Antiproliferative and uncoupling effects of delocalized, lipophilic, cationic gallic acid derivatives on cancer cell lines. Validation in vivo in singenic mice

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Tumor cells principally exhibit increased mitochondrial transmembrane potential (??m) and altered metabolic pathways. The therapeutic targeting and delivery of anticancer drugs to the mitochondria might improve treatment efficacy. Gallic acid exhibits a variety of biological activities, and its ester derivatives can induce mitochondrial dysfunction. Four alkyl gallate triphenylphosphonium lipophilic cations were synthesized, each differing in the size of the linker chain at the cationic moiety. These derivatives were selectively cytotoxic toward tumor cells. The better compound (TPP+C10) contained 10 carbon atoms within the linker chain and exhibited an IC50 value of approximately 0.4-1.6 ?M for tumor cells and a selectivity index of approximately 17-fold for tumor compared with normal cells. Consequently, its antiproliferative effect was also assessed in vivo. The oxygen consumption rate and NAD(P)H oxidation levels increased in the tumor cell lines (uncoupling effect), resulting in a