Design, Synthesis and Biological Evaluation of Novel Curcumin Glucoside Derivatives as Anticancer Agents

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Abstract :
Curcumin is long regarded as a chemopreventative and chemotherapeutic agent but its clinical use is limited due to the very low water solubility and fast metabolized in liver. One strategy to improve the bioavailability is the synthesis of curcumin analogues. Curcumin glucoside is a modified form of curcumin by covalent-bonding sugar to the curcumin. Our recent research data showed that C-MG harbored more antitumor growth activity than curcumin. The higher bioavailability of C-MG than that of curcumin was anticipated. In order to increase the bioavailability of curcumin, we derivatized curcumin into new hydrophilic prodrugs to increase its water solubility and bioavailability. The newly synthesized curcumin derivatives, named as C-S-MG, was expeteded to show better pharmacokinetic profiles than curcumin.

Introduction:
Curcumin, a polyphenolic compound derived from rhizome of turmeric, exhibits a wealth of pharmacologic effects including anti-inflammatory, antioxidant, antiproliferative and antiangiogenic activities. Curcumin is long regarded as a chemopreventative and chemotherapeutic agent but the clinical use is limited due to the very low water solubility and fast metabolism. Phase I clinical trials showed that curcumin exhibited poor oral bioavailability (about 1%).
One strategy to improve the bioavailability is the synthesis of curcumin analogues. Curcumin glucoside is a modified form of curcumin by covalent-bonding sugar to the curcumin. According to literature reports, the water solubility of curcumin mono-glucoside (C-MG) is 230 times higher than curcumin. But there is not report regarding to the anticancer acticity of C-MG.

Result and discussion:
To test the bio-availability of C-MG, we used the CL1-5 xenograft animal model and monitored the tumor growth for evaluating the bio-availability efficacy. The results indicated that the C-MG might significantly inhibit tumor growth compared to the vehicle control and the curcumin group at the same dosage (Fig. 1). Besides, while combined with gefitinib, mono-glucoside (C-MG) also might significantly reduce the tumor size compared to the gefitinib group (Fig. 1). The data indicated the mono-glucoside (C-MG) is more effective than curcumin in inhibition of tumor growth and within synergistic as combining with gefitinib. *Therefore, the higher bioavailability of C-MG than that of curcumin is anticipated.*

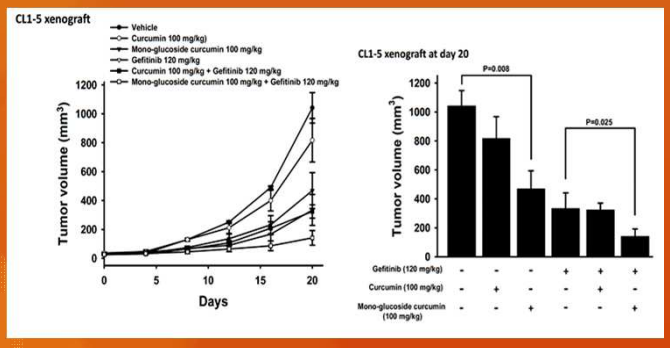


Fig. 1. Anti-tumor activity of gefitinib combining with curcumin and mono-glucoside (C-MG) in CL1-5 xenograft animal model

In addition, the in vitro enzyme pharmacokinetic studies of C-MG was carried. As shown in Fig 2, the C-MG was readily hydrolyzed in very short tmie (10 min) by glucosidase at 37 degree into curcumin.
As part of our efforts to discover new anticancer agents, we designed and synthesized a series of new curcumin derivatives. We modified curcumin into hydrophilic prodrugs to increase its water solubility and bioavailability.

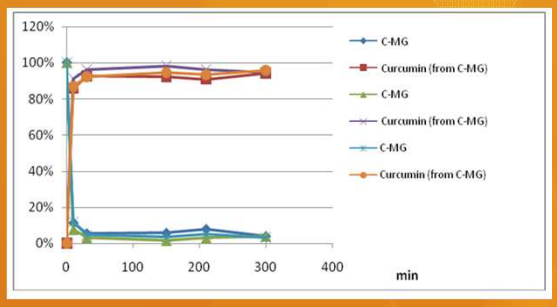


Fig. 2 In vitro enzyme pharmacokinetic studies of C-MG

As shown in Fig 3, the newly synthesized curcumin derivatives, named as C-S-MG, is composed of curcumin, a linker and a glucoside. The features of C-S-MG are higher water solubility compared to curcumin and easily transform back to its parent compound by enzymatic hydrolysis in vitro and in vivo. Therefore, C-S-MG is expected to exhibit better bioavailability than curcumin

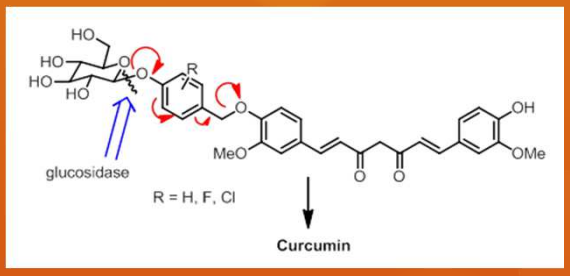
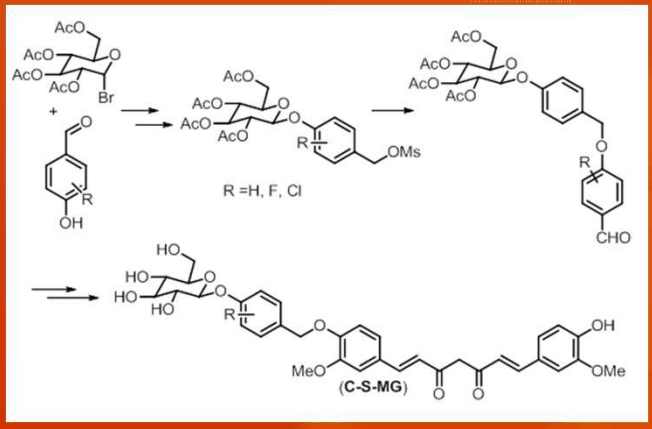


Fig. 3

Alone these lines, we have synthesized a series of C-S-MG bearing different functional groups including hydrogen , fluorine and chlorine atom on the linker. The synthesis of C-S-MG is listed in Scheme 1. Future works including pharmacokinetic study, animal test and acute toxicity study are ongoing.



Scheme 1 The synthetic scheme of C-S-MG

Acknowledgement: This work was supported by grants from the National Science Council of Taiwan and China Medical University (CMU102-N-03).