Areca catechu L. and gastrointestinal toxicity: Potential mixture effects?

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Introduction: Relatively unknown in the Western societies, the masticatory Areca nut (*Areca catechu* L.) features as the fourth most used psychoactive substance worldwide, despite its carcinogenic properties mainly associated with the development of oral submucosal fibrosis and oral cancer. Knowledge of its effects on other organs and physiological functions remains limited, with most toxic effects being attributed exclusively to areca alkaloids[1]. **Aims:** We aimed to evaluate the impact of *A. catechu* aqueous extract and relevant phytochemical constituents (arecoline, arecaidine, guvacine, isoguvacine, *N*-nitrosoguvacine, catechin and epicatechin) on radical stress and gastrointestinal toxicity. **Methods:** Viability of human colorectal adenocarcinoma Caco2 and hepatocarcinoma HepG2 cells was evaluated through the MTT and lactate dehydrogenase assays, upon exposure to *A. catechu* aqueous extract or its single phytochemicals (up to 1000 µg/mL or 200 µM, respectively). Radical neutralizing potential was assessed by the nitric oxide ($^{\bullet}NO$) and superoxide ($O_2^{\bullet-}$) scavenging assays. **Results:** Concentration-dependent antiradical activity upon $^{\bullet}NO$ and $O_2^{\bullet-}$ was verified for *A. catechu* extract (IC_{50} of 48.99 µg/mL and 36.63 µg/mL, respectively). Although $O_2^{\bullet-}$ production was increased by 32% at 7.81 µg/mL, the opposite effect was observed at concentrations starting at 31.25 µg/mL, with an almost complete neutralization (96.47%, $p<0.0001$) being achieved at 250 µg/mL of extract. Increased $O_2^{\bullet-}$ levels were also observed with guvacine, isoguvacine and *N*-nitrosoguvacine. As for $^{\bullet}NO$, besides the extract, neutralizing properties were also observed with (+)-catechin and (-)-epicatechin at 3.125 µM upwards. While *A. catechu'* extract impaired metabolic competence above 500 µg/mL in intestinal and hepatic cells, leading to cell membrane integrity loss at the highest concentration, no significant effects were found for individual compounds. **Conclusions:** Although radical stress exacerbation by some compounds, cytotoxicity in intestinal and hepatic cells might stem from minor constituents of *A. catechu* nut or synergistic effects among tested compounds.

Keywords: herbal high; psychoactive substance; areca nut alkaloids; hepatotoxicity; carcinogenicity.

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