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Effects of Epidermal Growth Factor Receptor Inhibitor Genistein on Proliferative Cholangitis in Rats

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Background. **Many strategies for treating hepatolithiasis neglect the therapy for associated proliferative cholangitis (PC), which is the root cause of residual and recurrent stones and biliary strictures, resulting in an unsatisfactory therapeutic outcome. Epidermal growth factor receptor (EGFR) expression is a dominant component in cell proliferation. The aim of this study was to investigate the effect of EGFR inhibitor genistein on PC in rats.**

Methods. **The rat PC model was established by introducing a nylon thread into the bile duct. Different doses of genistein were administered directly into the bile duct. The effectiveness of genistein on PC was assessed by histology, immunohistochemistry for EGFR, and RT-PCR for EGFR mRNA.**

Results. **The proliferation of biliary epithelium, and fibrous tissue, and the hyperplasia of peribiliary gland in PC were indeed suppressed by genistein, and this antiproliferative effect presented a significant dose–response relationship. The structure of biliary tissue in the high-dose group (genistein 6.0mg/kg) had approached that of the normal bile duct. Compared with the PC model, the levels of expression of EGFR mRNA and protein in the genistein-treated groups were reduced gradually with the increase of genistein dosage, and the level of expression of EGFR mRNA and protein in the high-dose group had neared that of the normal bile duct.**

Conclusions. **Direct administration of genistein into the bile duct suppressed PC in a rat model, and may provide a novel strategy towards improving the prognosis of patients with hepatolithiasis.** © 2010 Elsevier Inc. All rights reserved.

Key Words: **proliferative cholangitis; hepatolithiasis; biliary stricture; epidermal growth factor receptor; epidermal growth factor receptor inhibitor; genistein.**

INTRODUCTION

Hepatolithiasis is a common disease in Southeast Asia, but it has been quite difficult to treat this disease until now because conventional therapeutic strategies for hepatolithiasis fail to significantly reduce the rates of residual and recurrent stones and resolve the problem of secondary biliary strictures [1–3]. Thus, some additional approaches with higher efficacy are urgently required for the treatment of hepatolithiasis.

In recent years, some researches [3–7] have demonstrated that proliferative cholangitis (PC), which is characterized by proliferation of biliary epithelium and fibrous tissue and hyperplasia of peribiliary gland, is the most significant pathologic feature of hepatolithiasis and the root cause of residual and recurrent stones and biliary strictures. PC plays a significant role in the pathogenesis of hepatolithiasis and is associated with about 75% of hepatolithiasis cases in Asia [8]. Therefore, PC should serve as a target for the therapy of hepatolithiasis. On the other hand, Kim *et al.* [9] have verified that the level of expression of epidermal growth factor receptor (EGFR) is rather high in patients with hepatolithiasis. In other words, EGFR expression appears to be the dominant component in the periductular hyperplasia of hepatolithiasis. Additionally, epidermal growth factor (EGF) is secreted into bile and has been shown to enhance the proliferation of bile duct

