C-glucosylation, the miracle for preventing polyphenol pan-assay interference compound behavior

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Polyphenol health benefits are worldwide recognized [1] but many such products are Pan-Assay Interference Compounds (PAINS). They are bioactive but react non-specifically with various targets instead of acting on one specific target, thus giving false positive results in cell-based biological evaluations. We disclose now our results demonstrating that *C*-glucosylation is a synthetic tool generating compounds which do not induce changes in cell membrane dipole potential and are able to prevent the threat of polyphenol PAINS behavior, based on the established fact that altered membrane dipole potential translates into changes in transmembrane protein conformation and function. By investigating the planar lipophilic polyphenols resveratrol, genistein and phloretin, we synthesized their *C*-glucosyl derivatives and obtained polyphenols that are not able to modify dipole membrane, thus preventing their aglycone PAINS behavior.

We also discovered that *C*-glucosylation may increase polyphenol bioactivity and sometimes selectivity, as well as polyphenol bioavailability, as shown with antidiabetic glucosyldihydrochalcones, and with antioxidant glucosylflavones, some of which found to rescue neurons from β-amyloid (Aβ) toxicity, some block A_{β}-induced Fyn kinase activation and decrease derived Tau hyperphosphorylation, others disrupt Prion (PrP^{C})-Aβ oligomers interactions, which are key for the Aβ-induced neurodegeneration. We will also disclose their pharmacokinetic properties, in some of them ideal for further developments, aiming to reach new candidates for the treatment of Alzheimer's disease [2] which is unfortunately still uncurable.

We hope, with this presentation, to motivate glycoscientists to pursue methodologies for polyphenol *C*-glycosylation, a new technology towards liberating polyphenols from PAINS behavior, and generating more potent, selective, less toxic and more bioavailable polyphenols than their aglycones.

Bibliographic references:

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