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PROMISING TOXICOLOGICAL BIOMARKERS FOR DIAGNOSIS OF LIVER INJURY TYPES: BILE ACID METABOLIC PROFILES AS SCREENING TOOL IN DRUG DEVELOPMENT
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[Purpose] To provide diagnostic information to evaluate the types of liver injury in preclinical study, bile acid (BA) profiles as the promising biomarkers were investigated for toxicological screening of new chemical entities (NCEs).

[Methods] Male SD rats received following treatments: (a) a single oral dosing of 150 mg/kg α-naphthylisothiocyanate; (b) bile duct ligation; (c) repeated oral dosing of NCE. Serum biochemistry, liver histopathology, BA profiles by LC-MS/MS, and mRNA expression of transporters and CYPs by RT-PCR were evaluated.

[Results and Discussion] Serum total BAs and bilirubin concentrations elevated in all groups. However, the BA profiles of NCE treated group, in which observed the high components of hydrophobic and more toxic BAs, were significantly different from that of typical cholestasis models. In addition, NCE treated group showed high levels in serum sulfated BA concentrations and hepatic heme oxygenase-1 expression, whereas the profiles of biochemistry and mRNAs of hepatic transporters and CYPs of all groups were similar. Histopathological changes in the liver corresponding to cholestasis were similar among all treatment groups, but other pathology seemed to be different in the NCE group. These results indicated that NCE induced cholestasis and also oxidative stress which might lead to hepatocellular injury. Therefore, the biomarkers such as BA profiles could provide the information to diagnose the liver injury type and to elucidate the mechanisms of hepatotoxicity.

[Conclusions] BA profiles and sulfated BA are likely to be as crucial biomarkers to discriminate the diagnosis of liver injury types. They can be screening tools in lead optimization phase of toxicological study to evaluate NCEs.

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ALKOXYALKYL ESTERS OF ASIATIC ACID AS ASIATICOSIDE MIMETICS
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[Purpose] Molecular modification of asiaticoside by changing sugar moiety to simple alkoxyalkyl groups may prove useful in the identification of asiaticoside pharmacophore as well as the development of more active wound healing agents.

[Methods] Novel asiaticoside mimetics simplified the sugar moiety by alkoxyalkyl groups were synthesized, and tested their wound healing effects by tensile strength measurement.

[Results and Discussion] It is well known that glycosides of therapeutic importance having appropriate sugar molecules will be more effective than free aglycone. The pharmacological action of asiaticoside has been well documented, however, the role of sugar in asiaticoside is still unclear. Even if the sugar moiety in asiaticoside may not be necessary for biological activity, it may be possible to change the efficacy of asiatic acid aglycone by regulating the pharmacokinetic parameters such as absorption, distribution, bioavailability, or therapeutic width. We have prepared a series of asiaticoside derivatives, and tested their wound healing effect by tensile strength measurement. Asiaticoside mimetic describes here represents one of very few examples of glycoside mimetic from the simplification of sugar moiety by alkoxyalkyl group, and this approach provides valuable insight for the elaboration of sugar moiety in asiaticoside.

[Conclusions] From this study, it is speculated that sugar portion of asiaticoside is not the essential pharmacophore for biological activity, but enhance the wound healing effect of asiatic acid in topical application, and could be greatly simplified to alkoxyalkyl group without loss of biological activity.