

**CANCER CHEMOPREVENTION: MANIPULATION OF XENOBIOTIC METABOLIZING ENZYMES BY GLUCORAPHASATIN AND GLUCORAPHENIN FOUND IN *BRASSICACEAE***

Barbara Bonamassa<sup>1</sup>, Jessica Barillari<sup>2</sup>, Donatella Canistro<sup>1</sup>, Laura Pozzetti<sup>1</sup>, Andrea Sapone<sup>1</sup>, Renato Iori<sup>2</sup>, Gian Luigi Biagi<sup>1</sup> and Moreno Paolini<sup>1</sup>.

<sup>1</sup>Department of Pharmacology, Molecular Toxicology Unit, *Alma Mater Studiorum* - University of Bologna, Via Irnerio 48 - 40126 Bologna, Italy. <sup>2</sup>Agricultural Research Council - Research Institute for Industrial Crops (CRA-ISCI), via Corticella 133, Bologna, Italy

Epidemiological and animal studies linking high and varied fruit and vegetable intake to lower cancer risk, suggest the theoretical possibility that regular, long-term mass administration of isolated, naturally occurring, dietary constituents can provide a way of controlling cancer incidence. *Brassicaceae*, in particular, have aroused a great interest because of their content in glucosinolates (GLs), a particular class of phytochemicals, hydrolyzed into bioactive isothiocyanates (ITCs) by myrosinase or by intestinal microflora. Although the exact mechanism of chemoprevention is not known, it is believed that the GL-derived ITCs could down-regulate Phase I (“bioactivating”) and/or up-regulate Phase II (“detoxifying”) xenobiotic metabolizing enzymes (XMEs), enhancing carcinogen clearance. The biological activities of ITCs seem to be primarily due to the presence of an  $-N=C=S$  group, but the side-chain of the GL could strategically be relevant. To verify whether GLs affect XMEs as well as the role of side-chain, glucoraphasatin (GRH) and glucoraphenin (GRE), two alkylthio GLs differing only in the oxidation degree of the side-chain sulphur, were purified in gram scale and singularly administered by gavage to male Sprague-Dawley rats at scalar doses in single or repeated fashion (daily for four consecutive days). Liver subcellular preparations were tested for various cytochrome P450 (CYP) linked-monoxygenases and phase II-supported XMEs such as glutathione S-transferase and UDP-glucuronosyl transferase. Both GLs were able to bifunctionally affect XMEs. However, while the inductive effect of GRH was present mainly after multiple administration of higher dosage (CYP3A1 and UDP-glucuronosyl transferase), a single administration of GRE at lower dose was more effective in inducing CYPs (especially CYP1A2) as well as phase II enzymes such as glutathione S-transferase. The profiles of induction recorded suggest that the oxidation degree of the chain-side sulphur of GLs exerts an important role in XME modulation. Moreover, the manipulation of rat microsomal metabolism by GLs is not in line with the “chemopreventive hypothesis”, suggesting that caution should be exercised before using single, naturally occurring dietary constituents on a large scale before preventive toxicological testings. Noteworthy, the National Cancer Institute has adopted the slogan “5 to 9 a day for a better health” to educate to a varied fruit and vegetable rich diet.