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Betulin, betulinic acid and butein are inhibitors of acetaldehyde-induced activation of liver stellate cells

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Abstract:
Liver fibrosis has been reported to be inhibited *in vivo* by oleanolic and ursolic acids; however, the activity of other triterpenes like betulin and betulinic acid has not been examined. Butein has also been reported to prevent and partly reverse liver fibrosis *in vivo*, although its mechanism of action is poorly understood. Therefore, the aim of this study was to determine the antifibrotic potential of butein, betulin, and betulinic acid and examine their mechanisms of action *in vitro*. This study was conducted in rat stellate cells (HSCs) that were treated with acetaldehyde, which is the most reactive product of ethanol metabolism.
Butein, betulin, and betulinic acid were preincubated with rat HSCs at non-toxic concentrations. Treatment effects were measured in regard to acetaldehyde-induced toxicity and cell migration, and several markers of HSC activation were evaluated, including smooth muscle α-actin (α-SMA) and procollagen I expression. In addition, changes in the release of reactive oxygen species (ROS) and cytokines such as tumor necrosis factor-α (TNF-α) and tumor growth factor-β1 (TGF-β1) and changes in the production of metalloproteinase-2 (MMP-2) and tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2) were determined.
In vitro, HSCs were protected against acetaldehyde-induced toxicity by betulin but not by betulinic acid and butein. However, butein, betulin, and betulinic acid inhibited the production of ROS by HSCs treated with acetaldehyde and inhibited their migration. Butein also inhibited acetaldehyde-induced TGF-β1 production. Butein, betulin, and betulinic acid down-regulated acetaldehyde-induced production of TIMP-1 and TIMP-2. Betulin decreased the acetaldehyde-induced activity of MMP-2, but butein and betulinic acid did not.
The results indicated that butein, betulin, and betulinic acid inhibited the acetaldehyde-induced activation of HSCs. Each drug functioned in a different manner, whereby some were acting as either antioxidants or inhibitors of TIMPs expression and butein additionally acted as an inhibitor of TGF-β production.

Key words:
liver stellate cells, acetaldehyde, butein, betulin, betulinic acid, cytokines, MMP-2, TIMPs