/kg, which suggested linear pharmacokinetic properties. There were no statistically significant differences in the pharmacokinetics of ¥â-sitosterol, campesterol, and stigmasterol after oral administration of respectively pure ¥â-sitosterol, campesterol, and stigmasterol compared with oral administration of Insadol extract, 1000 mg/kg. These indicated that the presence of other components of Insadol extract extract did not influence the pharmacokinetic behavior of three marker phytosterols. After oral dosing of Insadol extract, especially, stigmasterol was distributed mainly to gums in rats.

Conclusion
Our finding may help to understand pharmacokinetic characteristics of ¥â-sitosterol, campesterol, and stigmasterol, comprehensively, and provide useful information in clinical application of the titrated extract of the unsaponifiable fraction of Zea mays L.