Legend to Figures:

Figure 1. Metabolism of glucoraphanin and glucobrassicin to biologically active metabolites. (A) Sulforaphane is released from glucoraphanin by the plant enzyme myrosinase. Red dashed arrow marks the reactive carbon atom subject to glutathione conjugation. (B) Sulforaphane is metabolized via the mercapturic acid pathway into active metabolites. Glutathione-S-transferase (GST) first conjugates a GSH molecule (Glu-Cys-Gly) to the reactive carbon on sulforaphane. Glutamate is then removed by γ-glutamyltranspeptidase (GTP), followed by removal of the glycine residue by cysteinylglycinase (CGase). Cysteine is then acetylated by an acetyltransferase (AT) to sulforaphane-N-acetylcysteine, which is excreted in the urine. (C) Indole-3-carbinol is released from the glucosinolate glucobrassicin by myrosinase and undergoes spontaneous condensation in the acidic environment of the gut. Diindolylmethane (DIM) is the most abundant post-absorption acid condensation product. Acid condensation products can be modified further post-absorption. LTr₁: Linear trimer 1. LTr₂: Linear trimer 2. Structures from PubChem at National Center for Biotechnology Information (NCBI).

Figure 2. Selected non-epigenetic effects of sulforaphane and I3C/DIM on prostate cancer cells. Sulforaphane (SFN) and I3C/DIM inhibit the Akt signaling axis, a signaling pathway often hyperactive in prostate cancer. Inhibition of this pathway decreases pro-survival signaling by mTOR, Akt, and NFkB. Sulforaphane and I3C/DIM treatment also lead to changes in gene expression (blue arrow) that trigger growth arrest and apoptosis. The expression of proteins controlling the cell cycle (e.g. p21, p27, CDK6) are altered to effect growth arrest, and apoptosis is finally induced through the mitochondrial pathway. Abbreviations: AR – Androgen Receptor, CDK6 – cyclin dependant kinase 6, IAP – inhibitors of apoptosis.

Figure 3. Sulforaphane and I3C/DIM suppress prostate cancer through epigenetic modulation. Sulforaphane (SFN) decreases cellular DNA methyltransferase (DNMT) and histone deacetylase (HDAC) activity, leading to altered chromatin structure and gene expression (blue arrow). Sulforaphane also directly inhibits cytoplasmic HDAC6, which controls the acetylation of many non-histone proteins, leading to a decrease in AR signaling, altered cytoskeletal dynamics, disrupted protein turnover, and, ultimately, increased cell stress. I3C/DIM also decreases cellular HDAC activity, leading to changes in gene expression (blue arrow). The expression levels of microRNAs (miRNAs) are also disrupted, and lead to changes in protein levels of chromatin associated protein EZH2 and nuclear receptor AR through post-transcriptional regulation.