In vitro 3D colon tumor penetrability of SRJ09, a new anti-cancer andrographolide analog

ABSTRACT

Limited tumor penetrability of anti-cancer drugs is recognized as one of the major factors that lead to poor anti-tumor activity. SRJ09 (3,19-(2-bromobenzylidene) andrographolide) has been identified as a lead anti-cancer agent for colon cancer. Recently, this compound was shown by us to be a mutant K-Ras binder. In this present study, the penetrability of SRJ09 through the DLD-1 colon cancer multicell layer (MCL) was evaluated. The amount of SRJ09 that penetrated through the MCL was quantitated by utilizing high performance liquid chromatography (HPLC). Histopathological staining was used to visualize the morphology of MCL. A chemosensitivity assay was performed to assess the anti-cancer activity of SRJ09 in DLD-1 cells. SRJ09 was able to penetrate through DLD-1 MCL and is inversely proportional with the MCL thickness. The flow rates for SRJ09 through MCL were 0.90±0.20 εM/min/cm2 and 0.56±0.06 εM/min/cm2 for days 1 and 5, respectively, which are better than doxorubicin. Histopathological examination revealed that the integrity of the DLD-1 MCL was retained and no visible damage was inflicted on the cell membrane, confirming the penetration of SRJ09 was by diffusion. Short term exposure (1 h) in DLD-1 cells demonstrated SRJ09 had IC50 of 41 εM which was approximately 4-folds lower than andrographolide, the parent compound of SRJ09. In conclusion, SRJ09 successfully penetrated through DLD-1 MCL by diffusion and emerged as a potential candidate to be developed as a clinically viable anti-colon cancer drug.

Keyword: Andrographolide analogue; Coloncancer; DLD-1; Multi cell layer; Tumor penetration