Andrographolide as a template in the synthesis of new anticancer agents with potentially novel molecular targets

ABSTRACT

Using andrographolide (AGP) as a template, a series of semisynthetic analogues was synthesised for the discovery of new anticancer agent(s) with improved antitumour selectivity and potency. SRJ09, a lead compound displayed remarkable activity in the National Cancer Institute (NCI) of USA in vitro anticancer screen, particularly against breast and colon cancers. The treatment of MCF-7 breast and HCT-116 colon cancer cells with SRJ09 induced a G1 phase cell cycle arrest through the down-regulation of CDK-4 expression with concomitant up-regulation of p21 expression and without affecting the cyclin D1 expression. SRJ09 induced apoptotic cell death in both cells in a p53- and bcl-2-independent manner, implicating extrinsic apoptotic pathway. The compound showed impressive in vivo activity by delaying HCT-116 tumour xenograft growth in nude mice. Recently, a derivative of SRJ09, SRS07 showed vast improvement in the NCI anticancer activity screen compared with the parent compound. Additionally, NCI's in silico COMPARE and SOM analyses revealed that the new AGP derivatives have potentially novel molecular target(s). These findings although preliminary they are highly suggestive SRS07 have a great potential to be developed into a clinical anticancer agent. This research is funded by the Ministry of Science, Technology and Innovation of Malaysia (MOSTI) under the IRPA and ScienceFund grant schemes.

Keyword: Andrographolide; New anticancer agents; Novel molecular targets.