

SRS06, a new semisynthetic andrographolide derivative with improved anticancer potency and selectivity, inhibits nuclear factor- κ B nuclear binding in the A549 non-small cell lung cancer cell line

ABSTRACT

Background: Andrographolide has been reported with anticancer and anti-inflammatory properties through the inhibition of the activity of signaling molecules such as v-Src, nuclear factor- κ B (NF- κ B), STAT3, and PI3K. NF- κ B has been proven to promote cancer cell survival, and targeting this pathway will halt the growth of cancer cells. Efforts have been made to produce semisynthetic derivatives of andrographolide with improved anticancer potency and selectivity. Subsequently, the effect of a selected derivative, 3,14,19-tripropionylandrographolide (SRS06), was tested for its action against NF- κ B. *Methods:* Screening against 60 US National Cancer Institute (NCI) human cancer cell lines representing leukemia and non-small cell lung (NSCL), colon, CNS, melanoma, ovarian, renal, prostate, and breast cancers was performed to determine the tumor type selectivity and potency of SRS06. Microculture tetrazolium, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide and sulforhodamine B assays were used to determine the in vitro anticancer activity, while Western blot studies were performed to ascertain the inhibitory effect of SRS06 on the NF- κ B signaling cascade. The TransAM™ p65 assay kit was used to determine NF- κ B p65 DNA binding activity in the NSCL cancer cell line A549. *Results:* From the NCI screening, SRS06 was found to exhibit potent growth-inhibitory effects on multiple cancer cell lines with 10-fold lower 50% growth inhibition (GI₅₀) compared with andrographolide. It was also discerned that the compound preferentially targeted melanoma, CNS, renal, colon, ovarian, prostate, and NSCL cancer cell lines. The DNA fragmentation assay indicated that the main mode of cell death of SRS06-treated A549 cells was via apoptosis. At 5 μ mol/l the compound decreased NF- κ B protein expression and caused a significant reduction in the nuclear p65 DNA binding activity. *Conclusion:* SRS06 displayed improved anticancer selectivity and potency when compared with andrographolide. We alluded its anticancer activity to its effect of inhibiting NF- κ B nuclear binding.

Keyword: SRS06; Andrographolide; Anticancer; NF- κ B nuclear binding