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Why extracts of five Indian plants cure cancer? Enhanced protection of DNA but destruction of nucleotides through the endogenous Fenton reaction; Inhibition of human topoisomerases

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The influence of substoichiometric amounts of seven plant extracts in the Fenton reaction-mediated damage to deoxynucleosides, deoxynucleoside monophosphates, deoxynucleoside triphosphates and supercoiled plasmid DNA were studied to rationalize anticancer properties reported in the extracts *Acacia catechu*, *Emblica officinalis*, *Spondias dulcis*, *Terminalia belerica* and *Terminalia chebula*. Extracts from these five plants, as well as gallic acid, epicatechin, chebulagic acid and chebulinic acid enhance the extent of damage in Fenton reactions with all monomeric substrates but protect supercoiled plasmid DNA, compared to standard Fenton reactions. However, *Dolichos biflorus* and *Hemidesmus indicus* extracts generally do not show this enhancement for the monomeric substrates though they protect plasmid DNA. Compared to standard Fenton reactions for deoxynucleosides with ethanol, the presence of these five plant extracts render ethanol scavenging less effective as the radical is generated near the target. Since substoichiometric amounts of these extracts and the four compounds produce this effect, a catalytic mechanism involving the presence of a ternary complex of the nucleoside/nucleotide substrate, a plant compound and the hydroxyl radical was proposed. Such a mechanism cannot operate for plasmid DNA as the planar rings in the extract compounds cannot stack with the duplex DNA bases. These plant extracts, by enhancing Fenton reaction-mediated damage to deoxynucleoside triphosphates, slow down DNA replication in rapidly dividing cancer cells. In another set of experiments, extracts of *Acacia catechu*, *Emblica officinalis*, *Terminalia belerica*, *Terminalia chebula*, *Spondias dulcis*, completely inhibit human topoisomerase I at 40 µg/ml concentration while *Hemidesmus indicus* and *Dolichos biflorus* extracts inhibit partially at the same concentration when included in standard assays. Extracts of the same five plants which inhibit human topoisomerase I strongly are known to possess anticancer activity, while the other two are antioxidant only. Extracts of *Acacia catechu*, *Terminalia chebula* and *Spondias dulcis* show 20 to 80% inhibition of human topoisomerase I at even 9 µg/ml concentration. All seven plant extracts partially inhibit human topoisomerase II at 120 µg/ml concentration in the decatenation assay. Chebulagic and chebulinic acid purified from Terminalia chebula extract inhibited human topoisomerase I at around 2 µM and 3 µM respectively. The nuclear fragmentation leading to apoptosis observed earlier in cancerous cell lines in the presence of such plant extracts may thus be explained by the inhibition of topoisomerases in addition to modulation of Fenton reaction-mediated damage to DNA constituents.

Biography

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