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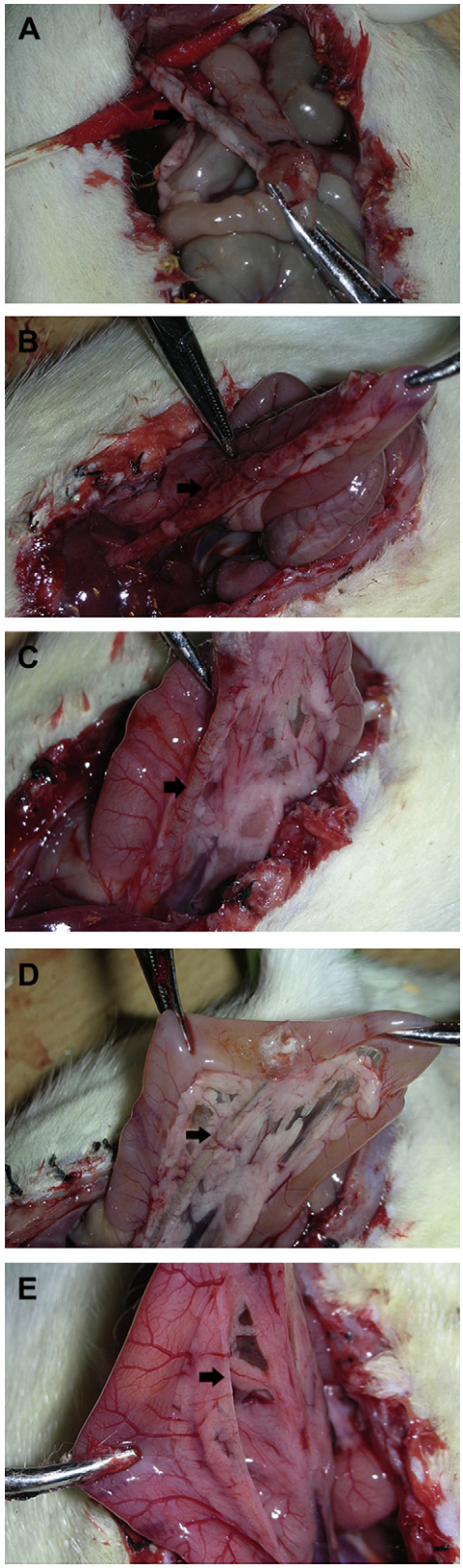

FIG. 1. Gross finding of the bile duct in the PC model group (A), genistein-treated groups (B)–(D), 1.5 mg/kg, 3.0 mg/kg, 6.0 mg/kg, and sham-operated group (E). The arrow indicates the bile duct. (Color version of figure is available online.)

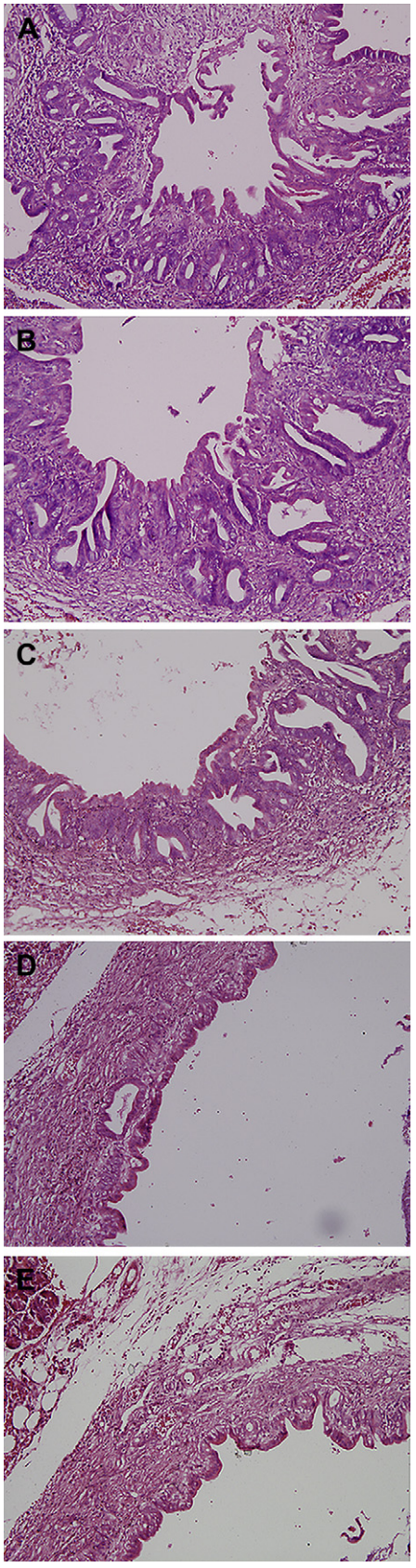

FIG. 2. Representative HE-stained bile duct from the rats (original magnification, ×200) in the PC model group (A), genistein-treated groups (B)–(D), 1.5 mg/kg, 3.0 mg/kg, 6.0 mg/kg, and sham-operated group (E). (Color version of figure is available online.)

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