

## **ANTITUMOR POTENCY AND TOXICITY EVALUATION OF FULLY-LINKED GLUCURONIDES OF N-(4-HYDROXYPHENYL) RETINAMIDE (4-HPR) IN MAMMARY CANCER**

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Natural and synthetic retinoids have shown promising chemopreventive and therapeutic activities against mammary cancer, but at effective pharmacological doses these agents cause numerous toxic side effects. Obviously, the development of retinoid analogues with improved therapeutic index and lower toxicity is needed. Previous studies from our laboratories have shown that the glucuronide conjugates of retinoids are potent and less toxic analogues of the parent molecules. The important oxygen-linked conjugate of the synthetic retinoid 4-HPR, 4-HPR-O-Glucuronide (4-HPROG) is, however, susceptible to in vivo  $\beta$ -glucuronidase activity and acid-catalyzed cleavage to liberate retinoic acid (RA). Further synthesis in our laboratories showed that a series of stable C-linked analogues of 4-HPR, such as the non-hydrolysable analogue 4-Hydroxybenzylretinone (4-HBR), or the 4-HPR-C- Glucuronide conjugate (4-HPRCG), possess significantly potent antitumor activities and significantly reduced side effects. Also, to further eliminate the possibility of in vivo limited hydrolysis of 4-HPRCG, a non-hydrolysable fully C-linked analogue, 4-HBR-C-Glucuronide (4-HBRCG) was synthesized.

The antitumor activity and the toxic side effects of this fully C-linked glucuronide analogue, 4-HBRCG, were tested in a 7,12 dimethylbenz(a) anthracene (DMBA) - induced rat mammary tumor model, against equimolar concentrations of 4-HPR and all-trans retinoic acid (atRA). In terms of effect on mean tumor volume and tumor numbers vis-à-vis cancer load, 4-HBRCG caused 33% regression in mean volume of the DMBA-induced mammary tumors, relative to 33% and 38% reduction in 4-HPR and atRA-treated animals, respectively. In contrast, the control animals showed 190% increase in mean tumor volume. In addition, two new tumors developed in the control group during the treatment period, whereas no new tumors were developed in any of the retinoids treated groups. More importantly, 4-HBRCG was the least toxic retinoid. Relative to the control group, it did not significantly reduce plasma retinol level (-29%, -63%, and -54%), nor raise the plasma triglyceride level (-5%, +100%, and +720%), or produce a decrease in bone mineral content (-2%, -3%, and -11%) for 4-HBRCG, 4-HPR and atRA, respectively, all of which are possible serious side effects of retinoids. The results indicate that the stable 4-HBRCG, with its demonstrated therapeutic potency and markedly lower toxicity, can be a better candidate for breast cancer treatment than 4-HPR.

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